



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON LEGAL STATUS FOR THE SUPPLY TO THE PATIENT OF CENTRALLY
AUTHORISED MEDICINAL PRODUCTS**

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DATE FOR COMING INTO EFFECT	15 August 2006

Note:

This guideline is based on a reformatting of the EMEA SOP “Legal Status for the Supply to the Patient of Centrally Approved Medicinal Products” (EMEA/SOP/003/95) according to the new template for Guidelines.

Since this guideline is based on existing guidance and introduces clarification rather than changing principles, the publication of a concept paper was not considered necessary. For the same reason, no consultation has been performed and the guideline will come into effect upon publication.

KEYWORDS	CHMP; LEGAL STATUS; CONDITIONS FOR SUPPLY; CENTRALISED PROCEDURE; CLASSIFICATION; PRESCRIPTION; DATA EXCLUSIVITY;
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EXECUTIVE SUMMARY

The pharmaceutical legislation, Regulation (EC) No 726/2004, requires that, when the Committee for Medicinal Products for Human Use (CHMP) gives a favourable opinion to the granting of a marketing authorisation for a medicinal product, the conditions and restrictions under which the medicinal product should be made available to patients, i.e. the so-called 'Legal Status' of the medicinal product, must be annexed to the opinion.

This guideline addresses the criteria to be followed by the CHMP when determining the Legal Status of a medicinal product, as well as the way the Legal Status is implemented in the CHMP opinion. The guideline also provides information on the possible change of the Legal Status.

This guideline will be complementary to existing guidance in this area, in particular the European Commission *Guideline on changing the classification for the supply of a medicinal product for human use* and *Guideline on the packaging information of medicinal products for human use authorised by the Community*.

1. INTRODUCTION (background)

In accordance with Article 9(4)(b) of Regulation (EC) No 726/2004, the documents annexed to the CHMP favourable opinion to the granting of a marketing authorisation shall include “*details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Title VI of Directive 2001/83/EC, as amended*”.

The classification for the supply of the medicinal product to the patient will be hereafter referred to as the 'Legal Status'.

In the case of an application for a marketing authorisation submitted in accordance with the centralised procedure, the CHMP within the European Medicines Agency (EMA) is responsible for recommending the Legal Status to the Commission, in accordance with article 9(4) of Regulation (EC) No 726/2004 as mentioned above. As a consequence the Legal Status has to be defined in several parts of the CHMP opinion (see Section 5 of this guideline).

According to Article 74 of Directive 2001/83/EC as amended, the Legal Status of a medicinal product may be amended if new facts are brought to the attention of the competent authorities. According to Article 74a of the same Directive, if a change of classification is authorised on the grounds of significant pre-clinical tests or clinical trials, the results of those tests or trials may benefit from a one-year period of protection.

2. SCOPE

This guideline addresses the criteria to be followed by the CHMP when determining the Legal Status of a medicinal product, as well as the implementation of the Legal Status in the CHMP opinion. The guideline also provides information on changes to the Legal Status.

This guideline is applicable to medicinal products for human use authorised according to the Community centralised procedure.

3. LEGAL BASIS

Article 9(4) of Regulation (EC) No 726/2004 and Title VI (i.e. Articles 70 to 75) of Directive 2001/83/EC as amended.

4. CRITERIA FOR DETERMINING THE LEGAL STATUS

Title VI (i.e. Articles 70 to 75) of Directive 2001/83/EC, as amended, lays down levels of categories in relation with the conditions for supply of the product and criteria for the establishment of the Legal Status by the competent authorities. On the first level, the medicinal product is classified either as:

- subject to medical prescription or
- not subject to medical prescription.

Article 71(1) of the above-mentioned Directive states that: “*medicinal products shall be subject to medical prescription where they:*

- *are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, or*
- *are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or*
- *contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or*
- *are normally prescribed by a doctor to be administered parenterally.”*

The factors to be addressed in considering whether these criteria apply are detailed in Part 1 of the “Guideline on changing the classification for the supply of a medicinal product for human use”.

According to Article 72 of Directive 2001/83/EC, as amended, medicinal products not subject to medical prescription are those which do not meet the criteria listed in Article 71. Article 71(4) of the Directive further specifies that a medicinal product, which does not meet any of the criteria for supply subject to medical prescription, may be classified for supply not subject to medical prescription if: the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use, can make supply without medical prescription appropriate.

In most cases, due to their novelty, the medicinal products for which a marketing authorisation application is submitted to the EMEA via the centralised procedure will be subject to **medical prescription** in accordance with Article 71 of Directive 2001/83/EC, as amended.

For products subject to **medical prescription**, where applicable, there is a second level and the EMEA may have to fix one of the following additional **sub-categories**, in accordance with Article 71 paragraphs 2 and 3 of Directive 2001/83/EC, as amended:

- Medicinal product subject to **special medical prescription**, where the medicinal product:
 - *contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or*
 - *is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or*
 - *contains a substance which, by reason of its novelty and properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.*

- Medicinal product subject to **restricted medical prescription**, where the medicinal product:
 - *is reserved for treatments which can only be followed in a hospital environment, because of its pharmaceutical characteristics or novelty or in the interests of public health,*
 - *is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or*
 - *is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.*

Medicinal products, which meet the criteria for both above-mentioned sub-categories, will be subject to **special and restricted medical prescription**.

The CHMP shall refer to the above-mentioned criteria and factors where it comes to take a decision on such categories.

There is another sub-category foreseen in Article 70(2) of Directive 2001/83/EC, as amended, i.e.: ‘medicinal products on medical prescription for renewable or non-renewable delivery’. The definition and therefore also the implementation may vary in those Member States where the sub-category exists. Therefore it has been decided that for centrally authorised products such sub-category will not be explicitly mentioned in the Opinion/Decision, leaving for Member States the possibility of the implementation of the sub-category in accordance with national measures and in compliance with the content of the SPC.

The levels of categories for the Legal Status are summarised in the Annex to this guideline.

5. IMPLEMENTATION OF THE LEGAL STATUS IN THE CHMP OPINION

- a) At the pre-submission stage applicants should include a proposed classification for the supply of the medicinal product in their “notification of intention to submit an application” to be sent to the EMEA at least 7 months before submission. At the time of the submission of the application applicants should indicate their proposal for Legal Status in the section 2.3 of the Module 1 application form.
- b) During the CHMP evaluation phase discussions on Legal Status should be reflected in the Assessment Report and, once the authorisation is granted, in the European Public Assessment Report (EPAR).
- c) In the CHMP opinion, the Legal Status will be determined in accordance with Article 9(4)(b) of Regulation (EC) No 726/2004 in the following way:

- Annex I of the CHMP opinion (Summary of Product Characteristics):

Wherever appropriate, the SPC will include an explanation on how the medicinal product should be **supplied to patients** (e.g. to be administered in a hospital setting or prescribed by specialists only, or specific type of care during the treatment of a chronic disease).

- Annex II.B of the CHMP opinion (Conditions or restrictions regarding supply and use) should mention one of the categories below:
 - medicinal product not subject to medical prescription
 - medicinal product subject to medical prescription

- medicinal product subject to special medical prescription
- medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)
- medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

It should be emphasised that any kind of restriction envisaged by the CHMP will be translated into the Legal Status in Annex II of the CHMP Opinion by the introduction of the word "restricted". In such case a cross-reference will be made to the section 4.2 of the SPC where the restriction will be reflected. This would guide national authorities when using any sub-category at national level.

The sub-categories of Renewable/Non-renewable may be used at national level even in cases where the main category in Annex II.B of the Opinion is simply "subject to medical prescription". In this case the guidance for Member States to use the sub-categories of Renewable/Non-renewable would come from the whole SPC (indication, posology....).

- Annex III.A of the CHMP opinion (Labelling):

In order to allow flexibility, given the different systems of distribution and supply of medicines in the Member States, the outer packaging should only mention either "medicinal product not subject to medical prescription" or "medicinal product subject to medical prescription" (for all other cases mentioned under Annex II.B).

The use of any sub-categories at national level (e.g. hospital use/renewable/non-renewable) and the information required to express this, should be addressed in the blue box only.

This information may concern as stated above either one, or more, sub-categories listed in Article 70(2) of Directive 2001/83/EC, as amended, or a specific way of conveying particular information about the Legal Status. Some Member States use symbols to express the Legal Status on the label. Such symbols are set out in the Annex to the "Guideline on the packaging information of medicinal products for human use authorised by the Community".

6. CHANGE OF THE CLASSIFICATION FOR THE SUPPLY OF A MEDICINAL PRODUCT

According to Article 74 of Directive 2001/83/EC as amended, when new facts are brought to their attention, the competent authorities shall, as appropriate, amend the classification of a medicinal product by applying the criteria listed in Article 71 of the same Directive.

It should also be highlighted that a change of Legal Status may concern only certain pharmaceutical forms/strengths/presentations within the same marketing authorisation. In that case, the Legal Status of each pharmaceutical form/strength/presentation of the medicinal product shall be specified in Annex IIB of the CHMP opinion.

The data requirements for an application to change the classification for the supply of a medicinal product from 'subject to medical prescription' to 'not subject to medical prescription' are outlined in Part 2 of the "Guideline on changing the classification for the supply of a medicinal product for human use".

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

It is to the applicant to claim the one-year data exclusivity at the time of the application for the change of classification. The applicant shall support its claim by providing a report justifying that its application includes significant pre-clinical tests or clinical trials which have been carried out in relation to this change of classification in accordance with Article 74a of Directive 2001/83/EC as amended and Part 3 of the “Guideline on changing the classification for the supply of a medicinal product for human use”. Such documentation should be submitted in Module 1.5.3 of the application for a variation or extension application to an existing marketing authorisation or for a standalone application for marketing authorisation. Related study reports and literature references shall be placed in relevant Modules of the dossier and thus cross-referred to accordingly.

The submission can be both within or separate from an existing marketing authorisation. Where a change in classification is submitted within an existing marketing authorisation, the change requires the submission of a type II variation application, unless it introduces the need for an extension application e.g. a new strength, pharmaceutical form or route of administration. Alternatively a separate standalone application for marketing authorisation could be submitted.

The CHMP will assess the pre-clinical tests or clinical trials and issue a single opinion for the change of the classification. A Commission Decision will authorise the change in classification including a clear statement of whether the change in classification is based on significant pre-clinical tests or clinical trials.

REFERENCES (scientific and / or legal)

- Regulation (EC) No 726/2004
- Directive 2001/83/EC, as amended
- “Centralised Procedure”, The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4
- "Guideline on the packaging information of medicinal products for human use authorised by the Community", the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- “Guideline on changing the classification for the supply of a medicinal product for human use”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C

ANNEX: levels of categories for the supply of centrally authorised medicinal products

<p>1st. Level EMEA/CHMP. Mentioned in the Commission Decision *</p>	<p>2nd. Level EMEA/CHMP. Mentioned in the Commission Decision *</p>	<p>Sub-categories, not mentioned in the Commission Decision (general description in SPC & national symbol in blue box, where appropriate fixed by MS)</p>
<p>Medicinal product NOT subject to medical prescription</p>		
<p>Medicinal product SUBJECT to medical prescription</p>	<p>Medicinal product subject to special medical prescription</p>	<p>Renewable/Non-renewable</p>
	<p>Medicinal product subject to restricted medical prescription</p>	<p>Renewable/Non-renewable</p>
		<p>Hospital use Specialists etc.</p>
	<p>Medicinal product subject to special and restricted medical prescription</p>	<p>Renewable/Non-renewable</p>
		<p>Hospital use Specialists etc.</p>

* Compliance with all the terms and conditions of the Commission Decision is binding and Member States must find suitable ways to allow MAHs of centrally authorised products to fulfil all the conditions laid down in the Commission Decision granting the Marketing Authorisation (Minutes of 42nd meeting of the Pharmaceutical Committee, 20 Feb. 97)