



The European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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

**GUIDELINE ON PROCEDURES FOR THE GRANTING OF A MARKETING
AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES, PURSUANT TO
ARTICLE 14 (8) OF REGULATION (EC) NO 726/2004**

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Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004¹

Legal basis and Purpose

Article 14(8) of Regulation (EC) 726/2004, states that “*in exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC, as amended. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.*”

Directive 2001/83/EC, as amended, Annex I, Part II, documentation for applications in exceptional circumstances, states that when, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information,

a marketing authorisation may be granted subject to certain specific obligations. These obligations may include the following:

- The applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
- The medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,
- The package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

This document describes the procedure and gives guidance for the scientific assessment of the grounds and conditions for the granting of a marketing authorisation under exceptional circumstances.

The procedure is applicable to marketing authorisation applications for medicinal products for human use falling within the scope of articles 3(1) and 3(2) of Regulation (EC) No 726/2004.

Specific procedures/obligations

According to article 14(8) of Regulation (EC) 726/2004 the exceptional circumstances marketing authorisation is granted provided “specific procedures” are introduced. The article particularly highlights the safety of the medicinal product, notification to the authorities of any incident relating to its use and action to be taken. It follows that this guideline should be read in conjunction with the “Guideline on risk management systems for medicinal products for human use” (EMA/CHMP/96268/2005) which sets out the different pharmacovigilance activities and interventions proactively designed to identify, characterise and prevent or minimise risks relating to medicinal products.

According to Annex I, part II of Directive 2001/83/EC, as amended specific obligations may encompass a programme of studies, prescription or administration conditions, or notification or product information obligations.

¹ Official Journal L 136, 30/4/2004 p. 1 - 33

Exceptional Circumstances vs. Conditional Marketing Authorisation vs. Normal marketing authorisation

Products for which the applicant can demonstrate that comprehensive data (in line with the requirements laid down in Annex I of Directive 2001/83/EC, as amended) cannot be provided (due to specific reasons foreseen in the legislation) might be eligible for marketing authorisation under exceptional circumstances. This type of authorisation is reviewed annually to reassess the risk-benefit balance. The fulfilment of any specific procedures/obligations imposed as part of the marketing authorisation under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a full dossier. In the rare cases where the applicant has finally been able to provide comprehensive data on the efficacy and safety under normal conditions of use (a “full dossier”) and no specific procedures/obligations remain, a “normal” marketing authorisation could be granted.

A marketing authorisation under exceptional circumstances may be varied with the addition of new indication(s). In such cases, the marketing authorisation will however remain under exceptional circumstances.

Products for which the applicant can demonstrate the positive benefit/risk balance, based for example on early evidence of effects that are expected to predict the clinical outcome from an ultimately comprehensive development, might be authorised under a conditional marketing authorisation (Article 14(8) of Regulation (EC) No 726/2004). This temporary authorisation is not intended to remain conditional. It is reviewed once a year and may be renewed and, once the data required for confirming the positive benefit/risk relationship are provided (a “full dossier”), it can become a “normal” marketing authorisation.

A distinction should thus be made between an approval under exceptional circumstances and a conditional marketing authorisation. A marketing authorisation under exceptional circumstances should not be granted when a conditional marketing authorisation is more appropriate. A conditional marketing authorisation is for example granted in the absence of comprehensive clinical data when it is likely that the applicant will be in the position to provide such data in a short timeframe. Further guidance on the criteria and procedures for granting a conditional marketing authorisation will be made available in guidelines from the EMEA.

It should be noted that designated orphan products, as in the case of other medicinal products, are eligible for approval under exceptional circumstances only if the criteria set out below are fulfilled (see further “ Documentation to be supplied”). Orphan designation criteria are independent from the criteria to be considered for approval under exceptional circumstances.

EMA advice prior to submission

The applicant may request advice from the EMA about the justification for applying for a marketing authorisation under exceptional circumstances.

Inability to provide comprehensive data should be discussed as early as possible during drug development. The applicant is encouraged to seek scientific advice on the limitations imposed by the rarity of the disease, or scientific knowledge to collecting comprehensive information on safety and efficacy. Scientific advice cannot be requested on the ethical aspects of such collection of information.

Any further discussion on the appropriateness should preferably occur in the context of the presubmission meeting between the EMA and applicant and occur at least 4-6 months before the marketing authorisation submission.

A request for EMA pre-submission advice should be accompanied by the justifications described in the section “Justifications on the grounds for approval under exceptional circumstances” with detailed questions and requests for comments on any specific issue for which advice is being sought.

The EMA advice should not be binding on the applicant and is without prejudice to the outcome of the CHMP assessment of the marketing authorisation application.

Timing of the submission

The applicant should submit a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances in the notification to the EMEA submitted in advance of the Marketing Authorisation Application, (Notice to Applicants: Procedures for marketing authorisation, Centralised Procedure, Volume 2 A, Chapter 4).

Documentation to be supplied

If the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should include its justification in module 1 (for further details, please refer to EMEA Pre-authorisation guidance document: <http://www.emea.eu.int/index/indexh1.htm>) the application covering the following aspects.

- 1) A claim that the applicant can show that he is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use
- 2) A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided.
- 3) Justifications on the grounds for approval under exceptional circumstances
- 4) Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information)

Justifications on the grounds for approval under exceptional circumstances

The justifications on the grounds for approval under exceptional circumstances shall be based on objective, verifiable reasons.

For non-clinical or clinical efficacy or safety data that cannot be comprehensively provided, the relevant section of the overview should describe the ground(s) (as referred to in the legislation) on why the applicant is unable to provide such data (several grounds may apply). The applicant should provide detailed justifications to demonstrate the existence of such grounds, together with a critical assessment of such justifications in module 1.

Inability to provide comprehensive efficacy and safety data due to rarity of the indication

The justification should consider relevant epidemiological evidence to quantify the rarity of the condition worldwide, and further quantify the size of the population that might be available for such studies. Previous studies conducted in similar populations should be described.

It should be mentioned if the medicinal product has obtained orphan designation in the EU. A reference to the EU orphan designation can be made when designation has been obtained on the basis of rarity. Nevertheless, orphan status is not sufficient to justify the inability to provide comprehensive efficacy and safety data.

The feasibility of conducting the required studies should be evaluated and discussed. This should include the possibility of conducting large co-operative multicentre studies.

The evaluation should include a detailed description of issues relating to the study design and statistical considerations, including error probabilities, hypotheses, and assumptions for recruitment and follow-up, sample size calculation and methodology.

The feasibility of conducting other studies that would yield more informative data (albeit not comprehensive) on the efficacy or safety of the product should be evaluated and discussed. Any suitable study designs, including exploratory designs or other designs, taking into account available guidance (e.g., EMEA workshop on methodological aspects of clinical trials for efficacy evaluation in small populations), should be considered.

Inability to provide comprehensive information due to the present state of scientific knowledge

Concerning the present state of scientific knowledge, the applicant should describe what scientific knowledge would be required to conduct such trials, justify the lack of such knowledge and that such knowledge cannot reasonably be expected to be developed by the applicant. It may for example be that

certain diagnostic tools have not yet been developed in order to specifically study defined patient populations.

The feasibility of conducting other studies that would yield more information (albeit not comprehensive) should be evaluated and discussed.

Inability to collect such information because it would be contrary to medical ethics

Concerning *medical ethics*, the applicant should describe the relevant principles of medical ethics with precise reference to internationally accepted standards or other guidelines on ethics. The applicant should further justify the general acceptance of such principles and their applicability in this case.

Decisions and statements by ethics committees or relevant health authorities on the ethics of collecting such information should be provided, if available.

The feasibility of conducting other studies that would yield more information (albeit not comprehensive) should be evaluated and discussed.

Grounds of medical ethics would generally apply only to clinical studies or studies using human biomaterials.

Proposals for detailed information on the specific procedures/obligations to be conducted

- *Safety procedures*

The proposals relating to safety should normally be provided in the form of an EU risk management plan (see draft guideline on risk management systems for medicinal products for human use (EMEA/96268/05))

It is important that the pharmacovigilance plan should provide full details of the pharmacovigilance activities which will be put in place to ensure that the marketing authorisation holder is informed of any incident relating to the use of the product, and the proposed methods by which the Competent Authorities will be informed. The pharmacovigilance plan should also include details of any studies which will be put in place to identify and characterise risks associated with the use of the product.

Since it is likely that information about the safety of the product is limited, the applicant should provide a detailed assessment of the need for risk minimisation activities and, if appropriate, a risk minimisation plan.

- *Programme of studies*

A detailed list of any ongoing, planned, or proposed studies, which may form the basis of future reassessments of the benefit/risk profile, together with the expected time period for the completion of such studies. For each study, the following should be provided if available:

1. Study outline (including design, endpoints and target indication)
2. Expected milestones for protocol submission, study start, recruitment, completion, analysis, submission of status reports, submission of interim and relevant study reports.

- *Prescription or conditions of use*

A detailed proposal for the conditions of use including whether the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, e.g. in a hospital or restricted to specific prescribers, and in the case of a radio-pharmaceutical, by an authorised person.

- *Product information*

A detailed proposal on how the SPC, package leaflet and any other medical information should draw the attention of the medical practitioners and patients to the fact that the particulars available concerning the medicinal product in question are as yet incomplete in certain specified respects.

CHMP assessment

The opinions adopted under exceptional circumstances may be adopted only for objective and verifiable reasons, as referred to in the Annex I, Part II, documentation for applications in exceptional circumstances, to Directive 2001/83/EC, as amended.

When comprehensive data on the efficacy and safety of the medicinal product is not available, the CHMP may propose the possibility of adopting an opinion under exceptional circumstances based on the criteria defined in the legislation even if the applicant has not raised this. This will usually occur at a time close to the adoption of the opinion. Such a proposal, including any specific obligations, will be communicated to and agreed with the applicant before adoption. Any assessment should be described in detail in the relevant CHMP assessment reports (e.g., Day 120 List of questions, List of outstanding issues, CHMP assessment report).

The CHMP assessment report should cover the following aspects, as appropriate:

- The studies that are lacking for a comprehensive demonstration of efficacy and safety, and the need for the CHMP to consider an approval under exceptional circumstances.
- Whether there are sufficient grounds (“scientific knowledge, rarity, ethics”) to demonstrate that comprehensive data on the efficacy and safety cannot be provided, including the statement and assessment of any claims made by the applicant as to the existence of such grounds. The CHMP may seek external advice in relation to issues related to ethics.
- The reasons for accepting or rejecting the existence of such grounds, and whether such grounds are objective and verifiable.
- An explanation as to why an exceptional marketing authorisation is appropriate, and if necessary, a justification of why a conditional marketing authorisation or a normal marketing authorisation could not be considered.
- An assessment of the EU risk management plan and how the proposed risk minimisation activities impact the benefit risk balance
- The need for a programme of studies as proposed by the applicant. The assessment will also address how such studies aim to provide additional information that is necessary since no comprehensive information has been made available, which are useful to inform about the safe and effective use of the medicinal product.
- The Committee may in addition to what has been proposed by the applicant also request additional studies to further inform on aspects that are important for the safe and effective use of the product. The assessment will for example address the need for any supplementary studies in addition to those proposed in the pharmacovigilance plan.
- The CHMP should assess the feasibility of carrying out these studies and assess their objectives in the context of the missing data.

As the formulation of specific obligations may require specific therapeutic knowledge, the CHMP may consult one of the relevant scientific advisory groups.

The list of these specific obligations will be made publicly accessible without delay, together with deadlines and dates of fulfilment.

- Conditions or restrictions regarding supply and use.
- Conditions or restrictions with regard to the safe and effective use of the medicinal product.

Such conditions are set out in the CHMP opinion and further reflected in the relevant parts of the product information.

- The SPC, package leaflet and any medical information that should draw the attention of the medical practitioner and patient to the fact that the particulars available concerning the medicinal product in question are inadequate in certain specified respects. (See Annex 1, Part II of Directive 2001/83 EC, as amended).

The summary of product characteristics and package leaflet should mention that a marketing authorisation has been granted subject to certain specific obligations to be reviewed annually.

Information in the package leaflet should follow the conventional standards for writing understandable patient material (e.g., readability), and should be in accordance with EMEA/QRD guidelines and templates.

Annual reassessment of the benefit/risk profile

The specific procedures/obligations that have been implemented and fulfilled by the applicant form the basis of a CHMP annual reassessment of the benefit/risk profile. Continuation of the authorisation should be linked to the annual reassessment of these conditions.

The renewal of the marketing authorisation (MA) of a medicinal product under exceptional circumstances follows the same rules as a “normal” marketing authorisation. This will be performed in accordance with Article 14 (1-3) of Regulation (EC) No. 726/2004 and the marketing authorisation will be valid for five years. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.