Chapter 17

Overview of Authorisation Procedures for Medicinal Products

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OBJECTIVES

- Gain an understanding of the regulatory procedures necessary to grant a medicinal product access to the marketplace
- Learn about aspects of compiling a Marketing Authorisation Application in different procedures
- Learn about legislation, procedural steps and the Competent Authorities

DIRECTIVES, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

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- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

- Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State


- The Rules Governing Medicinal Products in the European Union, Volume 2, Notice to Applicants (NTA)

  - “Chapter 1 Marketing Authorisation” (Updated November 2005),
  - “Chapter 2 Mutual Recognition” (Updated February 2007)
  - “Chapter 3 Community Referral” (Updated September 2007)
  - “Chapter 4 Centralised Procedure” (Updated April 2006)
  - “Chapter 6 Community Marketing Authorisation” (Updated version November 2005)
  - “Chapter 7 General Information” (Updated July 2008)

- The Rules Governing Medicinal Products in the European Union, Volume 2B, NTA, Presentation and Content of the Dossier
  - Module 1.2 Application Form (May 2008)
  - Questions and Answers (February 2008)
  - eCTD—electronic Common Technical Document

- The Rules Governing Medicinal Products in the European Union, Volume 2C, NTA Regulatory Guidelines
  - Guideline on Summary of Product Characteristics (SmPC) (September 2009)
  - Guideline on the Categorisation of New Applications (NA) versus Variations Applications (V) (October 2003)
Introduction

The EU utilises several types of legislative instruments to establish laws and policies, though not all are legally binding.

The legally binding instruments include:
- Regulations are directly enforceable laws, applicable and binding on all Member States; no national legislation is required to give them effect.
- Directives are binding on the Member States, must be transposed and adopted into national regulations within a specified timeframe. They may be effective in a Member State even before that state has enacted the corresponding national law.
- Decisions are binding in their entirety upon those to whom they are addressed (Member States or legal entities, e.g., legal persons or companies.)
- European Pharmacopoeia

Although these are not legally binding, they are strongly recommended either by the European Medicines Agency (EMA) or Member States’ Competent Authorities, and they often have considerable political force.

Guidances, recommendations, opinions and position and concept papers are issued by the Committee for Medicinal Products for Human Use (CHMP), scientific advisory groups and other committees at EMA, as well as by the Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh).

Communications are issued by the European Commission to explain Community law or programmes of actions to governments and economic partners.

Notices are not, strictly, legislation, neither are they enforceable in law; however, they often take the form of guidelines intended to help relevant bodies or applicants meet the terms of a specific directive.

Move Toward Harmonisation

In the EU, medicinal products are covered by the internal market principle of the free movement of goods. This chapter provides an overview of authorisation procedures that apply to medicinal products in the EU.

Throughout much of the 20th century, individual Member States enacted national legislation that regulated medicinal products for human use. With the adoption of Council Directive 65/65/EEC of 26 January 1965, which stipulated that a medicinal product may only be placed on the market in the EU after a Marketing Authorisation (MA) has been granted, the first major step was taken toward harmonising medicinal product authorisation procedures.

A final comprehensive document—the Notice to Applicants (NTA)—was issued by the European Commission in 1986 as part of The Rules Governing Medicinal Products in the European Union. The NTA is presented in three parts: Volume 2A deals with procedures for MAs; Volume 2B covers application dossier presentation and content; and Volume 2C contains regulatory guidelines. The NTA has been revised several times and represents the current harmonised view of Member States, EMA and the European Commission. It is not legally binding, however, and reference should always
be made to the appropriate Community directives and regulations.

In 1995, a new system for authorising medicinal products entered into force. It was based on two separate Community procedures for granting an MA for a medicinal product: the Centralised Procedure was administered through EMA, and Member State Competent Authorities were responsible for the Mutual Recognition Procedure.

In addition, a purely national authorisation was possible for a product that was marketed in only one Member State.

The new pharmaceutical regulations (Directive 2004/27/EC) that came into force in 2005 provided another option to authorise medicinal products within the EU: the Decentralised Procedure. The other procedures (Centralised Procedure and Mutual Recognition Procedure) were maintained, but important changes to them were introduced.

The European MA System for Medicinal Products

Definition of MA

A medicinal product may be placed on the EU market only when an MA (which initially lasts five years and is usually subject to one renewal) has been issued by the regulatory authority of a Member State for its own territory (so-called national authorisation, which can be a purely national authorisation, or can be granted following a Mutual Recognition Procedure or a Decentralised Procedure) or when an authorisation is granted for the entire Community (so-called Community authorisation, following the Centralised Procedure).

The Marketing Authorisation Holder (MAH) must be established in the European Economic Area (EEA), which comprises the 27 Member States plus Norway, Iceland and Liechtenstein.

The MA is granted to a single MAH and includes, when available, the International Nonproprietary Name (INN) of the active substance(s) and, when branded, a single invented name (i.e., the trade name). Companies that wish to market the same medicinal product with a second trade name must submit a separate Marketing Authorisation Application (MAA). The MAH, which may be a natural person or legal entity established in the EEA, is responsible for marketing the medicinal product. The MAH is bound by several obligations and responsibilities, including:

- taking into account any technical and scientific progress to update manufacturing and control operations
- when the MAH is not the manufacturer, signing a written agreement with the manufacturer to guarantee that manufacturing operations comply with dossier rules and conditions (Annex 5.11 to the application form)
- informing authorities of any information brought to the attention of the MAH that could lead to modification of the MA dossier or Summary of Product Characteristics (SmPC) and Product Information Leaflet (PIL)
- submitting the MA renewal application at least six months before the expiration date; usually an MA needs to be renewed only once, five years after the first MA is granted (the consequence of failure to submit the renewal application is a cancellation of the MA)
- paying the relevant fees (MAs, renewals, variations, yearly fees, etc.)
- having a Qualified Person (QP) in charge of pharmacovigilance and a scientific service in charge of each medicinal product's scientific information
- being responsible for medicinal product advertising
- retaining and archiving all medicinal product documentation and, in particular, any documents related to clinical trials
- submitting samples of the product, active pharmaceutical ingredient (API) and the reference product (for generic applications) upon request by the Competent Authority
- for immunological medicinal products and medicinal products derived from human blood or human plasma, submitting samples from each batch of the bulk and/or finished product for examination by a state laboratory or a laboratory designated for that purpose

Since the new legislation came into force in November 2005, the MAH additionally is required to:

- inform the authority that has granted the MA of any new data that may affect the risk:benefit balance of the medicinal product
- inform the authorities of the date of placing the product on the market, volume of sales (in each Member State), medicinal product presentations and cessation of marketing

Additionally, authorisations not used in the territory for a period of three consecutive years become invalid (the sunset clause).

Format for MAAs in the EU

MAAs comprise administrative information and documentation necessary to demonstrate the medicinal product's quality, safety and efficacy.

The Common Technical Document (CTD) went into force in July 2003 in all three regions (Europe, the US and Japan) covered by the International Conference on Harmonisation (ICH). The CTD is an internationally
agreed-upon format for preparing a well-structured presentation for applications to be submitted to regulatory authorities in the three ICH regions. It is organised into five modules. The content of Module 1 was defined by the European Commission in consultation with Member State Competent Authorities, EMA and interested parties. Module 1, which consists of administrative data, is not considered a part of the CTD. Modules 2, 3, 4 and 5 are common for all regions.

- Module 1 should provide administrative, regional or national information (e.g., the application form with 22 annexes, proposed summary of product characteristics, labelling and PIL, pharmacovigilance system description, risk management plan).
- Module 2 contains high-level summaries and overviews (the overall quality summary, nonclinical overview and summary and clinical overview and summary) that must be prepared by suitably qualified and experienced persons (i.e., experts). The experts must sign and add brief information on their educational background and specific expertise in a special section in Module 1.
- Module 3 provides chemical, pharmaceutical and biological documentation.
- Module 4 consists of the nonclinical study reports.
- Module 5 consists of the clinical study reports.

The applicant’s (open) part of the Active Substance Master File (ASMF) should be included in Section 3.2.S of the quality documentation presented in the CTD format. It is the applicant’s responsibility to ensure that the complete ASMF, consisting of the open part and the active substance manufacturer’s restricted (closed) part, is supplied to the authorities in CTD format. The ASMF closed part should be supplied directly by the active substance manufacturer, synchronised to arrive at the same time as the MAA (submitted by the applicant). An original, signed Letter of Access (LoA) addressed to the regulatory authority where the application is made must be attached to the ASMF restricted part, and a copy of the LoA must be included in Annex 5.10 of the application form in Module 1. The restricted part of the ASMF should follow the structure of CTD Module 3.2.S. A separate quality summary (2.3.S) for the information included in the restricted part should also be provided as part of the ASMF.

Acronyms and abbreviations should be defined the first time they are used in each module. When preparing product information for Centralised Procedure, Decentralised Procedure and Mutual Recognition Procedure applications (Module 1.3.1), use of the Quality Review of Documents (QRD) convention is mandatory. The QRD working group’s mission is to ensure clarity, consistency and accuracy of medicinal product information and its translations. The group has developed product information templates to provide practical advice on how to present product information.

For the National Procedure, Decentralised Procedure and Mutual Recognition Procedure, additional data might be requested, including the following:
- statement of MA transfer signed by both parties (Bulgaria, Greece, Hungary, Portugal, Spain)
- statement on having a QP responsible for pharmacovigilance activities in the national territory where the application is made (Portugal, Romania, Spain)
- packaging size declaration and samples declaration (Hungary, Poland)
- contractual technical agreement between MAH and manufacturer(s) (Spain)

Additional data required by different Member States are specified in Chapter 7 of NTA Volume 2A, but it is best practice to check the Competent Authority website or contact the Competent Authority via email a few months or weeks prior to submission of the MAA.

This international format applies to all medicinal product categories (including new chemical entities (NCEs), radiopharmaceuticals, vaccines and herbals) and all application types (standalone and abridged), although some adaptations may be necessary for specific application or product types. It is not designed to indicate what studies are required for successful approval, but rather to indicate appropriate information organisation for the application.

Throughout the CTD, information should be unambiguous and transparent to facilitate review of the basic data and to help reviewers become quickly oriented to the MAA contents. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently wide that information is not obscured by binding. Font sizes and styles for text and tables should be large enough to be easily legible, even after photocopying. Times New Roman 12-point font is recommended for narrative text.

**eCTD Format and Acceptability**

The electronic Common Technical Document (eCTD) is now the standard for submitting MAAs in the Community and most EU Member States. It is the mandatory format for centrally authorised products at EMA. Since January 2010, all National Competent Authorities are obliged to accept the eCTD and/or the Non eCTD electronic format (NeeS). However, acceptability of e-submissions in each Member State is sometimes difficult to determine. Often, there are some local requirements on submitting applications in eCTD format (e.g., in France, Spain, Germany, the UK and the Netherlands). It is highly advisable to check national agencies’ guidance documents and websites before submission. Additionally, it is good practice to check the list.
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The eCTD allows the applicant to submit the CTD in electronic format to the authorities and control the application’s lifecycle both during the procedure and once the MA has been granted (variations, renewals).

The registration documents in the electronic submission are organised according to version 3.2 of the ICH eCTD specification and the current version of the EU Module 1 specifications. In other words, an eCTD is the submission of (mostly) PDF documents, stored in the eCTD directory structure, accessed through an Internet browser (via index.xml).

Details on the requirements for eCTD submissions can be found in Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic submissions. This document assumes a basic understanding of eCTD applications and reflects the current situation with e-submissions. It is regularly updated to reflect changes in national and European legislation and experience gained during the ongoing applications handled in European procedures described below: Centralised Procedure,

of Member State contact points for e-submissions published on the EMA website.

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Decentralised Procedure, Mutual Recognition Procedure and National Procedure.

Community Authorisations

Centralised Procedure

Use of the Centralised Procedure is confined to certain categories of medicinal products as described in the annex to Regulation (EC) No 726/2004. EMA is responsible for evaluating MAAs for medicinal products for human and veterinary use in the following categories:

- Those developed by means of the following biotechnological processes:
  - recombinant DNA technology
  - controlled expression of gene coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells
  - hybridoma and monoclonal antibody methods

  This category includes any medicinal product containing a proteinaceous constituent obtained by recombinant DNA technology.

- Orphan medicinal products developed pursuant to Regulation (EC) No 141/2000.

- Medicinal products for human use that contain a new active substance that, on the date of entry into force of Regulation (EC) No 726/2004, were not authorised by any Member State for the following therapeutic indications:
  - acquired immune deficiency syndrome (AIDS)
  - cancer
  - neurodegenerative disorder
  - diabetes
  - autoimmune diseases and other immune dysfunctions
  - viral diseases

- Veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers to promote the growth of treated animals or increase yields from treated animals

The definition of “new chemical, biological or radiopharmaceutical active substances” includes the following:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the EU
- an isomer, a mixture of isomers, a complex or a derivative or salt of a chemical substance previously authorised as a medicinal product in the EU but differing in safety and efficacy properties from that previously authorised chemical substance
- a biological substance previously authorised as a medicinal product in the EU but differing in molecular structure, nature of the source material or manufacturing process
- a radiopharmaceutical substance that is a radionuclide or a ligand not previously authorised as a medicinal product in the EU, or for which the coupling mechanism to link the molecule and radionuclide has not been previously authorised in the EU

A fixed combination of active substances can be considered a new active substance if it has not previously been authorised as a medicinal product in the EU.

An applicant can utilise the Centralised Procedure for other medicinal products if it can show that a product constitutes a significant therapeutic, scientific or technical innovation, or that granting authorisation via the Centralised Procedure is in the interests of patients or animal health at the Community level. This option also may be used for generic medicinal products where the reference product is authorised by the Community.

To maintain coherence and preserve the unity of the single Community market, when the same MAH wishes to place another medicinal product on the market with an active substance that is already the subject of a Community authorisation, the Centralised Procedure should be used, particularly when the new medicinal product’s therapeutic indication is within the third level of the Anatomic, Therapeutic, Chemical Classification (ATC) code. However, a generic medicinal product of a reference medicinal product authorised by the Community also may be authorised by the Member States’ Competent Authorities in accordance with Directive 2001/83/EC, as amended, under certain conditions. In this case, applicants have a choice between the Centralised Procedure and Decentralised Procedure. This is discussed in more detail in Chapter 21 Generic Medicinal Products.

Applicants are strongly advised to notify EMA of their intended MAA submission date by sending the presubmission request form (Intent to submit MA) to the email address specified on EMA’s website. Submission dates must be realistic and accurate so the agency will have sufficient time to appoint the rapporteur and co-rapporteur and their assessment teams for submission evaluation. The deadline for sending the letter of intention to submit the MAA is seven months prior to the intended submission date. Rapporteurs and, if required, co-rapporteurs are appointed from among members and alternate members of CHMP. For Advanced Therapy Medicinal Products (ATMPs), rapporteurs are appointed from among members and alternate members of the Committee for Advanced Therapies (CAT). The rapporteur and co-rapporteur are supported by a team of assessors/experts (assessment team) during the various phases of the application’s evaluation. Normally,
postauthorisation activities are also assessed by the same group of people.

In cases where the applicant is not certain about some issues regarding the medicinal product that is the subject of the application or if there are some concerns about the product’s development, it may seek advice from EMA. Such
Scientific Advice and Protocol Assistance may be requested either during a medicinal product’s initial development (i.e., before submission of an MAA) or later, during the postauthorisation phase. Scientific Advice is subject to a fee, which varies depending on the scope of the advice; however, some fee reductions and/or waivers are available (e.g., orphan designation or paediatric use).

Since October 2009, EMA accepts only electronic requests for Scientific Advice and Protocol Assistance, including follow-up requests. Applicants should submit their applications only on a CD or DVD.

For more administrative issues and questions, the applicant may request a Presubmission Meeting. The Presubmission Meeting is strongly recommended, even for companies with experience with the Centralised Procedure and when the application is apparently straightforward. Such a meeting can significantly facilitate submission and validation of the MAA. To arrange such a meeting with EMA, the applicant must submit a Presubmission Meeting Request Form (available on EMA’s website). The form requires administrative details about the applicant, the contact person and medicinal product information: trade name, active substance(s), INN, proposed ATC code, pharmaceutical forms, strength(s), packaging and pack sizes, proposed indications and posology. Proposed dates for the meeting, the proposed date for submitting the application, a draft summary of product information (SmPC, PIL, labelling) and other relevant draft documentation must also be provided. In addition, the applicant must describe areas it wishes to discuss at the meeting (for example, if the proposed trade name is acceptable, when exactly the rapporteur(s) will be appointed, whether the product is eligible for accelerated assessment, whether the samples have to be submitted together with the application, what fees have to be paid, how to handle multiple applications, whether a risk management system is required, etc.). Following the meeting, the applicant must prepare minutes and send them to EMA for comments within two weeks.

Applications under the Centralised Procedure are made directly to EMA by a person based in the Community and authorised by the applicant and accompanied by a fee payable under Regulation (EC) No 297/95, with further amendments. A conventional, approved form of the dossier (all the documents that comprise the MAA) is described in detail in NTA Volume 2B. As noted previously, the mandatory format for the Centralised Procedure is the eCTD.

The application must include proof of establishment in the EEA as well as the following:

- a document identifying the QP responsible in the EEA for pharmacovigilance activities
- a document describing the scientific service in the EEA in charge of information about the medicinal product
- a document identifying the QP in the EEA responsible for batch release and the contact person for product defects and product recalls
- a document describing, in detail, the pharmacovigilance system and, where appropriate, the risk management system, as required in Article 8(ia) of Directive 2001/83/EC, as amended

Once the application is validated (administratively and technically) with a positive outcome, the applicant is informed in writing that the validation has been successfully completed and is given the names of CHMP members to whom full or partial copies of the dossier should be sent for review. Negative outcome of the validation is also provided in written format to the applicant and may result from failure to provide the data, information or clarifications requested or to adhere to the EU CTD format.

Once positively validated, and provided the rapporteur and co-rapporteur have confirmed that they have received the dossier (including any additional information requested during the validation phase), EMA starts the procedure at the monthly starting date published on its website. There is a set timetable for processing of centralised applications, and this stipulates that CHMP must deliver its opinion in not more than 210 days. The standard timetable for MAA evaluation is presented in Table 17-1.

For medicinal products that are of major public health interest, particularly from a therapeutic innovation point of view, the applicant may request the accelerated assessment procedure in accordance with Article 14(9) of Regulation (EC) No 726/2004. If the request is accepted by CHMP, the abovementioned standard timetable will be reduced to 150 days.

There are three main possible outcomes to the MAA:

- a negative/unfavourable CHMP opinion
- a conditional opinion (Conditional MA or MA under Exceptional Circumstances)
- a positive opinion

An unfavourable opinion is given when CHMP does not consider the MAA to fulfil the authorisation criteria set out in Regulation (EC) No 726/2004.

A Conditional MA is granted in accordance with Article 14(7) of Regulation (EC) No 726/2004. Under this regulation, CHMP may adopt an opinion recommending that an MA be granted subject to certain specific conditions and obligations that are to be reviewed annually. The list of these obligations shall be made publicly accessible. Such authorisation shall be valid for one year, on a renewable basis.

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In accordance with Article 14(8) of Regulation (EC) No 726/2004, in exceptional circumstances and following consultation with the applicant, an authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, particularly concerning the product's safety. Such authorisation must be based on one of the grounds set out in Part II.6 of Annex I to Directive 2001/83/EC. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.

Following positive scientific evaluation by CHMP, the European Commission drafts a decision on a Community MA. An MA granted under the Centralised Procedure is valid for the entire EU market; the medicinal product may be put on the market in all Member States. The European Free Trade Association (EFTA) states—Iceland, Liechtenstein and Norway—have, through the EEA agreement, adopted a complete Community acquis (EU laws and objectives) on medicinal products and are consequently parties to the Centralised Procedure, although they still issue national MAs following successful completion of the procedure.

With the positive CHMP opinion, and in accordance with Article 13 of Regulation (EC) No 726/2004, EMA shall publish the CHMP assessment report on the medicinal product, which includes the reasons for its opinion in favour of granting authorisation, after deleting any information of a commercially confidential nature. This document is called the European Public Assessment Report (EPAR). If the opinion is negative, a summary of opinion relating to the negative opinion is published at Day 0 (i.e., the day of adoption of the negative opinion). If a company withdraws the application, this fact also will be published.

Once the MA is granted, it can be subject to:
- Specific obligations (when the Conditional MA or MA under Exceptional Circumstances is granted)—In this case, the applicant is obliged to submit additional data (postauthorisation data) known as “specific obligations” set out in Annex IIC of the Commission Decision.
- Follow-up measures (FUMs)—whether or not for conditional approval or under exceptional circumstances—FUMs can be requested at the initial CHMP opinion or in addition to the CHMP assessment of any submitted additional data/applications.
- Variations (all MAs)—Variations may be required as a result of FUM or specific obligations when these data would require changes to the product information or to the MA (e.g., changes to the Quality Module).

The MAH must indicate realistic target dates for the submission of postauthorisation data in its Letter of Undertaking. If no documents are submitted or in case of non-fulfilment of the obligations, in accordance with Article 14(7) and 14(8) of Regulation (EC) No 726/2004, CHMP will formulate an opinion recommending the “variation/suspension/revocation” of the MA.

The European Commission MA issued under the Centralised Procedure is valid throughout the Community under the same trademark name in all Member States. Medicinal products that have been authorised through the Centralised Procedure shall benefit from the 10-year period of protection referred to in Article 10(1) of Directive 2001/83/EC, as amended. According to this article, this protection can be extended to a maximum of 11 years if, during the first eight years, the MAH obtains an authorisation for one or more new therapeutic indications that, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

In accordance with Article 13(4), the MAH shall inform EMA of the dates of the actual marketing of the product in all Member States, taking into account the various presentations authorised. Any authorisation that is not followed by actual marketing in the Community within three years after authorisation shall cease to be valid. Similarly, when a product previously marketed in the Community is no longer actually present on the market for three consecutive years, the authorisation shall cease to be valid. However, the European Commission, in exceptional circumstances, may grant exemptions from these provisions on duly justified public health grounds.

**Mutual Recognition Procedure**

The principle of mutual recognition is that an MA in one Member State (Reference Member State (RMS)) must be recognised by the regulatory authorities of other Member States (Concerned Member States (CMS)), unless there are grounds for supposing that the product may present a risk to the public health. The Mutual Recognition Procedure may be triggered by an applicant or a Member State. Under the new legislation, the Mutual Recognition Procedure can be used only when there is already an MA in at least one Member State. If there is no MA in any EU Member State, the Decentralised Procedure should be used (or the Centralised Procedure, if its requirements are met).

The Mutual Recognition Procedure must be used for the following products:
- medicinal products containing new active substances outside the centralised therapeutic areas
- OTC (over-the-counter) products
- homeopathic medicinal products
- generic products (also generic versions of products authorised by the Centralised Procedure before November 2005, with the exception of biotechnology-derived ones)
- “abridged” applications, “well-established use,” line extensions of “old Mutual Recognition Procedure”
As mentioned above, the Mutual Recognition Procedure can be used for standalone and abridged applications, provided the application is legally valid and meets the requirements of Article 28(2) of Directive 2001/83/EC, as amended. Once the procedure has been used, all variations, changes and line extensions (including changes falling under the scope of Annex I and II of Commission Regulation (EC) No 1234/2008) to these medicinal products must use the Mutual Recognition Procedure. The procedure is also applicable for line extensions of existing national MAs under certain conditions mentioned in Commission Communication 98/C229/03, which describes a case in which an applicant initially was granted two different national authorisations in different Member States for the same medicinal product. If, afterward, the same applicant wishes—to obtain harmonised national authorisations in different Member States, it would not be possible to exclude such a case from the scope of application of the Mutual Recognition Procedure.

For medicinal products with a well-established use demonstrated in accordance with Article 10(a) of Directive 2001/83/EC (bibliographic application), as amended, the Mutual Recognition Procedure is applicable. When the well-established use is based on data referring to an existing group of products for which no Community authorisation exists, the applicant still has the option to follow independent National Procedures as stated in Commission Communication 98/C229/03.

To fulfil the dossier criterion of identical product prior to a Mutual Recognition Procedure, the applicant must harmonise the already approved national SmPCs. This a priori harmonisation can be achieved through coordinated national variation procedures or through the procedure foreseen in Article 30 of Directive 2001/83/EC, as amended.

The Mutual Recognition Procedure is regarded as a two-stage process: first a national approval and then the mutual recognition process. If this second stage fails (due to refusal of one or more Member States to recognise the first approval), there may be a third stage—arbitration (see Community Referral below). If the Member States disagree about the product’s quality, safety and efficacy, a scientific evaluation of that matter is carried out by CHMP, leading to a single decision that is binding on all Member States. However, faced with this option, the applicant may decide to withdraw the application, at least in the “problem” countries. The arbitration process is lengthy and unpopular with pharmaceutical companies.

As mentioned above, the first phase of the Mutual Recognition Procedure is in many respects similar to the National Procedure, where the RMS authorises the medicinal product. Those National Procedures significantly differ across Member States and depend on the experience of the national Competent Authority in clinical, regulatory and marketing issues. Those factors have to be taken into account when selecting the RMS. In theory, the national process that results in an MA takes no longer than 210 days. The reality is that a number of factors can lead to substantial delays. The second phase of the procedure—the Mutual Recognition Procedure

### Table 17-2. Mutual Recognition Procedure Flowchart

<table>
<thead>
<tr>
<th>Approximately 90 days before submission to CMS</th>
<th>Applicant requests RMS to update Assessment Report (AR) and assign procedure number.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day -14</strong></td>
<td>Applicant submits the dossier to CMS; RMS circulates the AR including SmPC, PIL and labelling to CMSs. Validation of the application in the CMSs.</td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
<td>RMS starts the procedure.</td>
</tr>
<tr>
<td><strong>Day 50</strong></td>
<td>CMS send their comments to RMS and applicant.</td>
</tr>
<tr>
<td><strong>Day 60</strong></td>
<td>Applicant sends the response document to CMS and RMS.</td>
</tr>
<tr>
<td><strong>Until Day 68</strong></td>
<td>RMS circulates its assessment of the response document to CMS.</td>
</tr>
<tr>
<td><strong>Day 75</strong></td>
<td>CMS send their remaining comments to RMS and applicant. A break-out session can be organized between Days 73-80.</td>
</tr>
<tr>
<td><strong>Day 85</strong></td>
<td>CMS send any remaining comments to RMS and applicant.</td>
</tr>
<tr>
<td><strong>Day 90</strong></td>
<td>CMS notify RMS and applicant of final position (and, in case of negative position, also EMA’s CMD secretariat); if consensus is reached, RMS closes the procedure. If consensus is not reached, points of disagreement submitted by CMS are referred to CMDh by RMS within seven days after Day 90.</td>
</tr>
<tr>
<td><strong>Day 150</strong></td>
<td>For procedures referred to CMDh: if consensus is reached at the level of CMDh, RMS closes the procedure. If consensus is not reached at the level of CMDh, RMS refers the matter to CHMP for arbitration.</td>
</tr>
<tr>
<td><strong>5 days after close of procedure</strong></td>
<td>Applicant sends high-quality national translations of SmPC, PIL and labelling to CMS and RMS.</td>
</tr>
<tr>
<td><strong>30 days after close of procedure</strong></td>
<td>Granting of national MAs in the CMS, subject to submission of acceptable translations.</td>
</tr>
</tbody>
</table>

The repeat-use procedure(s) can be employed until all Member States are involved in the procedure. Before starting the procedure, the applicant should finalise all ongoing procedures (variations, renewals, updating SmPCs, etc.) and update the dossier. The next step is submission of the updated dossier to the RMS and to formally request an update of the AR. For more details see Procedural Advice on Repeat Use.³

In order to coordinate and facilitate Mutual Recognition Procedure operations, a Mutual Recognition Facilitation Group (MRFG) was established in 1995. The MRFG met monthly and comprised senior representatives from each Member State. Under the new legislation (Directive 2004/27/EC), the MRFG has been renamed the Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh). It is chaired by one of its members for a period of three years, who may be re-elected once. The vice chairperson shall be appointed from among the members of the coordination group by the Member State that has the presidency of the Council of the European Union for the duration of the term of the presidency. The secretariat for this group is provided by EMA. CMDh meets monthly at EMA, and can be joined by observers from the European Commission and EMA. When necessary, in connection with the plenary meeting, breakout sessions related to ongoing procedures may be held. Additional subgroup meetings are organised on specific topics.

The group provides a forum for discussing procedural issues arising from Mutual Recognition Procedures and Decentralised Procedures and resolving problems. It can undertake an overview of individual applications; however, scientific discussions related to individual applications are handled in breakout sessions organised and chaired by the specific RMS. CMDh considers points of disagreement raised by a Member State related to the AR, SmPC, labelling and PIL of a medicinal product on the grounds of “potential serious risk to public health” within Mutual Recognition Procedures and Decentralised Procedures, and facilitates the dialogue between Member States. On an annual basis, CMDh prepares a list of products that must be harmonised among all Member States. Furthermore, this group identifies issues to be referred to the European Commission, the Pharmaceutical Committee, the Heads of Medicines Agencies (HMA) or other regulatory bodies; works closely with the Pharmacovigilance Working Party (PhVWP) of CHMP to ensure best practice of risk management for medicinal products authorised via Mutual Recognition Procedures and Decentralised Procedures; and creates its own Rules of Procedure to be endorsed by the HMA and approved by the European Commission.

More information on the Mutual Recognition Procedure can be found in Directive 2001/83/EC, as amended, the NTA Volume 2A, Chapter 2 and the HMA/CMDh website.
Decentralised Procedure

As already mentioned, the Decentralised Procedure was established by Directive 2001/83/EC, as amended, and has been in force since November 2005. The newly created CMDh group has the same competencies for both the Mutual Recognition Procedure and Decentralised Procedure. In addition, in cases where serious public health issues are still raised by one or more of the participating Member States at the end of the procedure, and despite a withdrawal of the dossier in the CMS, automatic arbitration by EMA and the European Commission is applicable to both Mutual Recognition Procedures and Decentralised Procedures.

The Decentralised Procedure is used for medicinal products for which there is no existing MA in any EU Member State. In accordance with Article 17(2) of Directive 2001/83/EC, as amended, the MA for the same medicinal product cannot be granted in parallel in two or more Member States by separate National Procedures. In such cases, the Decentralised Procedure must be followed. The Decentralised Procedure covers all medicinal products not authorised in the EU (for which the Centralised Procedure is not mandatory). As in the Mutual Recognition Procedure, the applicant can select the RMS and list the CMS. In order to do so, the applicant has to request one Member State to act as the RMS for the particular product by filing the Common Request Form (the most current version of this document can be found on the HMA/CMDh website). Once the RMS has agreed, the date of intended submission is scheduled and a Decentralised Procedure number is assigned. Prior to the submission, the applicant may request a presubmission meeting to familiarise the national Competent Authority with the product and submission details. Usually the presubmission meeting is held three months before the intended submission date. The applicant is encouraged to discuss the necessity of conducting a presubmission meeting with the RMS. On the agreed date, the applicant submits the dossier simultaneously to RMS and CMS (Day -14) and the validation period begins. In theory, it is scheduled for 14 days, but, in practice, can last much longer (sometimes more than 30 days). The validation period depends on national requirements that have to be followed for each CMS and the applicant’s ability to meet those requirements on time. As soon as the dossier is submitted, the RMS initiates the procedure in the Communication and Tracking System (CTS) database, so the CMS and RMS are able to communicate on the procedure through the CTS record immediately after receipt of the dossier. CMS are obliged to update the CTS database daily to inform the RMS about the application’s validation status. The most common invalidation issues include:

- lack of original, signed documents (e.g., LoA for a person responsible for communication during and after the procedure (Annex 5.4), Manufacturer’s Commitment (Annex 5.11)
- improperly written statement on GMP compliance (Annex 5.22)
- lack of some nationally required documents (Application Form not translated into national language (Spain, Greece), technical agreements between the applicant and manufacturer(s), declaration on pack sizes and samples, etc.)
- mistakes in the application form
- wrong format of the submitted dossier (for example, if the dossier is not in the eCTD or NeeS format)
- technical issues related to the eCTD (wrong PDF files, improperly named folders, too many CDs, broken CDs/DVDs, etc.)
- lack of a paper version of administrative documents while submitting an eCTD in some Member States

The applicant has to respond to deficiencies on a daily basis in order to have the submission positively validated by the RMS and CMS. Once this goal is achieved, the procedure is started and Day 0 is assigned. The Decentralised Procedure consists of two steps. Assessment Step I corresponds to the Day 120 period in which the Draft Assessment Report (DAR) is prepared, followed by draft SmPC, labelling and PIL. During Assessment Step I, the Preliminary Assessment Report (PrAR) is prepared by the RMS and circulated to the applicant and CMS. By Day 100, CMS should communicate their comments to the RMS, other CMS and the applicant. Between Day 100 and 105, the RMS consults with the CMS on the comments submitted. If there are no potential serious risks to public health and consensus is reached, the RMS can update the PrAR and prepare the Final Assessment Report (FAR). The procedure is finalised on Day 105 and the national phase can be started.

If consensus is reached that the product is approvable but there are comments that can be easily resolved, the RMS stops the clock and forwards these comments to the applicant on Day 105. After receiving sufficient responses from the applicant, the RMS updates the PrAR, creates the FAR and finalises the procedure on Day 120, followed by national phases in each Member State.

If consensus is not reached, the RMS stops the clock at Day 105 and asks the applicant to answer all remaining issues within the specified timeframe. Usually, the clock stop is scheduled for three months, but its duration can be mutually agreed between the RMS and the applicant (it can be shortened or lengthened in justified cases). The applicant may submit draft responses, including updated SmPC, PIL and labelling proposals, to the RMS for preassessment. In any case, the applicant should reach agreement on the submission date of the final response with the RMS. After submission of the final response and receipt of the list of dispatch dates in all CMS, the RMS restarts the procedure at Day 106. Between Day 106 and 120, the RMS updates the PrAR to prepare the DAR and draft product
Table 17-3. Decentralised Procedure Flowchart

<table>
<thead>
<tr>
<th>Pre-procedural Step</th>
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<tbody>
<tr>
<td>Before Day -14</td>
<td>Applicant discussion with RMS. RMS allocated procedure number; creation in CTS.</td>
</tr>
<tr>
<td>Day -14</td>
<td>Submission of the dossier to RMS and CMS. Validation of the application.</td>
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<tr>
<th>Assessment Step I</th>
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<tbody>
<tr>
<td>Day 0</td>
<td>RMS starts the procedure.</td>
</tr>
<tr>
<td>Day 70</td>
<td>RMS forwards the Preliminary Assessment Report (PrAR), SmPC, PIL and labelling to CMS and applicant.</td>
</tr>
<tr>
<td>Until Day 100</td>
<td>CMS send their comments to RMS and applicant.</td>
</tr>
<tr>
<td>Until Day 105</td>
<td>Consultation between RMS, CMS and applicant. If consensus not reached, RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.</td>
</tr>
<tr>
<td>Clock Stop period</td>
<td>Applicant may send draft responses to RMS and agrees to final response submission date with RMS. Applicant sends the final response document to RMS and CMS within a recommended period of three months, which could be extended, if justified.</td>
</tr>
<tr>
<td>Day 106</td>
<td>Valid applicant response submission received. RMS restarts the procedure.</td>
</tr>
<tr>
<td>Day 106-120</td>
<td>RMS updates the PrAR to prepare Draft Assessment Report (DAR), draft SmPC, draft labelling and draft PIL to CMS and Applicant.</td>
</tr>
<tr>
<td>Day 120</td>
<td>RMS may close procedure if consensus is reached. Proceed to national 30-day step for granting MA.</td>
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<th>Assessment Step II</th>
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<tr>
<td>Day 120 (Day 0)</td>
<td>If consensus is not reached, RMS sends the DAR, draft SmPC, draft labelling and draft PIL to CMS and applicant.</td>
</tr>
<tr>
<td>Day 145 (Day 25)</td>
<td>CMS send final comments to RMS and applicant.</td>
</tr>
<tr>
<td>Day 150 (Day 30)</td>
<td>RMS may close procedure if consensus is reached. Proceed to national 30-day step for granting MA.</td>
</tr>
<tr>
<td>Until 180 (Day 60)</td>
<td>If consensus is not reached by Day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification and prepare a short report (Day 180 Report) for discussion at coordination group.</td>
</tr>
<tr>
<td>Until Day 205 (Day 85)</td>
<td>Breakout group of involved Member States reaches consensus on the matter (if applicable)</td>
</tr>
<tr>
<td>Day 210 (Day 90)</td>
<td>Closure of the procedure including CMS’ approval of Assessment Report, SmPC, labelling and PIL, or referral to coordination group. Proceed to national 30-day step for granting MA.</td>
</tr>
<tr>
<td>Day 210 (at the latest)</td>
<td>If consensus was not reached at Day 210, points of disagreement will be referred to the coordination group for resolution.</td>
</tr>
<tr>
<td>Day 270 (at the latest)</td>
<td>Final position adopted by coordination group with referral to CHMP for arbitration in case of unsolved disagreement.</td>
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<tr>
<th>National Step</th>
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<tbody>
<tr>
<td>Day 110/125/155/215/275</td>
<td>Applicant sends high-quality national translation of SmPC, labelling and PIL to CMS and RMS.</td>
</tr>
<tr>
<td>Day 135/150/180/240</td>
<td>Granting of national MA in RMS and CMS if no referral to the coordination group (national agencies will adopt the decision and issue the MA subject to submission of acceptable translations).</td>
</tr>
<tr>
<td>Day 300</td>
<td>Granting of national MA in RMS and CMS if positive conclusion by the coordination group and no referral to CHMP (national agencies will adopt the decision and issue the MA subject to submission of acceptable translations).</td>
</tr>
</tbody>
</table>

Source: Decentralised Procedure - Member States’ Standard Operating Procedure (MRFG, October 2005) & Best Practice Guide for Decentralised and Mutual Recognition (CMDh, Rev. 6 May 2007)

Information (SmPC, labelling, PIL). The DAR and draft informative texts are sent to the applicant and CMS. On Day 120, Assessment Step II is initiated and the RMS starts the 90-day period, corresponding to Day 0 of the 90-day period mentioned in 28(4) of Directive 2001/83/EC. Each CMS should send its final comments on the DAR no later than Day 145 of the procedure (i.e., Day 25 of the 90-day period). If consensus is reached, the RMS prepares the FAR and may close the procedure at Day 150 (i.e., Day 30 of the 90-day period). The procedure continues with the national step if the Member States consider the product approvable.

Between Day 145 and 150, the RMS consults with the CMS to discuss the comments submitted. If consensus is not reached by Day 150, the applicant is informed of outstanding issues by the RMS. The applicant must submit additional clarification by Day 160, including any revised proposal for the SmPC, PIL and labelling, and the RMS prepares a short report and forwards it to the CMS no later
than Day 180 (i.e., Day 60 of the 90-day period). This is called a Short Report or Day 180-Report and includes the RMS’ proposals for an update of the overview portion of the DAR to derive the FAR.

At the latest, at Day 205 (i.e., Day 85 of the 90-day period), a breakout session may be held at EMA with the involved Member States to reach consensus on major outstanding issues.

At Day 210 (i.e., Day 90 of the 90-day period), the RMS closes the procedure if consensus was reached with all Member States on the outstanding issues. The RMS includes information in the FAR about how major outstanding issues were resolved by discussions via written procedures and by discussion in the CMDh (if applicable). Together with the FAR, which includes the final product release and shelf-life specifications, the final informative texts are attached. If there are any conditions to be fulfilled or any FUMs recommended, they are specified in an End-of-Procedure letter, also attached to the FAR.

Once the procedure is finalised, the applicant must submit high-quality national translations of the SmPC, PIL and labelling to the RMS and CMS within five days.

For the Decentralised Procedure flowchart, see Table 17-3.

Applicants can multiply or duplicate their applications via either the Mutual Recognition Procedure or Decentralised Procedure but there is no definition of a “duplicate” in the pharmaceutical legislation. It can be done at the beginning of the procedure, during the procedure (i.e., Day 106 in the Decentralised Procedures) or after the procedure is finalised. The possibility of duplicating the application should be discussed and agreed with the RMS. In general, a duplicate application is defined by the reference to the first MA as follows:

- same dossier (copy of Modules 1, 2, 3, 4 and 5)
- same legal basis according to Directive 2001/83/EC, as amended
- different trade name
- same or different applicant/MAH

Applications for duplicates result in independent MAs that can be varied individually. However, MAHs are strongly encouraged to keep the SmPC, PIL and labelling of the duplicates harmonised whenever possible.4

**National Authorisations**

Each EU Member State’s Competent Authority is responsible for granting MAs for medicinal products placed on its market, except medicinal products authorised using Community procedures. Since January 1998, independent National Procedures have been strictly limited to the initial phase of mutual recognition and to medicinal products that are not to be authorised in more than one Member State. Under the new legislation, independent National Procedures are restricted to medicinal products that will be authorised in only one Member State.

Independent National Procedures can continue to be followed for medicinal products with a well-established use demonstrated in accordance with Article 10(a) Directive 2001/83/EC, as amended, and based on data referring to an existing group of products with different SmPCs in the Member States, as long as no Community harmonisation exists on the use of said product’s constituent(s). They also can be used for line extensions of authorised medicinal products as long as no a priori harmonisation has been achieved.

**Different Types of Applications and Legal Basis for the Submission**

**Complete/Full and Independent Applications**

In accordance with Article 8(3) of Directive 2001/83/EC, as amended, a full (standalone) MAA must include:

- physicochemical, biological or microbiological tests
- pharmacological and toxicological tests
- clinical trials

This type of application is compulsory for new chemical entities (new active substances), which are listed at the beginning of this chapter.

**Generic Applications for Essentially Similar Medicinal Products (Abridged Applications)**

Under Article 10(1) and Part II(2) of Directive 2001/83/EC, as amended, the applicant is not required to provide pharmacological and toxicological test or clinical trial results when the medicinal product is essentially similar to a product that has been authorised in the EU under the previous legislation for not less than six or 10 years (depending on the Member State) and is marketed in that Member State at the time of the application (generic application). The new legislation harmonises the timeframes to an eight-year data protection period (submission) and a 10-year period of marketing protection (approval). This period can be extended to 11 years if, during the first eight, the MAH obtains an authorisation for one or more new therapeutic indications that bring a significant clinical benefit in comparison with existing therapies. The new periods of protection (8–2–1) do not apply to reference medicinal products for which the initial application for authorisation (date of submission of the application, not validation) was submitted before 20 November 2005.5

For those products, the exclusivity period under the previous legislation applies:

- 10 years for all medicinal products authorised through the Centralised Procedure
- 10 years for all other medicinal products originally authorised in Belgium, Germany, France, Italy, the Netherlands, Sweden, the UK and Luxembourg
• 10 years for all medicinal products authorised following a CHMP opinion in accordance with Article 4 of Directive 87/22/EEC (ex-concertation procedure)
• six years in all other Member States, plus Norway and Iceland

A generic authorisation may be issued for all therapeutic indications and all pharmaceutical forms, strengths and posology already authorised for the reference drug. A generic authorisation may be extended to cover more or other indications, strengths and pharmaceutical forms than the original product if the applicant submits sufficient bridging data.

The European Court of Justice, in its judgment in Case C-368/96 (Medicinal products—MA—Abridged procedures—Essentially similar products), confirmed that if the four conditions listed above are fulfilled, a generic authorisation may be issued for all therapeutic indications, dosage forms, doses and dosage schedules already authorised for the reference drug, even if some of those indications, dosage forms and doses were authorised for a period shorter than six or 10 years (old legislation).

The concept of essential similarity implies the following criteria:

• the same qualitative and quantitative composition of active substances
• the same pharmaceutical form (all oral pharmaceutical forms for immediate release must be regarded as the same pharmaceutical form)
• well- and appropriately demonstrated bioequivalence

In accordance with Article 10.2(b) of Directive 2001/83/EC, as amended, different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms (i.e., tablets and capsules) shall be considered to be one and the same pharmaceutical form for the concept of essential similarity.

For biotechnology products, the concept of essential similarity is difficult to apply.

Generic and informed consent applications (please see below) are linked to the original authorisation granted on the basis of a complete dossier (abridged applications may not refer to an abridged dossier). The original product dossier must be at the disposal of the regulatory authorities. Generic applications are described in detail in Chapter 21 Generic Medicinal Products.

Hybrid Applications

In accordance with Article 10(3) of Directive 2001/83/EC, as amended, these types of applications may require inclusion in the dossier of the results of the appropriate preclinical tests and/or clinical trials, in cases where:

• the medicinal product does not fall within the definition of a generic medicinal product
• bioequivalence cannot be demonstrated through bioavailability studies
• there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration vis-à-vis the reference medicinal product

Bibliographic Applications (Well-established Use)

According to Article 10(a) of Directive 2001/83/EC, as amended, and Annex I, Part II(1), it is possible to replace pharmacological and toxicological tests or clinical trial results with detailed references to published scientific literature if a medicinal product’s constituent(s) has a well-established medicinal use, recognised efficacy and an acceptable safety level. The definition of a Bibliographic Application includes specific criteria associated with the time period over which the use has been established, quantitative aspects of use and scientific interest in the substance’s medicinal use. Therefore, different time periods may be necessary to verify well-established use of different substances. In any case, the time period required to establish a well-established use of a medicinal product constituent must not be less than one decade from that substance’s first systematic and documented use as a medicinal product in the EU. This applies to any medicinal product or chemical or biological substance for which there is no original/reference medicinal product to which essential similarity can be claimed. This is the case, for instance, for “old” medicinal products whose use is well-established in the medicinal practice, and for known indications, strengths and pharmaceutical forms, in view of the period of time over which they have been used and the information that has been publicly available about their safety and efficacy.

“Well-established use” refers to a specific therapeutic use. If well-known substances are used for entirely new therapeutic indications for which the Annex I requirements to Directive 2003/63/EC cannot be fulfilled, it is not possible to solely refer to a well-established use. Additional data on the new therapeutic indication should be provided together with appropriate safety data.

It must be stressed that such assessment reports as the EPAR for Community MAs, made publicly available by Competent Authorities for reasons of transparency, do not supply sufficient information to meet Directive 2001/83/EC Annex requirements.
Chapter 17

Fixed-combination Application

In accordance with Article 10(b) of Directive 2001/83/EC, as amended, and Annex I, Part II(5), fixed-combination applications are possible for medicinal products containing active substances used in the composition of authorised medicinal products (but not to be used in combination for therapeutic purposes). In that case, 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 is not necessary to provide scientific references relating to each individual active substance.

Moreover, any fixed combination may be considered a complete/full, independent application because it is a new and unique medicinal product requiring a separate SmPC.

Informed Consent Applications

Under Article 10(c) of Directive 2001/83/EC, as amended, these applications are appropriate in cases when the medicinal product is essentially similar to a product already authorised in the Member State and the original product’s MAH gave the second applicant rights to refer to its approved dossier.

For regulatory authorities, demonstration of informed consent is a formal prerequisite when the application is submitted. Withdrawing the informed consent at a later stage, however, has no direct consequences for the MA’s existence or validity.

Mixed Marketing Applications

Annex I, Part II(7) of Directive 2001/83/EC, as amended, specifies that mixed MAAs must present published scientific literature together with original results of tests and trials. Such applications must be submitted and processed following the complete, full and independent MA dossier requirements. These requirements apply to the use of bibliographic references in mixed dossiers both as supporting data for the applicant’s own tests and trials or in order to replace any tests or trials in Module 4 and/or 5. All other module(s) are in accordance with the structure described in Part I of the above-mentioned Annex 1.

The Competent Authority will accept the applicant’s proposed format on a case-by-case basis.

Herbal Medicinal Products

Regulation (EC) No 726/2004 established the Committee on Herbal Medicinal Products (HMPC). In addition, Directive 2004/24/EC was introduced as part of the new legislation amending Directive 2001/83/EC on the Community code relating to medicinal products for human use with regard to traditional herbal medicinal products. It created a simplified registration procedure (“traditional-use registration”) for herbal medicinal products that fulfil certain criteria.6

Referrals

European Community Referrals

EU pharmaceutical legislation has created a binding Community arbitration mechanism to achieve cooperation between Member States as needed. The EU legislation, however, recognises the need for urgent, unilateral measures by Member States when necessary to protect the public health and until a definitive action is adopted. In these specific cases, Member States may take temporary national measures suspending a medicinal product’s marketing and use. They must inform the European Commission, EMA and other Member States no later than the next working day.

The decision following a referral is applicable only to the specific medicinal products that have been the subject of the referral procedure and to the Member States involved in the procedure.

Mutual Recognition and Decentralised Procedure Referral

Under Articles 29, 32 and 33 of Directive 2001/83/EC, as amended, referral to CMDh may be initiated by the RMS or CMS in the course of a Mutual Recognition Procedure or Decentralised Procedure if a medicinal product’s MA presents a potential serious public health risk.

Within the coordination group, all Member States concerned give the applicant an opportunity to present its point of view orally or in writing. If the Member States have not reached agreement within 60 days, CHMP undertakes a scientific evaluation of the matter and issues an opinion, normally within 60 days of receiving the referral. From this opinion, the European Commission drafts a single decision binding the Member States and applicant.

Divergent Decision Referral

This referral may be started by any Member State, the European Commission or the applicant (or MAH), according to Article 30 of Directive 2001/83/EC, as amended, when divergent decisions have been made by Member States related to a particular medicinal product (e.g., suspension or withdrawal of an MA or divergence of the therapeutic indications of an authorised product).

CHMP is called upon to issue an opinion on the area(s) of divergence within 60 days of the procedure’s start date. This period can be extended by up to 90 days.

The resulting European Commission decision must be implemented in all Member States concerned (i.e., those in which the particular medicinal product’s MA has been granted, refused, suspended or withdrawn).
Community Interest Referral

According to Article 31 of Directive 2001/83/EC, as amended, this referral may be started by Member States, the European Commission or the applicant (or MAH) when Community interests are involved. This latter expression refers particularly to Community public health interests related to a marketed medicinal product for which new quality, safety and efficacy data or new pharmacovigilance information have become available.

CHMP issues a reasoned opinion within 60 days of the referral date. This period may be extended by a further 90 days. A binding decision of the European Commission follows.

Follow-up Referral

This referral may be started by an MAH or Member State, under Articles 35, 26 and 27 of Directive 2001/83/EC, as amended, where an MA has already undergone a Community procedure. A follow-up referral is initiated when a change or variation, suspension or withdrawal of a harmonised MA is necessary to protect the public health, or when mutual recognition by one or more national regulatory authorities of the RMS draft decision on a variation is not possible. This mechanism aims to resolve divergences among Member States after harmonisation is achieved.

CHMP issues a reasoned opinion within 60 days of the referral date. This period may be extended by another 90 days. A binding decision of the European Commission follows.

Summary

- EU laws and policies are established by several types of legislative instruments. Although not all are legally binding, the instruments without binding legal effect in many cases are strongly recommended either by EMA or Member States’ Competent Authorities.
- MAAs in the EU can be granted following the Centralised, Decentralised or Mutual Recognition Procedures, or can be a purely national authorisations; authorisations not used in the territory for a period of three consecutive years become invalid (sunset clause).
- The accepted format for MAAs is the Common Technical Document, organised into five modules; Module 1 is not a part of the CTD and consists of administrative application data (including specific national requirements for the CMS).
- The eCTD is a standard for submitting MAAs in the Community and most of the EU Member States. It is the mandatory format for centrally authorised products at EMA.
- The Centralised Procedure can be utilised for orphan and veterinary products, for medicinal products developed by biotechnological processes and for new active substances for specified therapeutic indications.
- Once an MA is granted, it can be subject to: specific obligations (Conditional MA or MA under Exceptional Circumstances), follow-up measures (FUMs) and variations.
- Applicants/MAHs can submit multiple and/or duplicate applications via the Mutual Recognition Procedure or Decentralised Procedure; the possibility to duplicate the application should be discussed and agreed with RMS.
- Several types of applications (standalone or abridged) are specified in Directive 2001/83/EC, with further amendments.
  - For difficult and specific cases, European pharmaceutical legislation has created a binding Community arbitration mechanism to manage cooperation between Member States and/or the applicant/MAH.

References
