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NOTICE TO APPLICANTS

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Procedures for marketing authorisation

CHAPTER 3

Union Referral Procedures

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This Chapter 3 Union Referral Procedures will be included in The Rules governing Medicinal Products in the European Union
The Notice to Applicants Volume 2A Procedures for marketing authorisation

CHAPTER 3 Union Referral Procedures

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Legal Basis and Purpose

Union pharmaceutical legislation has created a binding EU mechanism which may be invoked on the basis of the following articles:

1. Article 29 of Directive 2001/83/EC (“Mutual Recognition and Decentralised referral”)
2. Article 30 of Directive 2001/83/EC (“Harmonisation referral”)
3. Article 31 of Directive 2001/83/EC (“Union interest referral”)
4. Article 107i of Directive 2001/83/EC ("Urgent Union procedure")
5. Article 20 of Regulation (EC) 726/2004 ("referral for centrally authorised products only")
6. Article 13 of Commission Regulation (EC) No 1234/2008

Whenever this binding mechanism is invoked, a scientific evaluation of the matter is undertaken by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency’s (EMA) and/or by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. These referrals lead to a Commission decision or a Member States agreement as applicable, to be implemented by all Member States and/or applicants/marketing authorisation holder(s). This leads to a harmonisation at EU level of the changes decided.

Part A of this chapter sets out the details for the above procedures.

The Union pharmaceutical legislation has also created a mechanism by which Member States may refer certain matters to the Committee for Herbal Medicinal Products (HMPC) of the EMA, but which does not lead to a binding Union decision. These situations are foreseen in:

1. Article 16c(1)(c) of Directive 2001/83/EC (“Adequacy of evidence of the long standing use referral”)
2. Article 16c(4) of Directive 2001/83/EC (“Traditional use less than 15 years referral”)

These referrals to the HMPC lead to an opinion. Article 16c(4) referrals may lead to a EU monograph which Member States should take into account.

Part B of this chapter sets out the details for the above procedures.

PART A : REFERRALS UNDER ARTICLES 29, 30, 31, 107i OF DIRECTIVE 2001/83/EC, 20 of Regulation (EC) 726/2004 and 13 of Commission Regulation 1234/2008

1. Introduction

The specific conditions under which a referral procedure may be started and those entitled to initiate such referral differ in each of the cases and are specified in detail in sections 2 to 7.

Under certain, well-defined circumstances (where urgent action to protect public health is necessary) Member States and the Commission may adopt temporary measures whilst waiting for the outcome of a Union referral. These cases are illustrated in section 8.

The procedural elements of the referral procedures to the CHMP or to the PRAC, as applicable, are described in section 9.

Except if stated otherwise, reference to national marketing authorisations, by opposition to central marketing authorisations, covers marketing authorisations which have been granted following a mutual recognition or decentralised procedure and "purely" national marketing authorisation, i.e granted in only one Member State or granted before the MRP/DCP were mandatory. Please note that for traditional herbal medicinal products, as defined in Article 1(29) of Directive 2001/83/EC, the referrals of sections 2 to 4 of this Part A of this Chapter are also applicable and, in this case, the HMPC is the competent Committee, assuming the tasks which are normally carried out by the CHMP (Article 16h(1)(c) of Directive 2001/83/EC).

2. Article 29(4) of Directive 2001/83/EC ("Mutual Recognition and Decentralised referral")

2.1 Basic principles

This referral procedure refers to cases where the Member States involved in a mutual recognition or decentralised procedure fail to reach an agreement within the 60-day period in the coordination group procedure of Article 29(1) to (3) of Directive 2001/83/EC.[1].

The referral must be initiated by the reference Member State, on the grounds of potential serious risk to public health, where no agreement was reached during the coordination group procedure on the assessment report, the summary of product characteristics, or the labelling and the package leaflet, prepared by that reference Member State.

For a description of the coordination group procedure, see Chapter 2, section 5 of the Notice to Applicants.

For the definition of potential serious risk to public health, the Commission has adopted a guideline and annex of examples, available at
http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

2.2 Can the application be withdrawn or the referral be stopped?

It is in the public interest and in the interest of the Union that questions raised on potential serious risks to public health are answered, and that all medicinal products authorised in the EU fulfil the requirements of quality, safety and efficacy.

1 Homeopathic medicinal products subject to the special simplified registration procedure foreseen in Article 14 of Directive 2001/83/EC may not be referred to the CHMP. If agreement within the coordination group procedure is not reached, national authorities are competent to decide on the registration.

An application for mutual recognition of a marketing authorisation or an application in the decentralised procedure may be withdrawn by the applicant(s)/marketing authorisation holder(s) at any time in any Member State.

After a potential serious risk to public health has been raised in accordance with Article 29(1) by a concerned Member State, a withdrawal of the application in some of the Member States will not stop the matter from being discussed within the Coordination Group (CMDh) and, eventually, from a referral procedure being initiated.

The referral can only be stopped if the applicant(s)/marketing authorisation holder(s) withdraw the application/marketing authorisation in all EEA Member States.

2.3 Procedural steps leading to an Article 29 referral

If the Member States do not reach agreement in the coordination group procedure, the reference Member State will refer the matter to the EMA for the application of the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC.

Only a positive assessment by the reference Member State can lead a concerned Member State to raise a potential serious risk concern. Indeed, it is only if the concerned medicinal product would be authorised that it might present a "potential serious risk to public health". Consequently, a negative assessment by the reference Member State cannot be followed up by a referral under Article 29 of Directive 2001/83/EC.

In the referral, the reference Member State shall provide the Agency with a detailed statement of the matter(s) on which the Member States concerned have been unable to reach agreement and the reasons for their disagreement. The matter(s) referred to the EMA must be based on potential serious risk to public health grounds and should be precise. A notification form for a referral to the CHMP/EMA is provided in the Annex to this Chapter. The applicant/marketing authorisation holder is provided with a copy of this information. This detailed statement should focus on the following essential elements:

i. description of the product: the latest available summary of product characteristics, labelling and package leaflet as achieved during the coordination group procedure;

ii. description of the remaining areas of disagreement, giving a clear statement of the issues at referral, including in particular the reasons for disagreement and a proposal for question(s) to be addressed by the applicant/marketing authorisation holder.

In addition, the reference Member State should provide to the EMA a consolidated report addressing the following:

i. description of the scientific discussion during the various stages of the mutual recognition/decentralised procedure between the reference Member State and concerned Member State(s), including a brief summary of the resolution of other major issues between day 0 and day 60 of the coordination group procedure and a summary of the discussions and outcomes of the coordination group procedure;

ii. initial assessment report of the reference Member State and an updated assessment report following the coordination group procedure.

This report will be forwarded to the applicant/marketing authorisation holder at the start of the procedure.

As soon as the applicant/marketing authorisation holder is/are informed that the matter has been referred to the EMA, the applicant/marketing authorisation holder must forward to the EMA a copy of the application submitted to the competent authorities of the Member States concerned, containing the information and documents referred to in Articles 8, 10, 10a, 10b or 10c and 11 of Directive 2001/83/EC.

2.4 Scope of the referral

The CHMP is called upon to issue an opinion on the concerns that, in accordance with the assessment report and product information proposed by the reference Member State, the authorisation of the medicinal product concerned might present a "potential serious risk to public health".

The term 'risk' related to the use of medicinal products is defined in Directive 2001/83/EC, Article 1(28, first indent), as 'any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health'. In addition, on the basis of Article 29(2) of Directive 2001/83/EC, the Commission has adopted a guideline to define a potential serious risk to public health with an annex of examples, available at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

If the CHMP is asked about "potential serious risk to public health" concerns, it may consider aspects subsequently arising during the assessment, necessary to draft the summary of product characteristics, labelling and package leaflet which will be annexed to the opinion of the CHMP and to the decision of the Commission as provided in Articles 32, 33 and 34 of Directive 2001/83/EC.

In the case of a positive outcome of the referral a summary of product characteristics, labelling and the package leaflet will be annexed to the CHMP opinion.

In cases where the assessment of the CHMP is restricted to limited parts of the summary of product characteristics, labelling and package leaflet it will be possible to have in the annex of the opinion only those parts which were subject to amendment during the referral, together with a statement that, for the remaining parts, the summary of product characteristics, labelling and package leaflet are the final versions achieved during the coordination group procedure. It is also possible that the assessment of the CHMP concludes that no modifications of the summary of product characteristics, labelling and package leaflet are needed. In such case, the annex of the opinion shall reflect that conclusion.

However, in situations where the matters referred demand intervention across several sections of the SmPC a full summary of product characteristics, labelling and package leaflet will be annexed to the decision. Even in such cases, the names of the medicinal products, the names of the marketing authorisation holders and the legal supply status may be different between Member States concerned.

2.5 Marketing authorisations before completion of the referral procedure

According to Article 29(6), when there is a failure to reach an agreement within the coordination group procedure, "*Member States that have approved the assessment report, the draft 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. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure*."

The summary of product characteristics, the labelling and the package leaflet to be covered by those marketing authorisations shall be the ones proposed by the reference Member State or,

when these have been subject to amendments agreed within the coordination group procedure, the last version agreed therein.

3. Article 30 of Directive 2001/83/EC ("Harmonisation referral")

3.1 Basic principles

Any Member State, the Commission or the applicant/marketing authorisation holder of a particular medicinal product may initiate a referral if divergent decisions on the authorisation, suspension or revocation of a particular medicinal product have been taken by two or more Member States. The divergences are to be identified, in the notification form, in a sufficiently precise manner.

Article 30 of Directive 2001/83/EC applies to all national marketing authorisations in order to promote harmonisation of these authorisations through the Union.

According to Article 30(2) of Directive 2001/83/EC, "in order to promote harmonisation of authorisations for medicinal products authorised in the Union , Member States each year forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.

The coordination group lays down a list taking into account the proposals from all Member States and forward it to the Commission.

The Commission or a Member State, in agreement with the EMA and taking into account the views of interested parties, would then refer these products to the CHMP.

3.2 Can the referral be stopped?

Once the referral is initiated and the procedure started, the referral can only be stopped if marketing authorisation holder(s) withdraw the concerned marketing authorisations from all Member States. This condition applies regardless of whether the procedure was initiated by the European Commission, a Member State or the marketing authorisation holder.

3.3 Procedural steps leading to an Article 30 referral

The referrer (the Commission, a Member State or applicant/marketing authorisation holder) sends the question to the CHMP for consideration, together with a detailed explanation of the issue(s) raised. A notification form for this referral is provided in the Annex to this Chapter.

The divergences have to be presented and described to support the notification of the referral.

If the referrer is a Member State or the Commission, the applicant/marketing authorisation holder must be informed of the referral.

If the referrer is an applicant/marketing authorisation holder, in advance of initiating a referral under Article 30(1), he is recommended to have a pre-referral meeting with the EMA. Pre-referral meetings are also possible in cases where the referrer is a Member State or the Commission.

Following notification of the referral, the applicant(s)/marketing authorisation holder(s) and the Member States concerned forward to the EMA any information relevant to the referral. In particular, the applicant/ marketing authorisation holder is requested to forward copies of the relevant parts of the dossiers of the national marketing authorisations/applications in the Member States concerned.

3.4 Scope of the referral

The CHMP is called upon to issue an opinion on the area(s) of divergence amongst the national decisions, on the basis of the question(s) referred to it relating to a particular medicinal product.

The scope of the referral is to resolve the divergences between the national decisions, and therefore the referral leads to a full harmonisation of the summary of product characteristics, labelling and package leaflet.

Certain differences may, however, remain, such as names, names of the marketing authorisation holders, legal supply status and certain pharmaceutical particulars (e.g shelf life and storage conditions).

4. Article 31 of Directive 2001/83/EC ("Union interest referral")

4.1 Basic principles

Article 31 provides that Member States, the Commission or the applicant(s)/marketing authorisation holder(s) of the concerned medicinal product must initiate a referral in case where the interests of the Union are involved, and before a decision is taken on an application for a marketing authorisation, or on the suspension, or revocation of a marketing authorisation or on any other variation to the terms of a marketing authorisation which appears necessary.

The term "interest of the Union" refers particularly to the interests of public health related to medicinal products in the Union in the light of quality, safety and efficacy data and to the free movement of products within the Union.

This procedure may, like the Urgent Union procedure, be initiated on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities. However when there is a need for urgent action, the Urgent Union procedure must be initiated, see section 5.

An Article 31 referral may concern:

- a specific medicinal product,
- a range of medicinal products, all containing the same active substance, which is present in several different medicinal products with different names and different marketing authorisation holders;
- or a therapeutic class of medicinal products, (different active substances and medicinal products belonging to the same therapeutic class.), .

When the referral concerns a range of medicinal products or a therapeutic class the EMA may limit the procedure to certain specific parts of the authorisation.

4.2 Can the referral be stopped?

Once the referral is initiated and the procedure started, the referral can only be stopped if applicant(s)/marketing authorisation holder(s) withdraw all the concerned applications/authorisations from all Member States. This condition applies regardless of whether the procedure was initiated by the Commission, a Member State or the marketing authorisation holder.

The adoption of temporary measures by Member States/Commission will not stop the procedure.

4.3 Procedural steps leading to an Article 31 referral

The PRAC is the referred committee in case the referral is initiated on the basis of pharmacovigilance data, otherwise it is the CHMP.

While the Member States, the Commission or the applicant/marketing authorisation holder must, where the interest of the Union are involved, refer the matter to the CHMP/PRAC; it is only the Member State concerned or the Commission which must clearly identify the question. Thus, if the referrer is an applicant/marketing authorisation holder, in advance of initiating a referral under this Article, he must contact a Member State or the Commission with a request to assess and confirm the Union interest before the matter is referred to the relevant Committee/EMA. The applicant/marketing authorisation holder can include in the scope of the referral only its own product, with justification of potential extension to others. A pre-referral meeting with the EMA is recommended.

The referrer (Member State concerned or the Commission) clearly identifies the question which is referred for consideration to the CHMP or to the PRAC (where the referral results from the evaluation of data relating to pharmacovigilance) together with a detailed explanation on how the Union interests are involved. The applicant(s)/marketing authorisation holder(s) is then informed on the issues rose in the referral.

Pre-referral meetings between the applicant/marketing authorisation holder and the EMA are also possible in cases where the referrer is a Member State or the Commission.

Following the start of the referral procedure, the Member States and the applicant(s)/marketing authorisation holder(s) must forward to the relevant Committee all relevant information relating to the medicinal product(s).

A notification form for this referral is provided in the Annex to this Chapter.

4.4 Scope of the referral

4.4.1 Referral relating to a specific medicinal product

The PRAC/CHMP is called upon to issue a recommendation/opinion on a matter involving Union interests, on the basis of the question referred to it.

However, the committee may consider aspects other than those explicitly mentioned in the referral which are necessary to evaluate the medicinal product under consideration and to harmonise the SmPC, labelling and package leaflet to be annexed to the recommendation/opinion, as applicable.

Certain differences may, however, remain, such as names of the medicinal products, names of the marketing authorisation holders, legal status and certain pharmaceutical particulars (e.g shelf life and storage conditions).

4.4.2 'Class' referral

Where the referral concerns a range of medicinal products or a therapeutic class, the EMA may limit the procedure to certain specific parts of the authorisation. If the EMA decides to limit the procedure in this way, only specific sections, or parts of them, of the summary of product characteristics will be harmonised with the corresponding changes to the relevant package leaflet section and labelling.

A class referral covers all medicinal products concerned by the matter (products authorised nationally and centrally).

However, in case the matter referred concerns only centrally authorised medicinal products, then a referral procedure will be initiated in accordance with Article 20 of Regulation (EC) 726/2004 (see section 7).

5. Article 107i of Directive 2001/83/EC ('Urgent Union procedure')

5.1 Basic principles

This procedure should be initiated when there is a need to take urgent action regarding concerns resulting from the evaluation of data from pharmacovigilance activities. The PRAC is therefore the referred committee

This procedure must be initiated automatically when a Member State or the Commission:

- considers suspending or revoking a marketing authorisation;
- considers prohibiting the supply of a medicinal product;
- considers refusing the renewal of a marketing authorisation;
- is informed by the marketing authorisation holder that, on basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or that he intends to do so or has not applied for the renewal of a marketing authorisation.

In cases when a contraindication, a reduction in the recommended dose or a restriction in the indication of a medicinal product is considered necessary, a Member State or the Commission must when urgent action is considered necessary, initiate the referral procedure. Otherwise, they must inform the other Member States, the EMA and the Commission, as appropriate. This information must cover not only the action considered but also of the reasons for such an action.

When the medicinal products concerned are authorised in more than one Member States, through national marketing authorisations the case is brought to the attention of the coordination group. Where this group did not conclude on the matter, the Union interest procedure (Article 31) would be applicable when the interests of the Union are involved.

5.2 Can the procedure be stopped?

Once the referral is initiated and the procedure started, it can only be stopped if all marketing authorisation holder(s) withdraw the concerned marketing authorisations in all Member States.

The adoption of temporary measures by Member States/Commission will not stop the procedure.

5.3 Procedural steps leading to an Article 107i procedure

A Member State or the Commission, as appropriate, must initiate the procedure laid down in Article 107i. A notification form for this procedure is in the annex to this Chapter.

The PRAC is the referred committee in this procedure.

5.4 Scope of the referral

The initiator of the procedure (Member State concerned or the Commission) must inform the other Member States, the EMA and the Commission on the safety concern(s) supporting the urgent action and regulatory action(s) considered.

The scope of the procedure will be extended as appropriate, if EMA identifies that:

- the safety concern relates to other medicinal product(s) in addition to the one covered by the notification,
- the safety concern is common to all products belonging to the same range or therapeutic class;
- the medicinal product(s) covered by the notification is authorised in more than one Member State.

When the medicinal product(s) concerned is authorised:

- in only one Member State, the safety concern will be addressed by the concerned Member State at national level without the initiation of an Urgent Union procedure.
- only at central level, then a referral procedure will be initiated in accordance with Article 20 of Regulation (EC) 726/2004 (see section 6).

6. Article 20 of Regulation (EC) 726/2004 ('referral of centrally authorised products')

6.1 Basic principles

This procedure covers any concerns detailed in section 6.3 relating to only centrally authorised medicinal products. It is initiated by the Commission, requesting the opinion of the EMA.

6.2 Can the procedure be stopped?

Following the start of the procedure, this procedure can be stopped if the marketing authorisation holder(s) withdraw all the central marketing authorisation(s) concerned.

The adoption of temporary measures by Member States/Commission will not stop the procedure.

6.3 Procedural steps leading to an Article 20 procedure

The Commission will initiate the referral in case a Member State or the Commission considers that:

- a manufacturer or an importer does not fulfilled its obligations laid down in Title IV (manufacture and importation) of Directive 2001/83/EC,
- the measures envisaged under titles IX (pharmacovigilance) and XI (supervision and sanctions) of Directive 2001/83/EC must be applied,
- or the CHMP has delivered an opinion in that effect on the basis of Article 5 of Regulation 726/2004.

The Commission, in view of the urgency, determines the time limit within which the committee must deliver its opinion. The CHMP is the referred committee; however in case the procedure is initiated as the result of the evaluation of data relating to pharmacovigilance, the CHMP opinion must be adopted on the basis of a PRAC recommendation following the procedure described in section 9.

A notification form for this referral is provided in the Annex to this Chapter.

Following the start of the referral's procedure, the applicant(s)/marketing authorisation holder(s) forwards to the EMA all relevant information relating to the medicinal product(s).

6.4 Scope of the procedure

An article 20 procedure is initiated when the matter referred concerns only centrally authorised medicinal products. It can concern:

- a range of centrally authorised medicinal products, all containing the same active substance, which is present in several different medicinal products with different names and different marketing authorisation holders;
- a therapeutic class of centrally authorised medicinal products, several active substances concerned and medicinal products belonging to the same therapeutic class.

In case the matter referred resulting from the evaluation of data relating to pharmacovigilance concerns a range or a therapeutic class involving also nationally authorised medicinal products, the procedure under Article 20 will not run and only the procedure under Article 31 or 107i of Directive 20001/83/EC, as appropriate, will be processed.

7. Article 13 of Commission Regulation (EC) No 1234/2008

7.1 Basic principles

This referral may be initiated by Member States in respect of medicinal products which have been granted a national marketing authorisation

If a Member State, on grounds of potential serious risk to public health, cannot:

- Recognise the decision[2] on a major variation of Type II within 30 days, by reference to Article 10(4) of Commission Regulation (EC) No 1234/2008 or;

- Approve an opinion on a worksharing procedure within 30 days, by reference to Article 20(8) of Commission Regulation (EC) No 1234/2008.

It should refer the matter of disagreement to the CMDh, in accordance with Article 13 of Commission Regulation (EC) No 1234/2008 and the procedure under article 29(3), (4) and (5) of Directive 2001/83/EC applies.

If the Member States fail to reach an agreement within the 60-day period in the CMDh, a referral by reference to Article 13 of Commission Regulation (EC) No 1234/2008 will be initiated by the Reference Member State on grounds of potential serious risk to public health.

2 Only a positive assessment by the reference Member State can lead a concerned Member State to raise a potential serious risk concern. Indeed, it is only if the concerned medicinal product would be authorised that it might present a "potential serious risk to public health".

The term 'risk' related to the use of medicinal products' is defined in Directive 2001/83/EC, Article 1(28), as 'any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health'. In addition, on the basis of Article 29(2) of Directive 2001/83/EC, the Commission has adopted a guideline to define a potential serious risk to public health, available at with an annex of examples:

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

7.2 Can the variation application be withdrawn or the referral be stopped?

After a potential serious risk to public health has been raised in accordance with Article 13 of Commission Regulation (EC) No 1234/2008 by a concerned Member State, a withdrawal of the application in some of the Member States will not stop the matter from being discussed within the CMDh and, eventually, from a referral procedure being started.

The referral can only be stopped if the marketing authorisation holder(s) withdraw the variation applications in all Member States.

7.3 Procedural steps leading to an Article 13 referral

The procedural steps of Article 29 referral apply.

7.4 Scope of the referral

As provided for in Article 13(2) of Commission Regulation (EC) No 1234/2008, the procedure referred to in Article 29 of Directive 2001/83/EC (i.e. the procedure for referral to CHMP) applies where it has not been possible to achieve agreement under the mutual recognition procedure for a major variation of type II or a worksharing procedure of marketing authorisation(s).

The CHMP should limit its opinion to the question referred. Within the scope of the referral, the CHMP may nevertheless consider aspects subsequently arising during the assessment, which may affect the SmPC, labelling and package leaflet which will be annexed to the opinion of the CHMP and to the decision of the Commission as provided in Articles 32, 33 and 34 of Directive 2001/83/EC.

Only those parts of the SmPC, labelling and package leaflet which were subject to the variation and/or amendments during the referral will be annexed to the CHMP opinion and to the decision of the Commission.

However, in situations where the matters referred demand intervention across several sections of the SmPC, for clarity purpose, a full summary of product characteristics, labelling and package leaflet may be annexed to the decision. Even in such cases, the names of the medicinal products, the names of the marketing authorisation holder(s), the legal supply status and certain pharmaceutical particulars (e.g shelf life and storage conditions) may be different between Member States concerned.

8. Temporary Measures

EU pharmaceutical legislation enables the Member States and/or the Commission to take temporary measures, at any stage of the procedure, in exceptional cases, where urgent action is necessary to protect public health and until a definitive decision is adopted at EU level through the adequate referral procedure previously described.

8.1 In the context of Articles 31 and 107i procedure (nationally and centrally authorised medicinal products)

A Member State may, at any stage of the procedure where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product on its territory until a definitive decision is adopted.

In cases where the procedure includes centrally authorised medicinal product(s), the Commission may, at any stage of the procedure where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product until a definitive decision is adopted.

In any case, the Member States, the Commission and the EMA must be informed by the Member State or the Commission of the reason for their action no later than the following working day.

In addition, in the context of the procedure under Article 107i of Directive 2001/83/EC, the Commission may request Member States in which the medicinal product is authorised to take temporary measures.

8.2 In the context of an Article 20 procedure (centrally authorised medicinal products)

When urgent action is essential to protect human health or the environment, a Member State may, on its own initiative or at the of the Commission's request, suspend the use on its territory of a centrally authorised medicinal product.

When it does so, on its own initiative, the Member State must inform the Commission and the EMA of the reasons for its action at the latest on the next working day following the suspension. The EMA must inform the other Member States.

The Commission will initiate the Article 20 procedure, if not already pending.

9. General procedural elements

If the matter supporting the referral results from the evaluation of data resulting from pharmacovigilance activities, the PRAC is the referred committee. The recommendation will be forwarded to:

- The CHMP, when at least one centrally authorised product is involved. The CHMP will then adopt an opinion which will be the basis for the Commission decision;
- The CMDh, when only nationally authorised medicinal products are involved. The CMDh will either reach agreement by consensus or will adopt a majority position that will be forwarded to the Commission for decision.

In other cases, the referred committee is the CHMP whose opinion will be the basis for the Commission decision.

Notwithstanding the legal provisions described above, it is suggested to carry out some preliminary procedural steps in order to streamline the operation of the EU referral procedures.

In advance of initiating a referral, it is strongly encouraged to send to the EMA:

- A draft notification including a clear and concise identification of the concern to be referred to the CHMP/PRAC, indicating the medicinal product(s), active substance(s), pharmaceutical form(s) and/or strength(s), route of administration, applicant(s)/ marketing authorisation holder(s) concerned;

- Scientific documentation (scientific information that is available at the time the referral is triggered) in support of the referral;

- Where appropriate, request for a meeting with the EMA to discuss regulatory and procedural issues linked to the referral.

When an issue is referred to the CHMP/PRAC, each Member State is asked to make available to the EMA before the end of the first committee meeting following the notification for the referral a list of the names of the medicinal product(s) affected by the referral (including pending applications), together with information on the respective applicant(s)/marketing authorisation holder(s), strength(s), pharmaceutical form(s) and route(s) of administration.

In the case of Article 29 referrals initiated in the frame of a repeat use mutual recognition procedure, the list of the names of the medicinal product affected by the referral shall also include those authorised by the previous mutual recognition procedure(s).

In the case of referrals initiated by (an) applicant(s)/marketing authorisation holder(s), the referral should be accompanied by expert reports/overviews which have been updated to include data supporting the reasons for referral. In addition the applicant(s)/marketing authorisation holder(s) should ensure that all available information relating to the matter in question is forwarded to the CHMP/PRAC members, the competent authorities of the Member States and the EMA.

To ensure a smooth implementation of the above-mentioned requirements, the EMA will inform the applicant(s)/marketing authorisation holder(s) for each initiated referral on the documentation needed as well as on the number of copies to be sent to the Rapporteur, the Co-Rapporteur and other committees members, as appropriate.

For Article 30(1) and Article 31 referrals initiated by the applicant(s)/marketing authorisation holder(s), the EMA will inform the applicant(s)/marketing authorisation holder(s) of the appropriate fee to be paid.

9.1 Organisation of work within the CHMP, PRAC and EMA secretariat

The CHMP/PRAC appoints rapporteur and co-rapporteur(s).

Once the appointments have been made, the EMA informs the applicant(s)/marketing authorisation holder(s).

For the procedures which may involve medicinal products authorised nationally and centrally, the PRAC appointed rapporteur must closely collaborate with the rapporteur appointed by the CHMP (for centrally authorised medicinal products) and by the Member State(s) with leading role (for nationally authorised medicinal products).

The CHMP/PRAC may also consult individual experts to advise it on specific questions. When it does so, the committee defines their tasks and specifies the time limit for the completion of these tasks.

For referrals initiated by a Member State or by the Commission, at the first CHMP/PRAC meeting following the initiation of the referral, the CHMP/PRAC formulates the question(s) to be addressed to the applicant(s)/marketing authorisation holder(s) and discusses the scope of the documentation actually requested or needed.

For referrals initiated by the applicant(s)/marketing authorisation holder(s), at the first CHMP/PRAC meeting following the initiation of the referral, the committee starts its assessment of the issues referred. A list of questions may be adopted at day 30 of the procedure.

When a referral on the basis an Article 107i, 31 or 20 on grounds of pharmacovigilance is initiated the EMA publically announces it by means of the European medicines-portal[3]. The announcement specifies the matter submitted, medicinal products and active substances concerned. It also informs on the questions of the PRAC to be addressed to the marketing authorisation holders, healthcare professionals and the public information stating how relevant information can be submitted.

The committee may also take into account any other information at its disposal which relates to the quality, safety and efficacy, as appropriate, of the medicinal product(s) concerned and which may help in arriving at its opinion.

It should be stressed that all members of the committee are equally concerned by the question submitted in the matter referred to the committee. They take part in the evaluation procedure and the adoption of opinion/recommendation independently of the Member State, which has designated the CHMP/PRAC member, and of the situation of the medicinal product in the Member States.

9.2 Hearing of the applicant(s)/marketing authorisation holder(s)/ the public/

Before issuing its opinion/recommendation, the CHMP/PRAC provides the applicant(s)/marketing authorisation holder(s) with an opportunity to present written or oral explanations. As a general principle the oral explanation is based on data that was submitted in advanced and assessed by the committee.

In case the PRAC is the referred committee and where the urgency of the matter permits, public hearings may be held, where PRAC considers it is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern.

The announcement of the public hearing will be made on the European medicines web-portal[4] and will specify the modalities of participation.

If a marketing authorisation holder or another person intends to submit information that has confidential data relevant for the matter under assessment, it can request permission to present that data to the PRAC in a non-public hearing.

9.3 Timetable

The standard timetable for assessment by the CHMP/PRAC after notification of the referral is 60 days of the date the matter was referred to it.

3 This web-portal is hosted by EMA website.

4 This web-portal is hosted by EMA website.

For Article 30 and Article 31 referrals, the CHMP may extend that period to 150 days, taking into account the views of the applicant(s)/marketing authorisation holder(s).

In case of Article 31 procedure resulting from pharmacovigilance data, the PRAC may extend that period to 150 days. In case of Article 107i procedure, the PRAC will make a recommendation within 60 calendar days of the receipt of the information. For all referrals, in case of urgency, on a proposal from its Chairperson, the CHMP/PRAC may agree on a shorter deadline.

The time points provided within the referral timetable below are given as the key steps in the referral procedure. They can be altered in order to reflect the particularities of a referral.

The time points refer to active days, i.e. correspond to the real time the CHMP/PRAC takes to assess the data provided. The CHMP/PRAC will not exceed the overall timeframe provided in the legislation.

The CHMP/PRAC may, however, suspend the time limit of 60/150 days (clock-stop) in order to allow the applicant(s)/marketing authorisation holder(s) to prepare the responses to CHMP/PRAC List of Questions, List of Outstanding Issues or an oral explanation (as appropriate).

9.3.1 Timetable for referral procedures under Articles 29(4), 30, 31 of Directive 2001/83/EC and Article 20 of regulation (EC) No 726/2004

Referral initiated by a Member State or the Commission - **Timetable for the procedure**

Day 0	Notification of a referral to the CHMP/PRAC/EMA Secretariat
Day 1	First meeting of the CHMP/PRAC following notification of referral. The CHMP/PRAC discusses the question(s) referred during the plenary meeting. Rapporteur/(Co)-Rapporteur appointed/confirmed, as applicable
	Adoption of List of questions to be addressed by the MAHs/ applicant(s) and timetable
Clock stop	For the MAHs/applicant(s) to answer CHMP/PRAC List of questions
Clock re-start (day 2)	Following submission of responses (in accordance with published submission dates) (and if applicable including English SPC, Labelling and PL)
Day 20	Rapporteur and Co-Rapporteur(s) circulate their report on the written responses from the applicant(s)/Marketing Authorisation Holder(s)in parallel , if applicable, with the draft SmPC/Labelling/PL to be annexed to the opinion
Day 25	Comments from CHMP/PRAC members on the (Co-)Rapporteur(s) assessment report(s) and draft SmPC/Labelling/PL (if applicable)

Day 30	Discussion at the CHMP/PRAC: Adoption of the CHMP Opinion/PRAC recommendation, or Adoption of List of outstanding issues to be answered by the applicant(s)/MAH(s) in writing and/or in oral explanation and timetable for the rest of the procedure
Clock stop	If necessary, for the applicant(s)/MAH(s) for the preparation and submission of written and/or oral explanations
Clock re-start	If necessary, following the submission of written explanations (in accordance with the published submission dates) and/or at the time of oral explanations
Day 60	Adoption of the CHMP opinion or PRAC recommendation (with annexes as provided in Article 32 of Directive 2001/83/EC)

Referral initiated by the applicant(s)/marketing authorisation holder(s) - **Timetable for the procedure**

As in principle there is no "list of questions" at day 1 of the procedure, the timetable is as follows:

Day 0	Notification of a referral to the CHMP/PRAC/EMA Secretariat
Day 1	CHMP/PRAC meeting following notification of referral and provided relevant documentation has been submitted by the MAH/Applicant in advance of the start of the procedure. The CHMP/PRAC discusses the question(s) referred during the plenary meeting. Rapporteur/(Co)-Rapporteur appointed/confirmed. Adoption of the timetable. No adoption of List of questions.
Day 20	Rapporteur and Co-Rapporteur(s) circulate assessment reports on the data provided from the MAH(s)/applicant(s) and, if applicable, comments on the proposed SmPC/Labelling/PL
Day 25	Comments from CHMP/PRAC members on the (Co-)Rapporteur(s) assessment reports and draft SmPC/Labelling/PL (if applicable)
Day 30	Discussion at the CHMP/PRAC: Adoption of the CHMP Opinion/PRAC recommendation, or Adoption of CHMP List of questions to be answered by the applicant(s)/MAH(s) in writing and/or in oral explanation and timetable for the rest of the procedure.
Clock stop	If necessary, for the preparation and submission of written and/or oral explanations
Clock re-start	If necessary, following the submission of written explanations (in accordance with the published submission dates) and/or at the time of oral explanations
Day 60	Adoption of the CHMP opinion/PRAC recommendation (with annexes as provided in Article 32 of Directive 2001/83/EC)

9.3.2 Timetable for an Article 107i urgent Union procedure

Referral initiated by a Member State or the Commission. The PRAC has 60 days maximum time limit to issue a recommendation. The timelines following a 60 days assessment period are:

Day 1	Assessment starts on the next PRAC meeting following submission of all data (corresponds to the 2nd PRAC meeting following the receipt of notification initiating the procedure);
Day 20	Rapporteur and Co-Rapporteur(s) circulate assessment reports on the data collected;
Day 35	Comments in writing by PRAC members, CHMP concerned Rapporteurs (if centrally authorised products concerned by the procedure), CMDh member (if applicable);
Day 45	PRAC Rapporteur(s) circulate an updated assessment report(s) based on the comments received and reflecting any additional information received (if applicable);
Day 60	Adoption of the PRAC recommendation (with conclusion as provided in Article 107j (3) of Directive 2001/83/EC)

Additional procedural steps within the same timeframe (i.e. maximum of 60 days) may be necessary before the PRAC issues a recommendation. This applies in case of oral explanation(s) by the concerned marketing authorisation holders, public (and non-public) hearings or in case the PRAC requires input from a scientific advisory group (SAG) or from an ad-hoc expert meeting to support the PRAC recommendation.

The above timelines are provided for guidance purposes only. The PRAC may agree on a shorter timetable if required by the urgency of the issue.

9.4 Re-examination mechanism

The re-examination mechanism is provided by Article 32(4) of Directive 2001/83/EC and it is not foreseen in the case of Articles 20 and 107i procedures.

The opinion of the CHMP/ recommendation of the PRAC may have implications for the applicant(s)/marketing authorisation holder(s), i.e., where the CHMP/PRAC finds, as appropriate, that:

- The application does not satisfy the criteria for authorisation, or
- The summary of the product characteristics proposed by the applicant(s)/ marketing authorisation holder(s) in accordance with Article 11 of Directive 2001/83/EC should be amended, or

- The authorisation should be granted subject to conditions, considered essential for the safe and effective use of the medicinal product including pharmacovigilance, or

- The marketing authorisation should be suspended, varied or revoked.

Once the opinion of the CHMP or the recommendation of the PRAC is adopted, the EMA informs the applicant(s)/ marketing authorisation holder(s).

Within 15 days of the receipt of the opinion/recommendation, the applicant(s)/marketing authorisation holder(s) may notify EMA in writing of his/their intention to request a re-examination of the opinion/recommendation. In that case, he/they forward the detailed grounds for the request to the EMA within 60 days after receipt of the opinion/recommendation. In case these deadlines are not respected, the request for re-examination is considered inadmissible and the opinion/recommendation becomes final.

The re-examination procedure can only deal with the points of the opinion/recommendation initially identified by the applicant in its request for re-examination and may be based only on the scientific data available when the CHMP/PRAC adopted the initial opinion/recommendation. Therefore no new data can be submitted and considered.

Within 60 days from receipt of the detailed grounds for the request, the CHMP/PRAC must re-examine its opinion/recommendation. In order to do so, it will appoint a new rapporteur and, where necessary, a new co-rapporteur different from those appointed for the initial opinion. The rapporteur (and co-rapporteur where appropriate) is responsible for making an assessment of the detailed grounds for re-examination. Each of the grounds for re-examination should be dealt with separately and a reasoned conclusion on all relevant points must be included in the assessment report.

The conclusions of the re-examination are an integral part of the evaluation and are therefore integrated within the final assessment report appended to the final opinion/recommendation and reflected in scientific conclusions.

If no request for re-examination is notified in writing to the EMA within 15 days of receipt of the opinion/recommendation by the applicant(s)/marketing authorisation holder(s), the opinion/recommendation automatically becomes a final opinion/recommendation.

9.5 Final recommendation/opinion

9.5.1 PRAC recommendation

The PRAC makes a recommendation on referral procedures initiated on safety concerns following evaluation of data resulting from pharmacovigilance activities in accordance with Articles 31, 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004. The recommendation of the PRAC states the reasons on which it is based. The recommendation will include one or a combination of the following conclusions:

(a) no further evaluation or action is required at Union level;

(b) the marketing authorisation holder should conduct further evaluation of data together with the follow-up of the results of that evaluation;

(c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;

(d) the Member States or marketing authorisation holder should implement risk minimisation measures; the recommendation of the PRAC will specify the risk

minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject to;

(e) the marketing authorisation should be suspended, revoked or not renewed;

(f) the marketing authorisation should be varied. Where it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation will suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording will be placed.

Whenever possible the PRAC recommendations are adopted by consensus. In the event of adoption by majority, the divergent positions of PRAC members and the grounds on which they are based will be reflected in the recommendation issued by the PRAC and transmitted to the relevant Committee/CoordinationGroup/MAH(s), as appropriate.

The (final) PRAC recommendation is sent to :

- the CHMP for adoption of an opinion where at least one centrally authorised product is included in the procedure;
- the Coordination Group (CMDh) where solely nationally authorised products are included in the procedure, to reach an agreement (consensus) or a position (by majority).

9.5.2 CHMP Opinion

The CHMP adopts an opinion in cases of:

- referral procedures initiated in accordance with Articles 20 of Regulation (EC) No 726/2004, 29, 30 or 31 of Directive 2001/83/EC;
- referral procedures initiated on safety concerns following evaluation of data resulting from pharmacovigilance activities in accordance with Articles 20 of Regulation (EC) No 726/2004, 31 or 107i of Directive 2001/83/EC when at least one centrally authorised medicinal product is concerned.

Within 15 days of the adoption of the final opinion of the CHMP, the EMA forwards it to the Member States, the Commission and the applicant(s)/marketing authorisation holder(s) together with a report describing the assessment of the referral concerning the medicinal product(s) and stating the reasons for its conclusions.

In the event of an opinion in favour of granting, maintaining or varying a marketing authorisation for the medicinal product concerned, in accordance with Article 32(5) of Directive 2001/83/EC, the following documents are annexed to the opinion:

- **for nationally authorised products:**

i. Draft summary of the product characteristics or proposed changes to part of the summary of the products characteristics, as appropriate;

ii. Any conditions affecting the authorisation considered essential for the safe and effective use of the medicinal product including pharmacovigilance, if applicable;

iii. Details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product, if applicable;

iv. The proposed text of the labelling and package leaflet or proposed change to part of the text of the labelling and package leaflet, as appropriate.

In addition, a list of the medicinal products and marketing authorisation holders concerned by the procedure and the scientific conclusions justifying the outcome of the referral are attached to the opinion.

- **for centrally authorised products:**

i. Draft summary of the product characteristics;

ii. Any conditions affecting the authorisation considered essential for the safe and effective use of the medicinal product including pharmacovigilance, if applicable;

iii. Details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product, if applicable;

iv. The proposed text of the labelling and package leaflet.

In addition, a list of all presentations of medicinal products concerned by the procedure and the scientific conclusions justifying the outcome of the referral are attached to the opinion.

In the event of a CHMP opinion, based or not on a PRAC recommendation, recommending the suspension, revocation or non-renewal of the marketing authorisation(s) for the medicinal product concerned, the 'scientific conclusions with the grounds and conditions, as applicable are annexed to the opinion.

In case the CHMP bases its opinion on the PRAC recommendation and differs from it, a detailed explanation of the scientific grounds for the differences together with the recommendation is attached to the CHMP opinion. Any divergent positions of the CHMP members are also attached to the final CHMP Opinion.

The final assessment conclusions are published on the European medicines web-portal[5].

10. Regulatory decision at EU level

10.1 CMDh agreement/position

In case of Article 31 referral on basis of pharmacovigilance data and Article 107i referral of Directive 2001/83/EC, the PRAC recommendation is forwarded to the coordination group when the referral procedure does not include centrally authorised medicinal products.

The PRAC recommendation must be considered within 30 days of its receipt by the CMDh. In case of Article 31 procedure, where a re-examination may be requested, the PRAC recommendations will be transmitted to CMDh after the expiry of 15 days after the PRAC

5 This web-portal is hosted by EMA website.

recommendation has been received by the marketing authorisation holder(s), the legal deadline for a request for re-examination.

The CMDh will consider the assessment report and recommendation and will reach an agreement/position on the maintenance, variation, suspension or revocation or refusal of the renewal of the marketing authorisation(s) concerned.

Where the agreement or the position reached by majority of the CMDh differs from the recommendation of the PRAC, a detailed explanation of the scientific grounds for the differences together with the recommendation is attached to the agreement or to the position.

The CMDh endeavours to reach an agreement by consensus. If this cannot be obtained its position is adopted by majority of its members.

The followings are attached to the agreement/ position:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable;
- in the case of a CMDh position to vary the marketing authorisation(s), an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information, as applicable. This annex also includes timelines for implementation by the marketing authorisation holder to submit a variation;
- in the case of a CMDh position to suspend, revoke or not renew the marketing authorisation(s), the overall scientific conclusions together with the grounds and conditions as applicable. This annex also includes timelines for implementation by the competent authorities in Member States;
- divergent position(s) for the CMDh members, where applicable.
- the national translations of the agreed wording to change the product information, as applicable;

The CMDh position and the above mentioned attachments are published on the European medicines web-portal[6].

If the CMDh reaches an agreement by consensus:

The agreement including the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting. The CMDh agreement and its appendices are sent to the marketing authorisation holder(s) and competent authorities of the Member States.

Further to receipt of the CMDh agreement stating that regulatory action to the concerned marketing authorisation is necessary, the competent authorities of the Member States must adopt necessary measures to vary, suspend, revoke or not renew the marketing authorisation(s) concerned in accordance with the timetable for implementation determined in the agreed position.

6 This web-portal is hosted by EMA website.

When the agreement of the CMDh is that the terms of the marketing authorisation must be varied, the marketing authorisation holder(s) must submit the relevant variation to that effect within the timetable for implementation as appended to the agreed position.

If the CMDh reached a majority position:

The majority position on the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting. The majority position of the CMDh together with its attachments is forwarded to the Commission, to the competent authorities in Member States and to marketing authorisation holders.

10.2 Commission decision

The Commission starts the Union decision-making procedure when receiving:

- The CHMP opinion in case of:
  - referral procedures initiated in accordance with Articles 20 of Regulation (EC) No 726/2004, 29, 30 or 31 of Directive 2001/83/EC;
  - referrals procedures initiated on safety concerns following evaluation of data resulting from pharmacovigilance activities in accordance with Articles 20 of Regulation (EC) No 726/2004, 31 or Article 107i of Directive 2001/83/EC when at least one centrally authorised medicinal product is concerned;
- The CMDh position by majority.

For nationally authorised medicinal products, the Commission decision is addressed to Member States. The information about decision will be reported for information to the applicant(s)/marketing authorisation holder(s). The Member States are required to either grant, maintain, suspend, or withdraw/revoke the marketing authorisation, or vary the terms of the marketing authorisation as necessary to comply with the decision within 30 days of its notification and are required to inform the Commission and the Agency of the measures taken.

For centrally authorised medicinal products, the Commission decision is addressed to applicant(s)/the marketing authorisation holder(s) and implements directly the changes to the product information required. In case of conditions or restrictions as provided in Article 9(4) points c, ca, cb or cc of Regulation (EC) No 724/2004, the Commission may adopt another decision addressed to the Member States for the implementation of those conditions or restrictions.

When the Commission decision provides for granting, varying or maintaining a marketing authorisation, the documents annexed to the decision are: the summary of product characteristics, the text of the labelling and package leaflet, the scientific conclusions and, as the case may be, any condition affecting the authorisation considered essential for the safe and effective use of the medicinal product including pharmacovigilance, and any conditions or restrictions with regard to the safe and effective use of the medicinal product. In addition when the decision concerned nationally authorised medicinal products, is annexed the list of the names, pharmaceutical forms, strengths and routes of administration of these nationally authorised medicinal product(s) and their applicants/marketing authorisation holders in the Member States.

When the Commission decision provides for the suspension of the marketing authorisation, the conditions for the lifting of the suspension will also be annexed.

11. Consequences of a referral

Member States national requirements for the implementation of a referral decision, as well as details on the national procedure(s) to be followed to the Commission decision are included in CMDh and EMA relevant websites.

11.1 Actions to be taken by the Member States after a referral

Commission decisions/CMDh agreement following a Union referral procedure are addressed to all Member States.

Commission decisions taken following a Union referral request Member States directly concerned by the referral procedure to comply with the Commission decision within 30 days of its notification and to inform the Commission and the Agency.

The marketing authorisation holder is urged to take appropriate steps necessary to allow the Member States to comply with the Commission decision..

In case of CMDh agreement, the marketing authorisation holders have to take appropriate steps necessary to comply with the CMDh agreement within the timeline fixed.

All Member States must consider whether any action is appropriate as regards products authorised by them and should take the decision into account in any future regulatory action.

In the case of a subsequent application for the same medicinal product, the evaluation must take into account the Commission decision/CMDh agreement and Member States should grant or refuse the national marketing authorisations according to the terms of the Commission decision/CMDh agreement unless there are issues which have not been previously considered. Any Member State or the Commission, as appropriate, would refer the new scientific issue in order to start a new referral procedure.

The same applies in case where a marketing authorisation is pending for the medicinal product, which was the subject of the referral. The Member States must grant or refuse national marketing authorisations in accordance with the Commission decision/CMDh agreement.

11.2 Independent applications for marketing authorisation submitted during a referral procedure

While a referral procedure is ongoing, independent applications for marketing authorisation concerning medicinal products with the same active substance(s) can be submitted. For instance, if an Article 30 referral concerns the “originator” medicinal product, applications for “generic” medicinal products of this “originator” medicinal product may be submitted.

However, where independent applications for products with the same active substance are submitted once a referral is ongoing, Member States should consider the outcome of the referral as far as it may be relevant for the assessment of such applications.

The same occurs in the frame of Article 31 “class” referrals, if applications for marketing authorisations of medicinal products of the same class or range are submitted.

Applications for variations can be submitted and ongoing procedures can be finalised, even if the medicinal product is involved in a referral. However, when a referral procedure based on

Article 29 is ongoing it is recommended that no new variation procedure is started for the medicinal product concerned, unless it relates to public health matters.

11.3 Subsequent applications occurring after finalisation of the referral

Subsequent applications for a specific medicinal product which has been the subject of a referral must use the harmonisation achieved following the referral. After Articles 29, 30 and 31 referrals subsequent applications for the same medicinal product must be submitted through the mutual recognition or decentralised procedure and must be mutually recognised in accordance with the relevant Commission decisions unless a new referral is initiated with respect to a new potential serious risk to public health. In accordance with Articles 8(3)(l) and 18 of Directive 2001/83/EC and Commission Communication C98/229/03, the mutual recognition procedure will also apply if the same company, or a company from the same group of companies, applies for a separate marketing authorisation for the product, regardless of whether the product has been the subject of full harmonisation.

However with regard to the Article 30(1) and Article 31 referrals there are some particularities that should be noted.

Where the referral leads to harmonisation (with the exception of partial harmonisation, as explained in section 4.4.2), the mutual recognition procedure has to be followed afterwards, in order to maintain the achieved harmonisation.

Where the procedure is limited to certain specific parts of the authorisation, the obligation to follow a mutual recognition procedure only applies if the marketing authorisations were granted initially by the decentralised or mutual recognition procedure. In this case, the marketing authorisations granted through "purely" national procedures stay national. Nevertheless it is the responsibility of the marketing authorisation holder and the Member State to keep the level of harmonisation reached by the referral procedure.

In case of an Article 31(2) referral, there may be a large number of products. In this case, different Reference Member States can be chosen for different medicinal products but the harmonisation should be maintained.

In the case of Article 30 or Article 31 referrals and where there is no reference Member State, the applicant(s)/marketing authorisation holder(s) must choose the reference Member State for the follow up of the procedure.

11.4 Follow-up of European Commission referral decisions

The follow-up of the measures imposed into the Commission decision following a referral procedure will be undertaken either at national or centralised level.

Where the follow-up condition is subject to a specific requirement laid down in the legislation, it should be followed, as for example for procedure for non-interventional safety studies post-authorisation involving the PRAC, as laid down by Article 107n to q of Directive 2001/83/EC.

As a general principle, the follow-up of a Commission decision following a referral procedure involving nationally authorised medicinal products will be undertaken by the Member States. The adoption of the referral decision concludes the referral procedure. It will normally be for the authorising national competent authorities to implement any conditions imposed on the marketing authorisation and to perform any subsequent assessments that may be necessary. If

this eventually leads to divergences amongst Member States, a new referral procedure would have to be initiated.

However, exceptionally, a referral decision may explicitly foresee further action to be taken at EU level.

PART B : REFERRALS UNDER ARTICLE 16C OF DIRECTIVE 2001/83/EC

1. Introduction

Part B of Chapter 3 deals with the situations where a referral is made to the Committee for Herbal Medicinal Products (HMPC) under Article 16c of Directive 2001/83/EC and intends to provide practical guidance on the referral procedure.

Please note that for traditional herbal medicinal products, as defined in Article 1(29) of Directive 2001/83/EC, the referrals of Part A of this Chapter are also applicable and, in this case, the HMPC is the competent Committee, assuming the tasks which are normally carried out by the CHMP (Article 16h(1)(c) of Directive 2001/83/EC).

For all other herbal medicinal products the CHMP remains the competent Committee for referrals. However, the HMPC is called to give its opinion on the herbal substance contained in the herbal medicinal product concerned, where appropriate (Article 16h(1)(d) of Directive 2001/83/EC).

2. Article 16c(1)(c) of Directive 2001/83/EC ("adequacy of evidence of the long standing use referral")

This referral may be started at the request of a Member State where an application for traditional use registration for a traditional herbal medicinal product has been submitted.

The HMPC is asked to draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product, where it has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years in the Union. Namely, it shall assess whether the data on long standing use and experience of the traditional herbal medicinal product are sufficient to demonstrate plausible efficacy and pharmacological effects. A notification form for a referral to the HMPC/EMA is added in the annex.

Although the legislation does not provide for a specific timeframe, the HMPC has agreed to endeavour to issue a reasoned opinion within 60 days of the date of referral. This time frame is indicative and may be subject to prolongation, namely when the applicant(s) is provided with an opportunity to present written or oral explanations.

It should be noted, nevertheless, that the limit of 210 days foreseen in Article 17(1) of Directive 2001/83/EC for the finalisation of the procedure for granting a marketing authorisation has to be respected.

3. Article 16c(4) of Directive 2001/83/EC ("Traditional use < 15 years referral")

This referral shall be started at the request of a Member State where an application for traditional use registration for a traditional herbal medicinal product has been submitted, in the specific case where the medicinal product has been used in the Union for less than 15 years, but is otherwise eligible for the simplified registration as determined by the referring Member State.

According to Article 16c(4) of Directive 2001/83/EC as amended, the Member States shall refer the matter to the HMPC for an opinion before taking a decision on an application for a traditional use registration.

The HMPC is called upon to issue an opinion on whether the medicinal product is eligible for simplified registration, although it has been used in the Union for less than 15 years. A notification form for a referral to the HMPC/EMA is added in the annex.

Although the legislation does not provide for a specific timeframe, the HMPC has agreed to endeavour to issue a reasoned opinion within 60 days of the date of referral. This time frame is indicative and may be subject to prolongation, namely when the applicant(s) is provided with an opportunity to present written or oral explanations.

It should be noted, nevertheless, that the limit of 210 days foreseen in Article 17(1) of Directive 2001/83/EC for the finalisation of the procedure for granting a marketing authorisation has to be respected.

In addition to issuing this opinion, the HMPC shall evaluate the possibility of establishing a Community herbal monograph for that medicinal product. When the monograph is established it shall be taken into account by the Member State when taking its final decision to register the product.

4. Organisation of work within the HMPC

In order to consider the matter, the HMPC appoints one of its members to act as rapporteur. The appointment of a rapporteur and, if appropriate, of a co-rapporteur is made by the HMPC on a case-by-case basis. Once the appointment of the (co-) rapporteur(s) has been made, the EMEA informs the applicant(s) and all Member States.

The HMPC may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee defines their tasks and specifies the time limit for the completion of these tasks.

At the first HMPC meeting following the submission of the referral, the HMPC adopts the question(s) to be addressed to the applicant(s) if any and discusses, on the basis of the proposal from the Member State making the referral, the scope of the documentation actually requested or needed. The HMPC may also take into account any other information at its disposal which concerns the quality, safety and the plausibility of the pharmacological effects or efficacy of the medicinal product and which may help in arriving at its opinion.

ANNEX: Notification forms

NOTIFICATION TO THE CHMP*/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 29(4) OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 29(4) of directive 2001/83/EC for arbitration to the CHMP made by the Reference Member State following the procedure in the Coordination Group (CMDh)

Reference Member State (RMS):----------

Concerned Member States (CMS):----------

Member State(s) who raised the potential serious risk to public health:----------

THIS NOTIFICATION IS TO BE COPIED BY THE REFERRING PARTY TO APPLICANT/ MARKETING AUTHORISATION HOLDER AND ALL CHMP MEMBERS

Product Name <in the RMS>, if appropriate, Strength and Pharmaceutical Form**	
Active substance(s)	
Applicant/Marketing Authorisation Holder(s)	
Mutual Recognition Procedure number	

< Member State(s) who raised the potential serious risk to public health> CONSIDER(S) THAT THE AUTHORISATION OF THIS MEDICINAL PRODUCT MAY PRESENT A POTENTIAL SERIOUS RISK TO PUBLIC HEALTH ON THE FOLLOWING GROUNDS
<Background :>
<Issues to be considered>
<Proposed list of questions>
(Please provide a summary of background information and clearly precise the question that initiates the referral, together with the latest version of the SmPC, labelling and package leaflet as achieved during the coordination group procedure)
(If this space is not sufficient, please summarise and add annex):

Signed

Date

* In case of herbal medicinal products as referred to in Article 16a, which are referred to the EMA under Chapter 4 of Title III, this form should be used by replacing CHMP by HMPC.
** In case of herbal medicinal products as referred to in Article 16a, which are referred to the EMA under Chapter 4 of Title III, this form should be used by including under "Product Name , if appropriate, Strength and Pharmaceutical Form" the following: <Herbal substance(s), preparation(s) or combination(s) thereof> <Qualitative/Quantitative composition>

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 30 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 30 of Directive 2001/83/EC to the CHMP made by the following
<Member State (MS) >:----------

<Applicant(s)> <Marketing Authorisation Holder(s) (MAH(s)) >:----------

<The European Commission>

THIS NOTIFICATION IS TO BE COPIED BY THE REFERRING PARTY TO APPLICANT/ MARKETING AUTHORISATION HOLDER AND ALL CHMP MEMBERS

Name(s) of particular medicinal product <in the Referring Member State>*	
<Active substance(s)>	
Pharmaceutical form(s) <in the Referring Member State>	
Strength(s) <in the Referring Member State>	
Route of administration(s) <in the Referring Member State>	
Presentations <in the Referring Member State>	
Marketing Authorisation Holder(s) <in the Referring Member State>	

Harmonisation of SmPC for {name of medicinal product} (and associated names):
Rationale for the notification of the Article 30 referral of Directive 2001/83/EC

{Please select the following text when the referral is initiated for products included in the list for SmPC harmonisation in accordance with Article30(2):}

<{name of medicinal product}was included in the list of products for SmPC harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC.

Having analysed the medicinal products included in such list and in agreement with EMA the European Commission has decided to initiate a referral on the basis of Article 30(2) of Directive 2001/83/EC, to promote harmonisation of the authorisations granted for this medicinal product.

The CMDh carried out the task of identifying the divergences between the available SmPCs for this product and has come to the conclusion that the above-mentioned medicinal product {name of medicinal product}(and associated names), does not have the same Summary of Product Characteristics (SmPC) across all EU Member States, Iceland and Norway with respect to <indications>, <posology>, <contra-indications>, <undesirable effects> <and sections dealing with the recommendations for use>. The following examples constitute a non-exhaustive list.

<4.1 Indications>
[please provide a detailed overview of the divergences]

<4.2 Posology>
[please provide a detailed overview of the divergences]

etc ….

<Discrepancies also exist between MS regarding sections {other SmPC sections with divergences but for which no detailed overview is provided above}>.

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product, {Member State}{Applicant} {Marketing Authorisation Holder} <the European Commission> notifies the EMEA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SmPCs for the above-mentioned product and thus to harmonise its divergent SmPCs across the EU.

Signed

Date

* When initiated by the MAH the whole range of names, pharmaceutical forms, strengths, rutes of administration and presentations of the medicinal product in all EU Member States (Iceland and Norway, if appropriate) should be mentioned

NOTIFICATION TO THE <CHMP><PRAC>/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the <CHMP><PRAC> made by the <following Member State>, <European Commission>:

<Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)> <Active Substance(s)/Therapeutic class> *Please clarify name(s) and total number(s) of active substance(s)*	

<Applicant(s)/Marketing Authorisation Holder(s)> <In the referring Member State>

<Background>

<Issues to be considered>

In view of the elements described above and the necessity to take an action at EU level, <above mentioned Member State>, <European Commission> considers that it is in the interest of the Union to refer the matter to the <CHMP> <PRAC> and requests that it gives its <recommendation><opinion> under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.
[If the referral results from data relating from pharmacovigilance and at least one centrally authorised products is concerned]<As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP on the basis of a recommendation of the PRAC recommendation must adopt an opinion >.

Signed

Date

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 107i of Directive 2001/83/EC to the PRAC made by the <following Member State>, <European Commission>:

<Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)> <Active Substance(s)/Therapeutic class> *Please clarify name(s) and total number(s) of active substance(s)*	
<Applicant(s)/Marketing Authorisation Holder(s)> <In the referring Member State>	

<Background :>
<Issues to be considered>

Therefore, <above mentioned Member State>, <European Commission> initiates a procedure under Article 107i of Directive 2001/83/EC, refers the matter to the PRAC and requests that it gives its <commendation> as to whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.

Signed Date

NOTIFICATION TO THE <CHMP><PRAC>/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 2001/83/EC to the <CHMP><PRAC> made by the European Commission:

<Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)> <Active Substance(s)/Therapeutic class> *Please clarify name(s) and total number(s) of active substance(s)*	
<Applicant(s)/Marketing Authorisation Holder(s)>	

<Background :>
<Issues to be considered>

Therefore, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for <medicinal product(s)><range of medicinal product(s)> <therapeutic class>. The EC requests the EMA to give its opinion by <date/timeline> on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.
[If the referral results from data relating from pharmacovigilance] <As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CHMP on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee>.

Signed Date

NOTIFICATION TO THE CHMP*/EMEA SECRETARIAT OF A REFERRAL UNDER ARTICLE 13 OF COMMISSION REGULATION (EC) No 1234/2008
E-mail: ReferralNotifications@ema.europa.eu

This notification is an referral under Article 13 of Commission Regulation (EC) No 1234/2008 to the CHMP made by the following:

Reference Member State:----------

Concerned Member State(s):----------

THIS NOTIFICATION IS TO BE COPIED BY THE REFERRING PARTY TO APPLICANT(S)/MARKETING AUTHORISATION HOLDER(S) AND ALL CHMP MEMBERS

Product Name<in the RMS>, if appropriate, Strength and Pharmaceutical Form**	
Marketing Authorisation Holder(s)	
Mutual Recognition variation procedure No.	

< Member State(s) who raised the potential serious risk to public health> CONSIDER(S) THAT THE VARIATION(S) TO TERMS OF MARKETING AUTHORISATION OF THIS MEDICINAL PRODUCT MAY PRESENT A POTENTIAL SERIOUS RISK TO PUBLIC HEALTH ON THE FOLLOWING GROUNDS:

<Background :>
<Issues to be considered>
<Questions to CHMP >

(please provide a summary of background information and clearly precise the question that initiates the referral, together with the latest version of the SPC, labelling and package leaflet as achieved during the coordination group procedure)
(if this space is not sufficient, please summarise and add annex):

Signed Date

* In case of herbal medicinal products as referred to in Article 16a, which are referred to the Agency under Chapter 4 of Title III, this form should be used by replacing CHMP by HMPC.
** In case of herbal medicinal products as referred to in Article 16a, which are referred to the Agency under Chapter 4 of Title III, this form should be used by including under "Product Name , if appropriate, Strength and Pharmaceutical Form" the following: <Herbal substance(s), preparation(s) or combination(s) thereof> <Qualitative/Quantitative composition>

NOTIFICATION TO THE HMPC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 16c(1)c OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is an official referral under Article 16c(1)c to the HMPC made by the following Member State: ----------

THIS NOTIFICATION IS COPIED TO APPLICANT AND ALL MEMBER STATES

Product Name, if appropriate, Strength(s) and Pharmaceutical Form(s)	
< Herbal substance(s), preparation(s) or combination(s) thereof> <Qualitative/Quantitative composition>	
Applicant	

Grounds for and scope of referral

THE ABOVE-MENTIONED MEMBER STATE HEREBY REFERS THIS TRADITIONAL HERBAL MEDICINAL PRODUCT, WHICH CLAIMS TO HAVE BEEN IN MEDICINAL USE THROUGHOUT A PERIOD OF AT LEAST 30 YEARS PRECEDING THE DATE OF THE APPLICATION, INCLUDING AT LEAST 15 YEARS IN THE UNION.

(please provide a summary of background information and clearly precise the question(s) that initiates the referral)
(if this space is not sufficient, please summarise and add annex):

Signed
Date

NOTIFICATION TO THE HMPC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 16c(4) OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is an official referral under Article 16c(4) to the HMPC made by the following Member State: ----------

THIS NOTIFICATION IS COPIED TO APPLICANT AND ALL MEMBER STATES

Product Name, if appropriate, Strength(s) and Pharmaceutical Form(s)	
< Herbal substance(s), preparation(s) or combination(s) thereof> <Qualitative/Quantitative composition>	
Applicant	

Grounds for and scope of referral

THE ABOVE-MENTIONED MEMBER STATE REFERS THIS TRADITIONAL HERBAL MEDICINAL PRODUCT, WHICH CLAIMS TO HAVE BEEN IN MEDICINAL USE THROUGHOUT A PERIOD OF AT LEAST 30 YEARS PRECEDING THE DATE OF THE APPLICATION BUT LESS THAN 15 YEARS IN THE UNION, AND IS OTHERWISE ELIGIBLE FOR SIMPLIFIED REGISTRATION.

(please provide a summary of background information and clearly precise the question(s) that initiates the referral)
(if this space is not sufficient, please summarise and add annex):

Signed
Date