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NOTICE TO APPLICANTS

VOLUME 2A Procedures for marketing authorisation CHAPTER 2 Mutual Recognition

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**This Chapter 2 Mutual Recognition will be included in The Rules governing
Medicinal Products in the European Community
The Notice to Applicants Volume 2A Procedures for marketing authorisation**

CHAPTER 2 Mutual recognition procedure and decentralised procedure

February 2007

1. LEGAL BASIS AND PURPOSE

The legal provisions covering the mutual recognition procedure and the decentralised procedure for human medicinal products are contained in Directive 2001/83/EC.

Both the mutual recognition procedure and the decentralised procedure aim at facilitating access to a single market by relying upon the principle of mutual recognition. Thus with the exception of those medicinal products which are subject to the centralised procedure (see Chapter 4 of the Notice to Applicants), a marketing authorisation or the assessment in one Member State (the so-called reference Member State) ought in principle to be recognised by the competent authorities of the other Member States (the so-called concerned Member States), unless there are grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health.

If a concerned Member State is requested to recognise a marketing authorisation granted or an application assessed by the reference Member State it can raise grounds that the medicinal product presents a potential serious risk to public health. Such grounds would have to be fully **justified** in order to ensure that they do not act as an indirect and artificial hindrance to the free movement of goods within the European Economic Area.

2. SCOPE

2.1 Applications eligible for the mutual recognition procedure and decentralised procedure

The mutual recognition procedure and decentralised procedure must be used for applications for marketing authorisation for medicinal products in more than one Member State¹. The requirements of submitting an application are described in section 3 and 4. Once the procedure has been used, all **variations** to these medicinal products must use the procedure foreseen in the Variations Regulation². In addition, variations to “ex-concertation” medicinal products authorised by Member States following an opinion of the Committee for Human Medicinal Products (CHMP) given before 1st January 1995 are required to use the mutual recognition procedure. These applications are converted to the mutual recognition procedure (see Commission Communication of 19.3.94, OJ C82 Vol. 37). Furthermore, variations of medicinal

¹ See Chapter 1 section 3.1 scope of the centralised procedure

² See Articles 4(1), 5(1) and 6(1) of Regulation (EC) No 1084/2003.

products that have been subject to referral procedures under Articles 30 and 31 of Directive 2001/83/EC made *after* 1st January 1995 are required to use the mutual recognition procedure. However, an exception is provided under Article 31(2) of Directive 2001/83/EC: when the referral procedure concerns a range of medicinal products or a therapeutic class and the EMEA may limit the procedure to certain parts of the authorisation (see Chapter 1 of the Notice to Applicants).

The mutual recognition procedure or the decentralised procedure is also applicable for **extensions**³ of existing national marketing authorisations ((cf. Chapter 1 of the Notice to Applicants). Before the applicant can use the mutual recognition or decentralised procedure, he has to ensure that the submitted dossiers are identical. This requires to harmonise the already approved national summary of product characteristics, package leaflet and labelling by using either national variations, a mutual recognition procedure, or a referral procedure under Article 30 of Directive 2001/83/EC. After a harmonised marketing authorisation in a mutual recognition procedure or decentralised procedure is reached, no national extension is possible.

The mutual recognition/decentralised procedure is required for applications referring to **well-established use** intended for authorisation in more than one Member State and for which the use of the centralised procedure is neither mandatory nor chosen by the applicant.

2.2 Repeat use

It is possible to use the mutual recognition procedure more than once for subsequent applications to other Member States in relation to the same medicinal product (so-called repeat use). It is recommended that, wherever feasible, the marketing authorisation holder considers involving all Member States where the product is intended to be marketed, in the first use of mutual recognition procedure or decentralised procedure.

In case the applicant withdraws its application for marketing authorisation during a decentralised or mutual recognition procedure, this does not prevent the marketing authorisation holder to initiate a second procedure of mutual recognition for that/those Member State(s) at a later stage. Each subsequent procedure will be treated as a new mutual recognition procedure including the possibility for the new concerned Member States to raise objections based on potential serious risk to public health.

In the case of such a repeat use procedure, the subsequent application for mutual recognition will have to comprise the original dossier updated by any variation or renewal which had been approved and/or amended after authorisation; if necessary, additional data accepted by all Member States involved in the previous procedure and a proposal for a summary of product characteristics, package leaflet and labelling identical to the currently authorised. The reference Member State will send the original assessment report including the assessment of the updated dossier and variations as an Annex or as an updated assessment report to the concerned Member States.

³ as defined in Annex II of Regulation (EC) 1084/2003

In order to initiate a repeat use after 30 October 2005 of a previous mutual recognition procedure, the applicant will have to obtain harmonisation of the package leaflet and labelling of the medicinal product concerned by a notification present to Article 61(3) of Directive 2001/83/EC prior to start the repeat use. Recommendations are given in relation to the repeat-use procedure on the coordination group website.

Member States concerned in any repeated mutual recognition procedure shall normally recognise the authorisation granted in the previous procedure. In exceptional circumstances, where a concerned Member State considers that there are grounds for supposing that authorisation of the medicinal product concerned may present a potential serious risk to public health, the Member State shall refer the matter to the coordination group for human medicinal products for mutual recognition and decentralised procedure (hereafter “the coordination group”). The applicant cannot stop this procedure by subsequently withdrawing the application in the referring Member State. If no agreement can be reached in this group the matter is referred for arbitration to the EMEA. Any matter dealt with by the coordination group in a previous mutual recognition procedure or decentralised procedure may not be raised again in any subsequent procedure except for justified reasons. Matters dealt with in an arbitration in a previous mutual recognition procedure or decentralised procedure may not be raised again in any subsequent procedure.

The coordination group has released a Position Paper on Repeat Use of The Mutual Recognition Procedure to clarify dossier requirements and the divided responsibility prior and during the procedure for the marketing authorisation holder and the involved Member States.

2.3 Exclusions

The mutual recognition procedure and decentralised procedure will not be used for applications for:

- products falling under the compulsory scope of the centralised procedure as set out in the Annex to Regulation (EC) 726/2004 i.e.:
 - i) products developed by certain biotechnological processes,
 - ii) products containing a new active substance not authorised in the Community at the time of entry into force of the Regulation and with therapeutic indication for treatment of certain diseases,
 - iii) products designated as orphan medicinal products pursuant to Regulation (EC) 141/2001;
- products where the company has selected to submit through the centralised procedure according to Article 3(2) and 3(3) of Regulation (EC) 726/2004, irrespective whether the marketing authorisation was granted, was rejected (negative opinion), or the applicant withdrew his application after an assessment by the EMEA of the submitted data;

However, if the dossier for a withdrawn medicinal product or a medicinal product which has had a negative opinion in the centralised procedure is supplemented with new data based on new pre-clinical studies and tests and clinical trials, the application is considered to be based on a new dossier. For those applications, the applicant **can apply** again through centralised, mutual recognition or decentralised procedure where applicable, in those cases where a centralised procedure is not compulsory.

- homeopathic products referred to under Article 16(2) of Directive 2001/83/EC cf. Article 39(2) of that Directive;
- special, simplified registration of traditional herbal medicinal products which are **not** falling within the scope of Article 16d(1), cf. Article 16g(1) of Directive 2001/83/EC
- products falling within the transitional arrangements for Cyprus, Lithuania, Malta, Poland and Slovenia upon their accession to the EU, cf. the Act of Accession⁴.
(see Chapter 1 of the Notice to Applicants for further details)

Extensions

- introducing in a human medicinal product a proteinaceous component obtained through a biotechnology process listed in Annex to Regulation (EC) 726/2004
- referring to original medicinal products which have not been
 - i) harmonised via national procedures,
 - ii) referred in accordance with Article 30 or 31 of Directive 2001/83/EC,
or
 - iii) authorised by Member States following Directive 87/22/EEC ("Ex-concertation" procedure)

Variations

- introducing in a human medicinal product a proteinaceous component obtained through a biotechnology process listed in Annex to Regulation (EC) 726/2004.

However, if the variation to a medicinal product not containing a proteinaceous constituent, concerns for instance a reagent like an enzyme prepared by rDNA technology, the medicinal product **remains in the procedure foreseen in the Variations Regulation** as this enzyme does not appear in the final composition and can therefore not be considered as an introduction of a proteinaceous

⁴ **The Treaty of Accession 2003** of the Czech Republic, Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia
Signed in Athens on 16 April, 2003
http://europa.eu.int/comm/enlargement/negotiations/treaty_of_accession_2003/treaty_accession_16.htm

component.⁵ Likewise, for a change in the manufacturing process of a non-proteinaceous component due to the introduction of a biotechnology step, the product remains in the procedure foreseen in the Variations Regulation⁶.

- referring to medicinal products which have not been considered through
 - i) mutual recognition procedure or decentralised procedure
 - ii) ex-concertation procedures
 - iii) referral in accordance with Article 30 or 31 of Directive 2001/83/EC

2.4 Coordination group for mutual recognition and decentralised procedure for human medicinal products – CMD(h)

The Mutual Recognition Facilitation Group started its work in 1995 as an informal group. With the adoption of Directive 2004/27/EC the Mutual Recognition Facilitation Group has an official status and is renamed as coordination group. According to Article 27 of Directive 2001/83/EC the group consists of one representative per Member State. An observer from the Commission and EMEA may participate at the meetings. The EMEA provides a secretariat to the coordination group. The group is responsible for the smooth functioning and good outcomes of mutual recognition and decentralised procedures with a mix of regulatory and scientific work.

The main tasks of the coordination group are:

- □ To address procedural and scientific issues arising from the mutual recognition and decentralised procedures.
- To consider points of disagreement raised by a Member State in relation to the assessment report, summary of product characteristics, labelling and package leaflet of a medicinal product on the grounds of “potential serious risk to public health” within an mutual recognition or decentralised procedure. In the case of unsolved disagreement, the coordination group will refer the matter to the EMEA/CHMP for arbitration with a detailed reasoning for the disagreement.
- To facilitate the establishment of dialogue between Member States, through meetings and oral explanations and to provide a forum to discuss any difficulties in dialogue and seek to overcome such difficulties.
- In order to promote harmonisation of marketing authorisations across the Community, to lay down a list of products where the summary of product characteristics needs to be harmonised taking into account proposals from Member States. This will be done on an annual basis.
- To facilitate the resolution of procedural and scientific issues arising from variation and renewal procedures, with a view to maintaining harmonisation of

⁵ See Annex I, Introductory statements, 6th paragraph to Regulation (EC) No 1084/2003.

⁶ See Annex I, Introductory statements, 6th paragraph to Regulation (EC) No 1084/2003.

a marketing authorisations following mutual recognition or the completion of a decentralised procedure or following a referral.

- To identify issues which will be referred to the Commission, the Pharmaceutical Committee, Heads of Medicines Agencies or other appropriate bodies.
- In close liaison with the Pharmacovigilance Working Party of the CHMP, to ensure best practice for risk management of marketing authorisations granted through the mutual recognition /decentralised procedure.
- To undertake tasks concerning the overall management of the mutual recognition and decentralised procedures, maintaining close interaction with Heads of Medicines Agencies.
- To draw up its own Rules of Procedure for endorsement by Heads of Medicines Agencies and for Commission approval.

The chairperson of the coordination group is elected by and from amongst its members for a period of three years, renewable once. The Vice-chairperson shall be appointed from among the members of the coordination group by the Member State which has the presidency of the Council of the European Union for the duration of the term of the presidency. The coordination group meets normally once a month at the EMEA. In connection to the plenary meeting, there are breakout sessions relating to ongoing procedures when considered necessary. Additional subgroup meetings are organised on specific topics. A press release is normally issued after each meeting.

The coordination group has a website where recommendations, position papers, standard operating procedures (SOPs) and other documents are published.
<http://www.hma.eu/>.

2.5 Arbitration procedure

In the case of unsolved disagreement in the coordination group procedure, the coordination group will refer the matter to the EMEA/CHMP for arbitration with a detailed reasoning for the disagreement.

During the arbitration procedure all members of the CHMP are involved in the evaluation and opinion taking process. The Commission decision following the arbitration procedure shall be addressed to all Member States. Those Member States where the medicinal product is authorised, or where an authorisation is pending, shall be required to take action following the Commission Decision on arbitration within 30 days. Member States in which an application has not been submitted are bound by the decision in the event that an application is subsequently submitted. However, in such cases of repeat use of the mutual recognition procedure, Member States can raise issues which they consider grounds of potential serious risk to public health provided that these grounds were not already covered in the earlier arbitration. In case such grounds are raised in the repeat use procedure, they will lead to a new discussion in the coordination group and, possibly, to a new arbitration procedure.

Further details on the arbitration procedure are contained in Chapter 3 of the Notice to Applicants.

3. THE MUTUAL RECOGNITION PROCEDURE

3.1 General principles

The mutual recognition procedure is to be used in order to obtain marketing authorisations in several Member States where the medicinal product in question has received a marketing authorisation in any Member State at the time of application.

The procedure to be followed will depend upon whether it is a Member State who triggers or the marketing authorisation holder who initiates the mutual recognition.

As set out in Directive 2001/83/EC, Member States have to approve during the mutual recognition procedure the assessment report, the summary of product characteristics, the package leaflet and the label.

Specific national requirements, for example information on reimbursement or a pictogram for medicines which cause tiredness, have to be presented in a so-called ‘blue box’.

See also the updated version of Chapter 7 of the Notice to Applicants section 10. ‘Blue-Box Requirements for the package leaflet and labelling in the decentralised or mutual recognition procedure’.

The mutual recognition procedure is divided in the following steps⁷:

- National validation by the reference Member State (not further described here)
- Preparation or update of assessment report by reference Member State (90 days)
- Validation by the concerned Member States
- Approval by the concerned Member States (90 days)
- Discussion at the coordination group level, if needed
- National Marketing Authorisation step

3.2 Procedure leading to mutual recognition

After the first marketing authorisation in the Community is granted, the marketing authorisation holder may request one or more Member State(s) to recognise an authorisation granted by the reference Member State by submitting an application in accordance with Article 28 of Directive 2001/83/EC (for details see below “making

⁷ See Annex 1 Flow Chart Mutual Recognition Procedure

the application”). Within 90 days of receipt of a valid application, the reference Member State will provide the assessment report together with the approved summary of product characteristics, labelling and package leaflet to the concerned Member States and to the marketing authorisation holder (Article 28(2) of Directive 2001/83/EC).

Within 90 days of the receipt of these documents, the concerned Member States shall recognise the decision of the reference Member State and the approved summary of product characteristics, package leaflet and labelling by granting a marketing authorisation with a harmonised summary of product characteristics, package leaflet and labelling (Article 28(4) of Directive 2001/83/EC). However, if there are grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health, the procedure according to Article 29(3) of Directive 2001/83/EC has to be followed and, if Member States fail to reach agreement, an arbitration shall be initiated.

Differences between the summary of product characteristics, package leaflet and labelling approved in one Member State and the summary of product characteristics, package leaflet and labelling submitted in another Member State, do not automatically prevent the latter from a mutual recognition procedure. If these differences have no therapeutic implications (no difference in the efficacy and safety profile) i.e. both products have the same qualitative and quantitative (strength) composition in active substance and the same pharmaceutical form, they have to be considered as being the same and a mutual recognition procedure has to be followed (cf. Chapter 1 of the Notice to Applicants).

It is not possible for the same applicant (e.g. company belonging to the same mother company or group of companies or exercising concerted practices) to apply for a further national application referring to the identical marketing authorisation in the reference Member State. Therefore, an application for a “duplicate” (multiple applications) would have to be submitted to the reference Member State followed by mutual recognition of this second authorisation in other concerned Member States. In this context, the fact that one company sells the right to use parts of its dossier to another company (allows an “informed consent” application) does not necessarily imply that these two companies must be considered as the same company. Pharmaceutical companies which are independent from the marketing authorisation holder of the first authorisation would be allowed to ask for subsequent marketing authorisations, “national duplicates” of nationally authorised medicinal products in any Member State (the concerned Member State or the reference Member State).

3.2.1 Triggering by a Member State

According to Article 18 of Directive 2001/83/EC, where a Member State is informed in accordance with Article 8(3)(I) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it was submitted in compliance with Articles 27 to 39, i.e. under the mutual recognition procedure.

In the context of Article 8(3)(I) of Directive 2001/83/EC (which obliges the applicant to submit copies of any authorisation granted for the medicinal product in question),

Member States have to consider applicants belonging to the same mother company or group of companies as one company. The same principle applies to applicants, which, without belonging to the same mother company or group of companies, have concluded agreements (e.g. “licensees”) or which exercise concerted practices concerning the placing on the market of the relevant medicinal product in different Member States.

The medicinal product in question encompasses any medicinal product which has the same qualitative and quantitative composition in active substance and same pharmaceutical form.

3.2.2 Initiation by the marketing authorisation holder

According to Article 28(1) of Directive 2001/83/EC with a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States, designating one Member State to act as reference Member State (for details see below under “making the application”). In the mutual recognition procedure Article 28(2) applies.

3.2.2.1 Discussion with the reference Member State

Before submitting an application under the mutual recognition procedure the marketing authorisation holder must inform the reference Member State that such an application is to be made.

The marketing authorisation holder is in any case advised to discuss, in advance, the proposed mutual recognition application with the reference Member State. Such discussion would include whether the dossier and Overall Summaries and Overviews should be updated to ensure that all relevant information is supplied according to current requirements, legal and technical aspects. The reference Member State may require the marketing authorisation holder to provide reassurance that the dossier submitted in other Member States is identical to that upon which it took its own decision.

Generic medicinal products: see also Chapter 1 of the Notice to Applicants.

For a generic application, the applicant will need to carefully consider the choice of the reference product for his product and should discuss this choice with the reference Member State. The applicant has to demonstrate that his medicinal product is bioequivalent with the reference medicinal product. Member States shall accept the demonstration of bioequivalence, independent of whether or not the reference medicinal product has been authorised in all Member States concerned.

The competent authority of the Member State in which the reference medicinal product has or has had a marketing authorisation, shall transmit upon request of the reference Member State within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and if necessary other relevant

documentation like the summary of product characteristics and information on the date of authorisation.

Information about the reference medicinal product used in the bioavailability/bioequivalence study will be given in the assessment report of the reference Member State in a **confidential attachment** stating the full qualitative and quantitative composition and finished product specification. In case of doubt, a concerned Member State may request additional information from the reference Member State (see guidelines on ‘Investigation of bioavailability and bioequivalence, and Clinical testing of prolonged action forms with special reference to extended release forms’ on the web-site of the Agency:

[http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.Assessment Report](http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.Assessment%20Report))

3.2.2.2 Updating the dossier and Overall Summaries and Overviews (if necessary)

Necessity to update

Article 23 of Directive 2001/83/EC requires the marketing authorisation holder to continuously update the dossier to take account of technical and scientific progress and to introduce any change that may be required for the manufacture and control of the medicinal product.

Updating should be taken up through the variations procedure, and reflected in the dossier and/or Overall Summaries and Overviews, as appropriate. Furthermore, it may be necessary to *consolidate* the dossier in order to reflect the changes made by variations since the first authorisation was granted. However, Module 3 (Part II) does not need to be supplemented, a discussion in the Quality Overall Summary is sufficient.

In case new guidelines were issued since the medicinal product has been placed on the market, they should be reflected in the Overall Summaries and Overviews in relation to the data presented in the dossier. If the applicant believes that, in addition, modifications are necessary in the summary of product characteristics, package leaflet and the labelling then such changes should be approved by the reference Member State.

Procedure for updating prior to starting the mutual recognition procedure

As stated previously, it is preferable for the marketing authorisation holder to give the reference Member State in advance notice of the intention to use the marketing authorisation in the mutual recognition procedure. In case the marketing authorisation holder needs to update the dossier prior to initiating a mutual recognition procedure, and this involves a large volume of data, it is necessary that the marketing authorisation holder and reference Member State will agree on a timetable.

Furthermore, the applicant is recommended to discuss with the reference Member State if the medicinal product has already been marketed for a long time as much of

the pre-clinical data are unlikely to be still relevant in light of clinical data and experience accumulated since marketing authorisation.

In addition, a detailed description may be required in the Overall Summaries and Overviews as to changes in medical practice and the development of the medicinal product in the intervening years. Even though the dossier is continuously added to and there is one renewal after 5 years after the authorisation is granted, there could be a need for a comprehensive review in both the pre-clinical and the clinical Overall Summaries and Overviews.

In any event, after the marketing authorisation holder has brought the dossier and the Overall Summaries and Overviews up to date and has included all variations, he must submit his formal application and thereby request the reference Member State in writing to supply an assessment report or an updated assessment report to the concerned Member States.

3.2.2.3 Before submission of the application to the concerned Member State(s)

Dialogue with the applicant, in particular on summary of product characteristics, package leaflet and labelling

In accordance with Article 28(4) of Directive 2001/83/EC, all Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet, submitted for mutual recognition.

In order to ensure a smooth procedure for this recognition, Member States have agreed to use the following procedure intended for clarification and dialogue

Before initiation of the mutual recognition procedure, the reference Member State is requested to achieve and agree on a summary of product characteristics, package leaflet and labelling through discussion with the applicant, which would take into account all existing national summaries of product characteristics, package leaflets and labelling for the medicinal product and for medicinal products with the same active substance which have been approved in earlier mutual recognition procedure and decentralised procedures.

Especially for applications according to Article 10(1) of Directive 2001/83/EC (generic medicinal products), the applicant will be requested to present to the reference Member State an overview of the sections: Indications, Posology, Contraindications and Special Warnings and Precautions for Use of the summary of product characteristics, package leaflet and labelling of the corresponding reference products of the intended concerned Member State(s) for this application. The reference Member State will discuss with the applicant to what extent a summary of product characteristics, package leaflet and labelling can be achieved on which a successful mutual recognition procedure can be based.

Both the reference Member State and the applicant are expected to react in a flexible manner. The marketing authorisation holder should ensure that:

- i) the product will be regarded as a medicinal product in all concerned Member States and that it will not be regarded, for example, as a cosmetic, a food supplement, a medical device or a biocide;
- ii) the product is falling under the scope of the mutual recognition procedure;
- iii) the application including the three Overall Summaries and Overviews on Module 3, 4 and 5 is updated appropriately (i.e. in accordance with relevant legislation);
- iv) either the clinical indications sought have been previously authorised for a medicinal product containing the same active substance in the concerned Member State(s)

or

adequate clinical data is available to support the claimed indications in the summary of product characteristics, package leaflet and labelling;

or

it is an application according to Article 14 of Directive 2001/83/EC (registration procedure for the homeopathic medicinal products)

- v) in the case of generic applications the requirements of Article 10(1) of Directive 2001/83/EC have been met, i.e. that there is a medicinal product which is or has been authorised in a Member State for the following period:
 - for more than 6 or 10 years (i.e. the period of protection of Directive 2001/83/EC before amendment by Directive 2004/27/EC) in case the application for authorisation of the reference product had been submitted **before** Directive 2004/27/EC started to apply;
 - for not less than 8 years in case the application for authorisation of the reference product had been submitted **after** the date of transposition of Directive 2004/27/EC;
 - vi) the dossiers in the reference Member State and concerned Member States are the same;
 - vii) variations or renewals to the original authorisation have been authorised by the reference Member State in advance of the initiation of the procedure;
- and
- viii) the final text of the approved summary of product characteristics, and that of the package leaflet and labelling, for information, in the national language of the reference Member State should be available, with appropriate translations and taking into account relevant guidelines.

3.2.2.4 Making the application

The marketing authorisation holder must submit an application to the competent authorities of each of the Member States where a marketing authorisation is to be sought. The application shall be submitted together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC.

The application shall include a list of all concerned Member States. The Member State who has already granted a marketing authorisation shall act as “reference Member State” and prepare an assessment report on the medicinal product.

The marketing authorisation holder must confirm (usually in the covering letter accompanying the application) that the dossier as well as the summary of product characteristics, package leaflet and labelling are identical to

- a) the ones accepted by the reference Member State, and
- b) the ones submitted to all other concerned Member States.

The dossier must include the EU Application Format Module 1 (Part IA).

The following information on the requirements on the application in the concerned Member States can be found in Chapter 7 of the Notice to Applicants:

- The numbers of copies of the dossier and required languages for submissions to the Member States
- Copies of the summary of product characteristics, label and package leaflet texts in the language(s) as set out for each Member State
- Requirements for samples of the active substance and finished product are set out for each Member State
- How the appropriate national fees have to be paid
- In some Member States, there may be different addresses for submission of the dossier and for correspondence in connection with an application.
- It is not part of the responsibility of the competent authorities to arrange customs clearance of applications. It is the responsibility of the marketing authorisation holder to deliver the application to the officially designated address, free of any charges to the addressee.
- A copy of the application should be available to be sent to the reference Member State on request, and also, **only** in the event of an arbitration, to the EMEA.
- Additional national requirements, if applicable
- Submission of electronic dossiers

3.3 Action following the submission of the application

3.3.1 Preparation or update of assessment report by reference Member State

In accordance with Article 28(2) of Directive 2001/83/EC, the reference Member State shall prepare or update the assessment report within 90 days of receipt of a valid application.

Normally, the assessment report prepared during the initial assessment of the medicinal product will be available, but the reference Member State needs to update it in order to maintain consistency between the dossier and the assessment report. The assessment report would include all variations and any additional information bearing upon quality, safety and efficacy reported since the initial marketing authorisation had been granted.

The reference Member State will notify the marketing authorisation holder when the assessment report is/will be available.

According to Article 28(2) of Directive 2001/83/EC, this assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be sent to the concerned Member States and to the applicant.

However, if an Active Substance Master File (ASMF) was submitted, the section of the assessment report referring to the closed part of the Active Substance Master File as well as any other confidential information will not be made available to the applicant (see guideline on European Active Substance Master File procedure for active substances in Rules Governing Medicinal Products in the European Union Volume 3A). Where it is made available to the marketing authorisation holder, the other concerned Member States will be informed. For the information provided in the Active Substance Master File the letter of access should be included

It also might be necessary that the assessment report needs to be translated. Arrangements for translation of the assessment report will be made by the reference Member State, but the costs of translation are borne by the marketing authorisation holder.

3.3.2. Procedure for validation of the application by the concerned Member States

The procedure for validation of the application by the concerned Member States starts when the marketing authorisation holder confirms both to the reference Member State and concerned Member States the dates of dispatch of the dossier to all concerned Member States and when the reference Member State has sent the assessment report to all concerned Member States. The application is validated by the concerned Member States within 14 days⁸ using the check-in procedure described in Chapter 7 of the Notice to Applicants. Notably, it will be verified that all necessary documentation and translations are available and that the fees have been paid. Any problems are notified

⁸ Days are considered as calendar days

immediately by the Communication and Tracking System⁹ (CTS) to the reference Member State and by other media to the marketing authorisation holder.

If a concerned Member State informs the reference Member State that the application is invalid, the clock will only start when that concerned Member State informs the reference Member State that the application has become valid or that the application has been withdrawn. The concerned Member State must inform the reference Member State that the application has become valid within 5 days of the missing information being supplied.

In case of minor problems, the marketing authorisation holder will be given the opportunity to rectify the application within two weeks after he has been notified of the problems.

In case of major problems or if the marketing authorisation holder failed to rectify minor problems, the application is deemed invalid and the applicant will be advised to withdraw the application. In the case of possible different views among Member States on the legal basis for the application, the matter can be discussed in the meeting of the coordination group.

In order to facilitate the check-in procedures in national competent authorities, the coordination group has published a Member State Standard Operating Procedure (SOP) “Procedure for automatic validation of mutual recognition procedure for new applications”.

3.3.3 Start of the 90-day period for approval by the concerned Member States

In accordance with Article 28(4) of Directive 2001/83/EC, all concerned Member States have 90 days to approve the assessment report, the summary of product characteristics and the labelling and package leaflet.

The reference Member State will start this 90-day period normally 14 days after it has sent the notifications for validation to the concerned Member States (automatic validation procedure), unless it has been informed by a concerned Member State that the application is invalid (see 3.3.2).

The reference Member State notifies all concerned Member States and the marketing authorisation holder of the start of the 90-day period referred to in Article 28(4) of Directive 2001/83/EC.

⁹ The Communication and Tracking System is used by the reference Member State and all concerned Member States to exchange information in all steps of the procedure such as validation and start of the procedure.

Flexible starting date

In order to facilitate the successful operation of the mutual recognition procedure, as an optional, *voluntary procedure in consultation with the applicant*, the reference Member State may start the mutual recognition procedure on a date that would facilitate liaison between the Member States i.e. for medicines for human use, a series of “start dates” would be used so that day 75 approximately would coincide with a meeting of the coordination group. The marketing authorisation holder should liaise with the reference Member State in this respect.

The coordination group regularly publishes a Guidance on submission dates for Applicants of the Mutual Recognition Procedure.

3.3.4 Clarification and dialogue - Operating procedure

Response of concerned Member States

During the operation of the mutual recognition procedure, the reference Member State will act as the central point between the concerned Member States and the marketing authorisation holder. All dialogue between the parties involved should be channelled through the reference Member State.

If a concerned Member State considers that there are grounds for supposing that the authorisation of the medicinal product may present a potential serious risk to public health, it is recommended to notify this concern as soon as possible to the reference Member State, the other concerned Member States and the applicant at latest on day 50 of the 90-day period. All objections, reasons for objections to grounds of potential serious risk to public health and any issues for clarification are carefully screened within the national agencies.

Member States have agreed to distinguish in their day 50 letter their concerns in potential serious risks to public health which, unresolved, could lead to the procedure within the coordination group according to Article 29(3) of Directive 2001/83/EC and if failed to an arbitration procedure.

If the situation could be solved, the reference Member State will inform the coordination group accordingly, so that all Member States can benefit from the information and, if relevant, adopt common positions.

If a break-out session takes place, the reference Member State will circulate the minutes of this meeting to the coordination group, the concerned Member States and the applicant.

Discussion on the summary of product characteristics, package leaflet and labelling

At the end of the 90-day period for approval by the concerned Member States, agreement must be reached on the summary of product characteristics, package leaflet and labelling.

In the period from day 50 to day 90 discussions would mainly concentrate on :

- indications
- posology and method of administration
- contra-indications
- special warnings and precautions for use
- shelf-life and storage requirements

The remainder of the summary of product characteristics, package leaflet and labelling of the reference Member State should be mutually recognised.

Response from the applicant

In response to the objections or questions communicated to the applicant by the concerned Member States, it is recommended that the applicant should provide a draft response document at latest before day 60 to the reference Member State, so that the reference Member State can comment on the responses and support the applicant's response document, when considered as satisfactory, with a letter.

Additional information from the applicant should always be sent to all concerned Member States and to the reference Member State **but** it should be noted that the applicant does not have the possibility of addressing questions/objections by providing additional studies during the procedure.

In this response document the applicant will provide, if requested, a new proposed summary of product characteristics, package leaflet and labelling in tabular form set against the original summary of product characteristics, package leaflet and labelling with the answers to the questions raised by the concerned Member State on the different sections of the summary of product characteristics, package leaflet and labelling.

The applicant should answer questions (if any) on Modules 3 to 5 (Part II, III and IV). Each objection or question should be mentioned and followed by the initials of the concerned Member State. Cross-references could be useful from one response to another.

In order to facilitate the procedure, the coordination group has published a recommended format of the applicant's response document "Applicant's response document in mutual recognition : recommended format".

The reference Member State should in all situations evaluate the response given by the applicant (to the issues raised by the concerned Member States) and communicate these in writing to all concerned Member States before the clarification and the break-out session of coordination group take place.

The applicant should send the whole response document to the concerned Member States in due time, not less than 10 calendar days before the scheduled date for the next coordination group meeting in order to facilitate assessment and if necessary, discussion during the break-out session.

Clarification of concerns and deficiencies will be carried out by dialogue between the reference Member State, and other concerned Member States using telephone, fax or e-mail as appropriate. It may be necessary for the marketing authorisation holder to discuss issues directly with the concerned Member States but the reference Member State must be kept informed.

The reference Member State will inform Member States of actions (e.g. modifications to the summary of product characteristics, package leaflet and labelling) suggested by other Member States in order to allow a consensus to be reached. During this 90-day period it is recommended that a person within the applicant company always be available to resolve any issues which may arise.

Break-out sessions

The meetings of the coordination group have been identified as occasions where all Member States can meet. Alongside these meetings, break-out sessions may be organised under responsibility of the reference Member State to discuss applications or to resolve outstanding questions. The reference Member State will inform the marketing authorisation holder if it is considered that representatives from the applicant might be available at the relevant meeting to aid in the resolution of these issues.

Although applicants should be aware that they may not be required to participate in the session they may be asked to agree amendments to the summary of product characteristics, package leaflet and labelling or to answer questions from the Member States. Applicants should ensure that their representatives are able to take decisions on amendments to the summary of product characteristics, package leaflet and labelling being proposed by Member States.

The same procedure applies to the decentralised procedure.

The coordination group has published a document on the organisation of these meetings “Best Practice Guide on Break-out sessions”.

Finalisation of the procedure

All concerned Member States should give their final opinion at latest on day 85. On occasion further discussion may be needed around day 85 to avoid a procedure in the coordination group or an arbitration (either by telephone conference, videoconference or in a meeting). Any further changes in the summary of product characteristics,

package leaflet and labelling should be agreed on by the reference Member State and all other concerned Member States.

No agreement could be reached during the mutual recognition procedure

See section 5 ‘Coordination Group procedure on disagreement on potential serious risk to public health’.

Withdrawal

Where an applicant withdraws an application regarding a medicinal product in one concerned Member State during a mutual recognition procedure, it is not allowed to submit a national application subsequently. Any such an application will be rejected.

An application for a marketing authorisation may be withdrawn by the applicant at any time during the mutual recognition procedure. However, once a potential serious risk to public health has been raised in accordance with Article 29(1) of Directive 2001/83/EC, to be dealt with by the coordination group (see section 5) and if failed by the CHMP in an arbitration procedure (see Chapter 3 of the Notice to Applicants), the opinion of the coordination group and of the CHMP will be given unless all applications and existing marketing authorisations for the product are withdrawn. In the latter case, the CHMP may decide either to close or to continue the referral procedure, if there still is a public health concern.

3.3 5 Recognition of the marketing authorisation (mutual recognition) and granting of national authorisations

In accordance with Article 28(4) of Directive 2001/83/EC, each concerned Member State will recognise the marketing authorisation and the summary of product characteristics, package leaflet and labelling granted by the reference Member State within the 90-day period.

According to Article 28(5) of Directive 2001/83/EC competent authorities shall adopt a decision within 30 days after acknowledgement of their agreement to the assessment report, the summary of product characteristics and the labelling and package leaflet as approved by the reference Member State. The applicant should therefore in his own interest provide the requisite documentation (adequate translation of the agreed summary of product characteristics, package leaflet and labelling) not later than 5 calendar days after the end of the procedure.

When mutual recognition occurs, the Member State which recognises a marketing authorisation informs the reference Member State, the other concerned Member States, the EMEA via the Communication and Tracking System as well as the marketing authorisation holder.

Further information can be found in the “Best practice guide for mutual recognition procedure” published and updated in a regular manner by the coordination group.

Granting of national marketing authorisation during an on-going arbitration procedure

According to Article 29(6) of Directive 2001/83/EC, even if there is no agreement among all Member States, those Member State(s) which have approved the summary of product characteristics, package leaflet and labelling may, on request of the applicant, grant a marketing authorization while the arbitration procedure is ongoing. This authorisation shall be without prejudice to the outcome of the arbitration procedure.

4. DECENTRALISED PROCEDURE

In order to facilitate the check-in procedure, the coordination group has published a Standard Operation Procedure (SOP): ‘Procedure for the decentralised procedure’¹⁰.

4.1 General principles

The decentralised procedure is to be used in order to obtain marketing authorisations in several Member States where the medicinal product in question has not yet received a marketing authorisation in any Member State at the time of application.

The procedure to be followed will depend upon whether it is a Member State or the marketing authorisation holder which initiates the decentralised procedure.

As set out in Directive 2001/83/EC Member States have to approve during the decentralised procedure the assessment report, the summary of product characteristics, the package leaflet and the label.

Specific national requirements have to be presented in a so-called ‘blue box’.

See also the updated version on the Chapter 7 of the Notice to Applicants section 10. ‘Blue-Box Requirements for the package leaflet and labelling in the decentralised or mutual recognition procedure’.

The decentralised procedure is divided in five steps¹¹:

- Validation step
- Assessment step I
- Assessment step II
- Discussion at the coordination group level, if needed
- National Marketing Authorisation step

¹⁰ [Decentralised procedure Member States's Standard Operating Procedure](http://www.hma.eu/) <http://www.hma.eu/>

¹¹ See Annex 2 Flow Chart Decentralised Porcedure

4.2 Procedure leading to decentralised procedure

4.2.1 Triggering by a Member State

According to Article 17(2) of Directive 2001/83/EC where a Member State receives an application for marketing authorisation and notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall remind the applicant that the decentralised procedure (Articles 27 to 39 of Directive 2001/83/EC) applies.

The Member State which already has started the examination will normally be the future reference Member State. It is within the responsibility of the reference Member State either to continue or to restart the procedure after receiving the information that in other Member States an application for the same medicinal product by the same applicant is pending. As soon as the reference Member State has prepared a draft assessment report, a draft summary of product characteristics and a draft labelling and package leaflet, the reference Member State shall forward it to the concerned Member States and to the applicant proposing the starting date for the procedure.

The coordination group has published a “Member States Standard Operating Procedure (SOP) on simultaneous applications“, Article 17(2) of Directive 2001/83/EC, which allows efficient utilisation of resources and the avoidance of duplication of effort.

4.2.2 Initiation by the applicant

According to Article 28(1) of Directive 2001/83/EC with a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, and where no marketing authorisation has been granted in the Community for that medicinal product, an applicant shall submit an application based on an identical dossier in these Member States, designating one Member State to act as reference Member State (for details see below under “making the application”). Article 28(3) applies.

4.2.2.1 Discussion with the reference Member State

Before submitting an application under the decentralised procedure, the applicant must inform the reference Member State that such an application is to be made.

The applicant is in any case **advised** to discuss, in advance, the proposed application with the reference Member State. The reference Member State may require the applicant to provide reassurance that the dossier submitted in other Member States is identical to that upon which it takes its own decision.

When an application is submitted in a Member State with the intention to request a decentralised procedure a timely notification to the reference Member State is advantageous as to provide advice. This would also facilitate the availability of the assessment report within the period of time according to Article 28(3) of Directive 2001/83/EC.

The reference Member State will allocate a procedure number to this application, according to the numbering system described in section 7 of this Chapter and will inform the applicant accordingly.

In the case of possible different views among Member States on the legal basis of the application, the matter can be discussed in the meeting of the coordination group prior to the application but also during the validation phase.

For a submission of a **generic application** see above under 3.2.2.1.

4.2.2.2 Before submitting the application to the reference and concerned Member State(s)

Dialogue with the applicant, especially on summary of product characteristics, package leaflet and labelling

In accordance with Article 28(4) of Directive 2001/83/EC, all Member States concerned shall approve the assessment report, the summary of product characteristics, package leaflet and label submitted. Therefore in order to maximise the efficiency of this clarification and dialogue stage, Member States have agreed to use the following procedure:

For applications according to Article 10(1) of Directive 2001/83/EC (generic medicinal products), the applicant will be requested to present to the reference Member State an overview of the sections: Indications, Posology, Contraindications and Special Warnings and Precautions for Use of the summary of product characteristics, package leaflet and labelling of the corresponding innovator products of the intended concerned Member State(s) for this application. The reference Member State will discuss with the applicant to what extent a summary of product characteristics, package leaflet and labelling can be achieved on which a successful decentralised procedure can be based.

Both the reference Member State and the applicant are expected to react in a flexible manner.

The applicant **should** ensure that all requirements as set out in section 3.2.2.3 (i) to (vi) are fulfilled accordingly.

4.2.3 Making the application

The applicant must submit an application to the competent authorities of each of the Member States where a marketing authorisation is to be sought. The application shall

be submitted together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC.

The application shall include a list of all concerned Member States and the applicant shall designate one Member State to act as “reference Member State” and to prepare an draft assessment report on the medicinal product.

The applicant must confirm (usually in the covering letter accompanying the application) that the dossier as well as the summary of product characteristics, package leaflet and labelling are identical in all Member States involved in the decentralised procedure.

Information on the requirements on the application in the reference Member State and the concerned Member States can be found in Chapter 7 of the Notice to Applicants (see section 3.2.2.4).

4.3 Action following the submission of the application

4.3.1 Validation Phase by the reference Member State and the concerned Member States

The procedure for validation of the application starts when the applicant confirms both to the reference Member State and concerned Member States the dates of dispatch of the dossier to all Member States.

The application should be validated by all concerned Member States and the reference Member State. The validation can be made according to the check-in procedure described in Chapter 7 of the Notice to Applicants or using any appropriate form.

Any validation issues are notified immediately by the Communication and Tracking System to the reference Member State or at latest within 14 days following the receipt of the notification of dispatch dates, to the applicant and the reference Member State.

In case of problems, the applicant will be given the opportunity to rectify the application within a given timeframe after he has been notified of the problems.

4.3.2 Start of the decentralised procedure: assessment step I¹²

In accordance with Article 28(3) of Directive 2001/83/EC, the reference Member State has 120 days to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. The reference Member State will start the assessment step I after the applications have been validated by all concerned Member States and the reference Member State.

In order to prepare the draft assessment report, the reference Member State forwards a preliminary assessment report on the dossier to the concerned Member States and the applicant within 70 days after the start of the assessment step I.

¹² Assessment step I corresponding to the national assessment phase Article 28(3) of Directive 2001/83/EC

The concerned Member States should communicate their comments on the dossier, the preliminary assessment report and the summary of product characteristics to the reference Member State within the timeframe set by the reference Member State.

If a concerned Member State can already identify at this early stage that it sees grounds for supposing that the authorisation of the medicinal product may present a potential serious risk to public health, it should notify its concerns as soon as possible to the reference Member State, the other concerned Member States and the applicant. All objections, reasons for objections to grounds of potential serious risk to public health and any issues for clarification should be carefully screened by the national agencies.

The concerned Member States are asked to give comments on the proposed national prescription status and to inform the reference Member State.

The reference Member State will forward all comments received from the concerned Member States without delay to the applicant. The reference Member State stops the clock if necessary in order to allow the applicant to prepare a response document (Article 19(3) of Directive 2001/83/EC). This clock-stop period will be determined in agreement with the applicant, depending on the complexity of the questions raised but will not exceed a recommended period of 3 months unless duly justified.

The applicant must submit the response document to the competent authorities of all concerned Member States and the reference Member State within the determined timeframe. He also must notify to the reference Member State and concerned Member States the dates of dispatch of the response document (for details see Chapter 7 of the Notice to Applicants as well as the coordination group guidance document “Applicant’s response document in CTD format”).

The procedure restarts when the applicant provides the requested data.

The reference Member State shall supply the draft assessment report, summary of product characteristics, package leaflet and labelling to the concerned Member States and the applicant not later than 120 days after the validation of the application (cf. Article 28(4) of Directive 2001/83/EC). The draft assessment report would include an appropriate evaluation of any information available upon quality, safety and efficacy. The reference Member State will notify the applicant when the draft report is/will be available.

Normally the reference Member State makes the draft assessment report available to the applicant. However, if an Active Substance Master File (ASMF) was submitted, the section of the assessment report referring to the closed part of the Active Substance Master File as well as any other confidential information would be excluded (see guideline on European Active Substance Master File procedure for active substances in Rules Governing Medicinal Products in the European Union Volume 3A). Where it is made available to the applicant, the other concerned Member States will be informed. For the information provided in the Active Substance Master File the letter of access should be included.

4.3.3 Assessment step II: 90-day period for approval by Member States

In accordance with Article 28(4) of Directive 2001/83/EC, all concerned Member States have 90 days to approve the (draft) assessment report, the summary of product characteristics and the labelling and package leaflet.

In agreement between the reference Member State, the concerned Member State(s) and the applicant the 90 day procedure can be shortened. The timelines given in the Directive 2001/83/EC are the maximal ones.

For further details for the flexible starting days see under 3.3.3 above

4.3.4 Clarification and dialogue - Operating procedure

Day 0 of the 90 days assessment step II corresponds with day 120 of the decentralised procedure. In case a break-out session is foreseen, the restart date of the assessment step II will be calculated in such a way that a meeting can be organised during the assessment phase II. The reference Member State will update the Communication and Tracking System database with the date of sending of those documents on Day 0.

Each concerned Member State should send its comments to the reference Member State, the other concerned Member States and the applicant on the draft assessment report and draft summary of product characteristics, draft package leaflet and labelling according to the timeframe agreed and after receipt of those documents and fill in the Communication and Tracking System database.

The applicant will send the response document to the reference Member State and the concerned Member States.

The reference Member State should evaluate the response document and communicate the result of this assessment in writing to all concerned Member States and the applicant. The concerned Member States should send by return their outstanding issues and confirm if there is a need for a break-out session.

If potential serious risks to public health are not resolved at this stage, a break-out session will be organised at the EMEA, upon request from the reference Member State and according to the coordination group 'Best Practice Guide on Break-out sessions'.

If solved, the reference Member State will inform the coordination group on how the situation has been solved, in order all Member States can benefit from the information and, if relevant, adopt common positions.

If a break-out session takes place, the reference Member State will circulate the minutes of this meeting to the coordination group, the concerned Member States and the applicant.

The concerned Member States should send their final comments on the timeframe agreed on the remaining potentially serious risks to public health and comments on the summary of product characteristics, package leaflet and labelling, to the reference Member State, to the other concerned Member States and to the applicant and fill in the Communication and Tracking System database.

The applicant will send the final response document to the reference Member State and the concerned Member States; the final assessment report will be sent by the reference Member State to the concerned Member States and the applicant and the concerned Member States send their final position to the reference Member State and the applicant.

On Day 90 the reference Member State closes the procedure sending to the concerned Member States and the applicant, the final agreed summary of product characteristics, labelling and package leaflet.

If no agreement could be reached within the 90-day period, and if potentially serious risks to public health remain for one or more Member States, which if unresolved would necessitate a call for arbitration under Article 29 of Directive 2001/83/EC, the reference Member State shall inform the coordination group by forwarding the detailed reasoning from the complaining Member States for discussion at the forthcoming meeting of the coordination group.

The points of disagreement should be referred to the coordination group by the reference Member State on day 90 at the latest.

Response of concerned Member States

In the operation of the decentralised procedure, the reference Member State will act as the central point between the concerned Member States and the applicant. All dialogue between the parties involved should be channelled through the reference Member State.

If a concerned Member State considers that there are grounds for supposing that the authorisation of the medicinal product may present a potential serious risk to public health, it will notify this concern as soon as possible to the reference Member State, the other concerned Member States and the applicant. Only objections which present a potential serious risk to public health, as defined in the guideline of the Commission, shall be presented to the reference Member State, the other concerned Member States and the applicant.

In any event these will be communicated within the 90-day period for mutual recognition in order to allow time to resolve the issue. Member States have agreed to distinguish in their letter their concerns in potential serious risks to public health which, unsolved, could lead to the procedure within the coordination group according to Article 29(3) of Directive 2001/83/EC and if failed to an arbitration procedure.

Discussion on the summary of product characteristics, package leaflet and labelling

At the end of the 90-day period for approval by the concerned Member States, agreement must be reached on the summary of product characteristics, package leaflet and labelling.

Response from the applicant

In response to the objections or questions communicated to the applicant by the concerned Member States, the applicant will provide, if requested, a new proposed summary of product characteristics, package leaflet and labelling in tabular form set against the 120-day draft summary of product characteristics, draft package leaflet and labelling from the reference Member State with the answers to the questions raised by the reference Member State and concerned Member State(s) on the different sections of the summary of product characteristics, package leaflet and labelling.

For further details see the relevant section under 3.3.3 above.

Break-out sessions

See section 3.3.4 of this Chapter.

Finalisation of the procedure

All concerned Member States should give their final opinion at latest on day 85 (day 205). On occasion further discussion may be needed around day 85 to avoid a procedure in the coordination group or an arbitration (alternatively a telephone conference or videoconference may be used). Any further changes in the summary of product characteristics, package leaflet and labelling should be agreed on by the reference Member State and all other concerned Member States.

No agreement could be reached during the decentralised procedure

See section 5 ‘Coordination Group procedure on disagreement on potential serious risk to public health’.

Withdrawal

Where an applicant withdraws an application regarding a medicinal product in one concerned Member State during a decentralised procedure, it is not allowed to submit a national application subsequently. Any such an application will be rejected.

In principle, an application for a marketing authorisation may be withdrawn by the applicant at any time during the decentralised procedure. However, during the assessment step II, once a potential serious risk to public health has been raised in accordance with Article 29(1) of Directive 2001/83/EC, to be dealt with by the coordination group (see section 5) and if failed by the CHMP in an arbitration procedure (see Chapter 3 of the Notice to Applicants), the opinion of the coordination group and of the CHMP will be given unless all applications and existing marketing authorisations for the product are withdrawn. In such a case, the CHMP may decide either to close or to continue the referral procedure, if there is still a public health concern.

4.4 Granting of national marketing authorisations

According to Article 28(5) of Directive 2001/83/EC competent authorities of the concerned Member State(s) and the reference Member State shall adopt a decision within 30 days after acknowledgement of their agreement to the assessment report, the Summary of Product Characteristics and the labelling and package leaflet.

The applicant should therefore in his own interest provide the requisite documentation (adequate translation of the agreed Summary of Product Characteristics, package leaflet and labelling) not later than 5 calendar days after the end of the procedure.

The Member State which will grant a marketing authorisation informs the reference Member State, the other concerned Member States, the EMEA via the Communication and Tracking System and the marketing authorisation holder.

Granting of national marketing authorisation during an on-going arbitration procedure

According to Article 29(6) of Directive 2001/83/EC, even if there is no agreement among all Member States, those Member State(s) which have approved the summary of product characteristics, package leaflet and labelling may, on request of the applicant, grant a marketing authorisation while the arbitration procedure is ongoing. This authorisation shall be without prejudice to the outcome of the arbitration procedure.

4.5 Choosing an EU Birth Date/Periodic Safety Update Report submission circle

If an international birth date is already known before the end of the decentralised procedure, the applicant may use the international birth date as the EU Birth Date (according to Volume 9 of Eudralex). In that case this should be communicated to the reference Member State in order that Periodic Safety Update Report submission cycle and first renewal date are included in the Day 90 closure letter.

If the applicant does not choose the international birth date as EU Birth Date, the applicant should be reminded to inform as soon as possible the reference Member State and concerned Member States of the date of granting of the first marketing authorisation in the EU (which will be the EU Birth Date), the Periodic Safety Update Report submission cycle and the common renewal Birth Date.

5. COORDINATION GROUP PROCEDURE ON DISAGREEMENT ON POTENTIAL SERIOUS RISK TO PUBLIC HEALTH¹³

According to Article 29(3) of Directive 2001/83/EC, all involved Member States shall use their best endeavours to reach agreement on the action to be taken within 60 days

¹³ [CMD\(h\) Standard Operating Procedure Disagreement in procedures - Referral to CMD\(h\)](http://www.hma.eu/) <http://www.hma.eu/>

of the communication of the points of disagreement, at the level of the coordination group. During the 60 days procedure no clock stop is foreseen. Coordination group guideline/standard operation procedure on the 60 days procedure within the coordination group should be followed¹⁴.

The coordination group shall allow the applicants, during the 60 day procedure, the opportunity to make their point of view known orally or in writing. Whether a written procedure or a hearing is the most appropriate way to reach an agreement has to be decided in consultation with the applicant .

Written procedure

A written procedure should be restricted to measures deemed urgent by the chairperson, to the adoption of draft statements previously discussed by the coordination group and to measures for the implementation of practices adopted earlier by the coordination group. A full report on the outcome of the written procedure should be made at the following meeting.

Draft statements are addressed to members of the coordination group, who may raise objections within 10 calendar days following transmission. In case of serious objections, the chairperson decides whether the written procedure should be suspended and the adoption of the draft statement postponed to the next meeting of the coordination group.

Hearing

The procedure to follow in case of a request for a hearing by the applicant will be defined in a Standard Operating Procedure to be adopted by the coordination group.

Hearings shall be indicated clearly in the draft agenda of the meeting during which it is deemed to take place. The scientific and/or regulatory argumentation on which a presentation will be based shall be sent to the members of the coordination group in advance. The coordination group shall not express any final positions during these presentations.

End of coordination procedure

If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly.

If the Member States fail to reach an agreement within the 60-day period, the EMEA shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34 of Directive 2001/83/EC. The EMEA shall be provided with a detailed statement of the matters on which the Member States have been unable to reach agreement and the reasons for their disagreement. A copy shall be forwarded to the applicant. The procedure described in Chapter 3 of the Notice to Applicants should be followed using the appropriate form to notify the EMEA.

¹⁴ See Annex 3 Flow chart coordination group procedure

Member States that have approved the assessment report, the summary of product characteristics and the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32 of Directive 2001/83/EC. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

The reference Member State should fill in the Communication and Tracking System database according to the outcome of the procedure.

6. PROCEDURE AFTER THE FINALISATION OF A MUTUAL RECOGNITION PROCEDURE OR A DECENTRALISED PROCEDURE

6.1 Changes to the marketing authorisation in the reference Member State after finalisation of the mutual recognition procedure

Where, in the course of the mutual recognition procedure, the reference Member State and concerned Member States agree that changes to the current authorisation in the reference Member State are necessary in order for mutual recognition to take place, the marketing authorisation holder/applicant and the reference Member State will introduce these using the appropriate national procedures. These changes can relate to the summary of product characteristics, package leaflet and labelling and Modules 3 to 5 (Part II, III or IV) of the dossier.

6.2 Maintenance of identical dossiers

Having the benefit of mutual recognition of the marketing authorisation or a decentralised procedure carries through the life of the medicinal product. Thus variations to a medicinal product which has benefited from mutual recognition or a referral in accordance with Articles 30 or 31 of Directive 2001/83/EC¹⁵ benefit from the procedure foreseen in the Variations Regulation¹⁶ which provides that notifications for variations have to be submitted simultaneously to all Member States where the medicinal product has been authorised. In this way, the summary of product characteristics, the package leaflet and labelling of the marketing authorisation, which has been harmonised, continues to be consistent and identical in all these Member States.

6.3 Renewals

In accordance with Article 24 of Directive 2001/83/EC the marketing authorisation may be renewed after 5 years on the basis of a re-evaluation of the risk/benefit balance by the competent authority of the authorising Member State. Once renewed, the

¹⁵ See Chapter 1 section 4 Community Referrals

¹⁶ See Articles 4(1), 5(1) and 6(1) of Regulation (EC) No 1084/2003.

marketing authorisation shall be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

6.3.1 Timing of submission

The application for renewal should be submitted at least 6 months before the marketing authorisation ceases to be valid. The basic principle is that the application can be submitted earlier but not later than this time. For mutual recognition products it is recommended to reach an agreement on a common renewal date for all Member States concerned by the mutual recognition or decentralised procedure at the time of granting the marketing authorisation to keep the harmonisation reached.

6.3.2 Documentation to be submitted

The marketing authorisation holder is responsible for ensuring that the dossier is kept up to date throughout the life of the product by way of the variation process (see Chapter 5 of the Notice to Applicants). At the time of introducing an application for renewal, a consolidated version of the file should be submitted according to the requirements set out in [MRFG Guideline on the processing of renewals in the mutual recognition and decentralised procedure](#)¹⁷.

The renewal application should be submitted in EU-CTD format.

6.3.3 Further renewal

In principle, after one renewal, the marketing authorisation is valid indefinitely. In some circumstances, however, the competent authority may decide that an additional 5-year renewal is required based on pharmacovigilance grounds.

Guidelines on processing of Renewals in the Mutual Recognition and Centralised procedures (Notice to applicants/Volume 2C) should also be consulted where appropriate.

6.4 Extension of application

Extensions to marketing authorisations can be made provided that the conditions reflected in Annex II of Regulation (EC) No 1084/2003 are met.

After receiving a marketing authorisation either in the mutual recognition procedure or in the decentralised procedure all follow-ups have to be handled according to the Regulation EC No 1084/2003 on variations. See also Chapter 1 of the Notice to Applicants.

¹⁷ <http://www.hma.eu/>

The coordination group has published recommendations on applications under Annex II of Regulation (EC) N°1084/2003 “Applications under Annex II of Regulation (EC) N° 1084/2003 in mutual recognition procedures Member States recommendations.

6.5 Product index and Assessment Report

The mutual recognition and decentralised procedures are based on the principle that medicinal products are approved or assessed by the reference Member State followed by a 90 days period where the concerned Member State(s) consider the reference Member State assessment report. This assessment report has to be publicly available according to Article 21(4) of Directive 2001/83/EC.

In order to manage the 90 days procedure the Members States operate a tracking system, Communication and Tracking System where reference Member State updates the product information. The reference Member State and concerned Member States update all events during the 90 days period. The coordination group created a European Product Index including all medicinal products going through the mutual recognition procedure and decentralised procedure. The index was launched in 1999 and the particulars (product name, name of marketing authorisation holder, pharmaceutical form, strength, active substance, reference Member State, concerned Member States and type of application) are transferred from the Communication and Tracking System. The maintenance of the index is a decentralised responsibility, which means that the competent authority acting as reference Member State or concerned Member State is responsible for keeping the product index up to date.

The product index and the assessment report are located on the Heads of Agencies website: <http://www.hma.eu>

6.6 Multiple applications

The application for multiple marketing authorisations for an identical medicinal product with a different name by the same or a different marketing authorisation holder is possible.

The coordination group has published recommendations on multiple applications “Recommendations on multiple applications in mutual recognition procedure”.

7. Numbering System for the Procedures for Mutual Recognition and Decentralised Procedure

The numbering system is used for identification of procedures for mutual recognition. Each procedure is therefore characterised by a specific and unique number for unambiguous identification.. The principle of the system is as follows :

- A. The procedure number is allocated by the Reference Member State.

- In case of a change of the Reference Member, a new sequential product number is allocated by the New Reference Member State (for details: <http://www.hma.eu/> - CMD(h) Position on changing the Reference Member State), even in the case the New Reference Member State is the only Member State in the procedure.
- For products which have been harmonised following referrals to the CHMP in accordance with Article 30 or 31(1) of Directive 2001/83/EC, as amended the Marketing Authorisation Holder has to choose a Reference Member State who is responsible for subsequent variations, renewals, repeat-use procedures or extensions procedures (according to Annex II of Commission Regulation (EC) 1084/2003) to the medicinal product (for details: <http://www.hma.eu/> - Recommendation for Mutual recognition procedure after finalisation of an arbitration procedure with a positive opinion by the CHMP and a positive decision by the EU-Commission).

B. The number for a specific procedure is a unique combination of six sections :

CC/D/nnnn/sss/X/vvv

The information in the sections are:

C: the initials (2 digits) of the Reference Member State

AT: Austria	IT: Italy
BE: Belgium	LV: Latvia
BG: Bulgaria	LI: Liechtenstein
CY: Cyprus	LT: Lithuanian
CZ: Czech Republic	LU: Luxemburg
DE: Germany	MT: Malta
DK: Denmark	PL: Poland
EE: Estonia	NL: The Netherlands
EL: Greece	NO: Norway
ES: Spain	PT: Portugal
FI: Finland	RO: Romania
FR: France	SK: Slovak Republic
HU: Hungary	SI: Slovenia
IE: Ireland	SE: Sweden
IS: Iceland	UK: United Kingdom

D: H for Human or V for Veterinary

n: specific number (4 digits) for the actual medicinal product. For products authorised following concertation procedures and transferred to the procedure for mutual recognition the former C number is used. For medicinal products authorised following mutual recognition procedure and decentralised procedures numbers from 100 and above are allocated sequentially.

- s: sequential speciality number. A separate number (3 digits) is allocated to each pharmaceutical form/strength and sequential numbering is used independent of whether the new presentation is a new pharmaceutical form or a new strength or a combination of both. The principle of a sequential speciality number is also applicable to any other extension application as defined in Annex II of Commission Regulation (EC) 1084/2003.
- X: Type of marketing application to the medicinal product :
- > “MR” for applications for marketing authorisation via MRP
 - > “DC” for applications for marketing authorisation via DCP
 - > “IA” for Type IA Notifications
 - > “IB” for Type IB Notifications
 - > “II” for Type II Variations
 - > “R” for Renewals
 - > “E” for Repeat-use Procedures
 - > “O” for data bases when information in this section is not relevant
- v: sequential number (3 digits) for notifications/variations, renewals or repeat-use procedures. The sequential numbering is only applicable to a specific type of procedure (notifications/variations or renewals or repeat-use), thus creating three independent circles of sequential numbers.
- C. In any database the complete number shall be used e.g. DE/H/0268/001/0/000, DE/H/0268/001/IA/075. In written documents sections can be omitted if not relevant and/or zeros indicating not applicable, but reserved positions e.g. DE/H/268/1 or DE/H/268/1/IA/75.
- D. The 4th section is filled in by “001” or “1” and not by “000” or “0” for the first application for a new product even if only one pharmaceutical form/strength is applied for.
- E. Pharmaceutical forms and strengths regarded as extension procedures or any other extension procedure in accordance with Annex II of Commission Regulation (EC) 1084/2003 are identified by the core information on the product included in the first 3 sections of the procedure number and allocated an identifier by a sequential number in the 4th section.
- F. Notifications/Variations of Type IA, IB and II are indicated separately with a IA, IB or a II. However notifications/variations of the three types allocated with identical sequential numbers could easily be mixed and confusion arise. Consequently this situation shall be avoided by allocation of the next available variation number - independent of the type of notification/variation - and not to use independent numbering sequences for the three types of variations (for details: <http://www.hma.eu/> - CMD(h) Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure. Chapter 1 . CMD(h) Best Practice Guide for the allocation of Mutual Recognition Variation Number for Type I Notifications and Type II Variations).

- G. If a variation, renewal or repeat-use procedure covers several presentations (as defined by the speciality number), a specific procedure number should be given for each of them (e.g. pharmaceutical form/strength). However, the same sequential variation, renewal or repeat-use number should be used in section 5 of the procedure number for all e.g. pharmaceutical forms/strengths, which are involved in the same variation or renewal or repeat-use procedure. Even if one variation applies for only one strength, the next one concerning only another strength will receive the next sequential number, in order to avoid confusion. One sequential number should always bear only one title of a variation.
- H. For product information changes not connected to a variation please refer to the specific information given in the draft document “MRFG/CMD(h) Standard Operating Procedure for Article 61(3) changes to patient information amendment under Article 61(3) (not accompanying a variation change)” (<http://www.hma.eu/>)

Annex I**FLOW CHART FOR THE MUTUAL RECOGNITION PROCEDURE**

Approx. 90 days before submission to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure
Day 50	CMSs send their comments to the RMS and applicant
Day 60	Applicant sends the response document to CMSs and RMS
Until Day 68	RMS circulates their assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A break-out session can be organised between day 73 – 80).
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMD secretariat of the EMEA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMS(s) are referred to CMD(h) by the RMS within 7 days after Day 90.
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), the RMS closes the procedure. If consensus is not reached at the level of CMD(h), the RMS refers the matter to CHMP for arbitration
5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and labelling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

Annex II

Flow Chart of the Decentralised Procedure

<u>Pre-procedural Step</u>	
Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day -14	Submission of the dossier to the RMS and CMSs Validation of the application –.
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PrAR), SPC, PL and labelling to the CMSs
Until Day 100	CMSs send their comments to the RMS
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a recommended period of 3 months, which could be extended if justified
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure.
Day 106 - 120	RMS updates PrAR to prepare Draft Assessment Report (DAR) draft SPC, draft labelling and draft PIL to CMSs.
Day 120	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Assessment step II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labelling and draft PIL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
Day 150 (Day 30)	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification and prepare a short report for discussion at Coordination Group
Until Day 205 (Day 85)	Breakout Group of involved Member States reaches consensus on the matter
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SPC, labelling and PIL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement
National step	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, labelling and PIL to CMS and RMS
Day 135/150/180/240	Granting of national marketing authorisation in RMS and CMSs if no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
Day 300	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).

Annex III**Flow Chart 60 Days Coordination group procedure**

<p>– Day 90/210 of MRP/DCP</p>	<p>Notification from disagreeing Member State(s), with a detailed exposition of the reasons for the negative position. This is sent to RMS, CMS(s), CMD(h) Secretariat and the applicant.</p> <p>This duty also applies to MS (s) where the application has been withdrawn in the MRP and DCP (if the withdrawal has been made after the draft documents have been sent by the RMS).</p>
<p>Day 90/120 + max 7</p>	<p>RMS formally initiate the referral by sending the final (latest) assessment report, proposed SPC, labelling and package leaflet and the explanation of the grounds for referral from disagreeing Member State(s) to <u>all</u> CMD(h) members, CMD(h) chair and CMD(h) secretariat. RMS is encouraged to discuss with the applicant before the first CMD meeting.</p> <p>Secretariat to put the item at the CMD(h) agenda.</p> <p>Secretariat and CMD(h) Chair decide on starting date.</p>
<p>Day 0 (not longer than 30 days from Day 90/210)</p>	<p>RMS starts the procedure and distributes a proposal for the list of questions to all Member States.</p>
<p>Around Day 20</p>	<p>CMD(h) meeting 1 – MSs to clarify the reasons for referral and the positions from RMS and CMS.</p> <p>Decide on the list of questions to be sent to the applicant.</p> <p>Agree on recommendation for oral hearing or written procedure.</p> <p>RMS to inform the applicant of decisions made.</p>
<p>Until Day 35</p>	<p>The applicant to send a response document on the list of questions to all CMD(h) members.</p>
<p>Around Day 45</p>	<p>RMS circulates an updated assessment to all CMD(h) members.</p>
<p>Around Day 50</p>	<p>CMD(h) meeting 2 – scientific discussion, possible hearing and decision. Members of CMD(h) should preferably state their view on the response document to all members ahead of the meeting.</p>
<p>Between Day 50 and 60</p>	<p>If agreement the RMS should record the agreement, close the</p>

	<p>procedure and inform the applicant. If no agreement the RMS should immediately inform the EMEA and the applicant and provide a detailed statement of the unresolved issues and the reasons for the disagreement.</p>
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