



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

London, 5 December 2006
Doc. Ref. EMEA/509951/2006

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

**GUIDELINE ON THE SCIENTIFIC APPLICATION AND THE PRACTICAL
ARRANGEMENTS NECESSARY TO IMPLEMENT COMMISSION REGULATION
(EC) No 507/2006 ON THE CONDITIONAL MARKETING AUTHORISATION FOR
MEDICINAL PRODUCTS FOR HUMAN USE FALLING WITHIN THE SCOPE OF
REGULATION (EC) No 726/2004**

CHMP DISCUSSION	July 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	14 December 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2007

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NOTE	This guideline currently focuses on the practical arrangements necessary to implement the conditional marketing authorisation Regulation. Guidance on the scientific application of a conditional marketing authorisation is currently provided in general terms. The guideline will be regularly updated to include more specific guidance and examples based on the CHMP experience with conditional marketing authorisations.
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Legal basis and Purpose

The purpose of this guideline is to provide advice on the scientific application and the practical arrangements necessary to implement the legal provisions on the conditional marketing authorisation. It forms the basis for requesting or renewing a conditional marketing authorisation, and should be followed unless otherwise justified. The legal basis for this guideline is Article 11 of Commission Regulation (EC) No. 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

The possibility of obtaining a conditional marketing authorisation only applies to new marketing authorisation applications. A conditional marketing authorisation does not apply to new indications submitted as part of a variation or extension procedure. Once granted as a 'marketing authorisation not subject to specific obligations' or as a 'marketing authorisation under exceptional circumstances', an authorisation cannot be changed into a conditional marketing authorisation.

This guideline currently focuses on the practical arrangements necessary to implement the conditional marketing authorisation regulation. Guidance on the scientific application of a conditional marketing authorisation is currently provided in general terms. The guideline will be regularly updated to include more specific guidance and examples based on the CHMP experience with conditional marketing authorisations.

A. Granting of a conditional marketing authorisation

1. Applicant's request for a conditional marketing authorisation

A conditional marketing authorisation may be requested by the applicant or proposed by the CHMP. The applicant is invited to notify the EMEA about its intention to request a conditional marketing authorisation as part of the "letter of intent" to be sent to the EMEA in advance of the marketing authorisation application submission.

The applicant may present a request for a conditional marketing authorisation at the time of the application for marketing authorisation. A request for conditional marketing authorisation shall be submitted in module 1.5.5 of the EU-CTD.

The request should consist of justifications to show that the medicinal product falls within the scope of the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional marketing authorisation are fulfilled (Article 4), together with the applicant's proposal for completion of ongoing or new studies, or the collection of pharmacovigilance data. The request may cross-refer to specific parts of the application.

Upon receipt of a valid application containing a request for conditional marketing authorisation, the EMEA will inform the Commission.

1.1 Justification that the medicinal product falls within the scope of the conditional marketing authorisation

The applicant should justify that the medicinal product falls within the scope of the conditional marketing authorisation regulation. The categories of medicinal products that fall within the scope of the conditional marketing authorisation regulation are defined in Article 2 of Commission Regulation (EC) No 507/2006. These are products for human use falling under Article 3(1) and (2) of Regulation (EC) No 726/2004, and belonging to at least one of the following categories:

1. Seriously debilitating diseases or life-threatening diseases

The severity of the disease, i.e., its seriously debilitating, or life-threatening nature needs to be justified, based on objective and quantifiable medical or epidemiologic information. Whereas a life-threatening disease is relatively easy to describe based on figures of mortality, justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. These aspects should be quantified in objective terms, as far as possible. Furthermore, serious debilitation, or fatal outcome should be a prominent feature of the target disease and therapeutic indication.

2. Medicinal products to be used in emergency situations

A justification should be provided that the medicinal product is intended for use in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No. 2119/98/EC). A reference to the relevant WHO Resolution or Decision, or to the measures adopted by the Commission in the framework of Council and Parliament Decision No. 2119/98/EC should be provided.

3. Orphan medicinal products

For requests submitted in accordance with article 2 (3) of Commission Regulation (EC) No. 507/2006, a copy of the Commission Decision on the designation as an orphan medicinal product should be provided.

1.2 Fulfilment of the requirements for conditional marketing authorisation

The requirements for a conditional marketing authorisation Regulation are described in Article 4 of Commission Regulation (EC) No. 507/2006. In its request for a conditional marketing authorisation, the applicant should justify why in their opinion each of these requirements are expected to be met:

(a) The risk-benefit balance of the product is positive

It is considered crucial that a medicinal product only ever receives a marketing authorisation when the CHMP judges that, based on the evidence available, the balance of risks and benefits is positive. This is based on Article 4 (a) of Commission Regulation (EC) No. 507/2006, which states that one of the criteria for granting of a conditional marketing authorisation is that the risk-benefit balance of the medicinal product is positive, as defined in Article 1(28a) of Directive 2001/83/EC.

In general, the demonstration of a positive benefit-risk balance should be based on (comprehensive) scientific evidence, in particular evidence from therapeutic confirmatory trials that can provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial (randomized controlled trials). In particular, the design of clinical studies pertinent to the claimed indication should in general be controlled and steps should be taken to avoid bias, including methods of randomisation and blinding. For the demonstration of a positive benefit-risk balance, the data requirements laid down in Annex 1 of Directive 2001/83, are also applicable for products granted conditional marketing authorisation. As for any other type of marketing authorisation, the design and choice of control of the confirmatory studies need to be justified, and should be adequate. However, if the benefit-risk balance is judged to be positive but based on less than comprehensive clinical data, this would lead to the granting of a conditional marketing authorisation. It should be possible, and indeed required, to obtain comprehensive data once ongoing or new studies have been completed. Methodological issues to be considered for the design and analysis of clinical efficacy trials that are relevant in the context of conditional marketing authorisations will be described in a separate appendix.

The uncertainties related to the lack of comprehensive clinical data in a conditional marketing authorisation generally require that uncertainty deriving from other parts of the application are kept to a minimum. For a conditional marketing authorisation, comprehensive non-clinical and pharmaceutical data should be available. Incomplete non-clinical or pharmaceutical data should only be accepted in emergency situations (see article 4 (1)).

The safety profile of the medicinal product should be adequately defined and appropriate to justify a positive benefit risk. The applicant is encouraged to present and seek agreement on the size of the safety

database with the CHMP during a scientific advice procedure during the development of the medicinal product.

To address the requirement of article 4 (1) (a), the applicant will have to provide a justification outlining the following points:

- Positive risk-benefit balance of the product.
- The robustness and degree of external validity of the results
- A discussion of any aspects of the positive benefit risk balance that require confirmation from further studies (e.g., confirmation of effect on other endpoints, long-term effects, effect in special populations or identification of responders)

(b) It is likely that the applicant will be able to provide comprehensive data

By way of specific obligations the holder of a conditional marketing authorisation shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk-benefit balance is positive. In emergency situations, specific obligations to provide comprehensive non-clinical or pharmaceutical data may also be required.

Comprehensive data are intended to confirm that the benefit risk balance is positive, for instance, by checking the coherence of the available data on primary or secondary endpoints in more mature data sets or in additional studies in related indications, investigating the effect duration, and generally providing a better estimate of the efficacy and safety of the product.

Specific obligations should aim to obtain evidence that has a consequence on confirming the benefit-risk in the approved indication. There should be a clear explanation and rationale on what are the remaining questions relating to the safety and efficacy in the proposed indication, and how fulfilment of the obligation results in a resolution these questions.

It is important that the development should be completed as soon as possible to ensure that any uncertainties due to the lack of comprehensive data do not persist indefinitely.

The applicant should explain that comprehensive data can be provided within an agreed timeframe. The applicant should provide reassurance as to the feasibility and quality of studies to be performed as specific obligations. A marketing authorisation early in the development may for instance lead to potential difficulties in recruitment, breaking of blinding in ongoing or future studies, or otherwise compromise the statistical analyses, particularly for trials with patients from the same population as covered by the authorisation.

Safety may need intense monitoring to allow an informed judgement on the positive benefit risk balance at the time of the annual reassessment. Specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The CHMP will assess the claims of the applicant about the feasibility and appropriateness of granting a conditional marketing authorisation. Where (timely) completion of further studies required for the confirmation of a positive benefit risk balance cannot be expected, this may lead to a negative opinion on the granting of a conditional marketing authorisation.

During the planning phases of the development, the applicant is strongly encouraged to seek scientific advice on the overall development plan and design of any studies that are planned to be completed or conducted as specific obligations following the granting of a conditional marketing authorisation.

For each ongoing or new study that is proposed to be provided as part of a specific obligation, a short description should be provided:

- Study synopsis. The structure and content of the synopsis will vary depending on the type of study and type of specific obligation. For a typical clinical efficacy study, the information provided might include)
 - Title
 - Introduction (rationale)
 - Treatments (specific drugs, doses and procedures)

- Patient population and the number of patients to be included
- Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators and unblinded patients and/or investigators)
- Kind of control(s) (e.g., placebo, no treatment, active drug, dose-response) and study configuration (parallel, cross-over)
- Method of assignment to treatment (randomization, stratification)
- Sequence and duration of all study periods, including pre-randomisation and post-treatment periods, therapy withdrawal periods and single- and double blind treatment periods.
- Primary and secondary efficacy and safety variables
- Description of main methods for interim and final analyses of efficacy or safety.
- Timing and description of important milestones for the study start, conduct, analysis, and reporting (including contents of interim reports).
- A discussion about the rationale and feasibility of the study

(c) Fulfilment of unmet medical need

Article 4 paragraph 1(c) of Commission Regulation (EC) No. 507/2006 states that one of the requirements for granting of a conditional marketing authorisation is that unmet medical needs will be fulfilled. Paragraph 2 specifies that unmet medical needs mean a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

To address this requirement, applicants should justify that there exists an unmet medical need and that it is necessary to introduce new methods in therapy when no methods exist, or that it is necessary to provide a major improvement on the existing methods. The demonstration of fulfilment of an unmet medical need has to be justified on a case-by-case basis. The justifications should quantify the unmet medical need based on quantifiable medical or epidemiologic data.

In general, major therapeutic advantage would normally be based on meaningful improvement of efficacy (or clinical safety), such as having an impact on the onset and duration of the condition, or improving the morbidity or mortality of the disease.

The advantages should be demonstrated over existing methods used in clinical practice (if any), using robust evidence, normally, from well conducted randomised controlled trials (evidence-based demonstration of benefit).

In order to support the claim that unmet medical needs will be fulfilled, the applicant will be expected to provide:

- A critical review of available methods of prevention, medical diagnosis or treatment, highlighting an unmet medical need
- Quantification of the unmet medical need taking into account technical argumentation (e.g., quantifiable medical or epidemiologic data)
- A justification of the extent to which the medicinal product addresses the unmet medical need

(d) The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

The applicant will have to provide a justification to substantiate the claim that the benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required. The justification should assess the impact of *immediate* availability on public health, based as far as possible on objective and quantifiable epidemiological information, as opposed to availability when comprehensive clinical data are expected to be available. Similarly, the risks inherent in the fact that additional data are still required shall be quantified as far as possible on objective and quantifiable terms.

In order to support the claim that the benefits to public health outweigh the risks inherent in the fact that additional data are still required, the applicant will have to provide a justification addressing the following points:

- Benefits to public health of the immediate availability on the market
- Risks inherent in the fact that additional data are still required
- How the benefits to public health in the context of immediate availability outweigh the risks (also taking into account the remaining questions)

2. Agency advice prior to submission of a request for conditional marketing authorisation

Article 10 of Commission Regulation (EC) No. 507/2006 addresses advice prior to submission of a marketing authorisation application. Applicants for a potential conditional marketing authorisation may request CHMP scientific advice or protocol assistance, as applicable, on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfils the requirement laid down in Article 4(1)(c) (“*unmet medical needs will be fulfilled*”). In addition, the intention to request a conditional marketing authorisation and any practical or procedural issues with regard to a potential request for conditional marketing authorisation should be addressed at pre-submission meetings with the EMEA and rapporteurs.

3. CHMP proposal for a conditional marketing authorisation

During the scientific assessment, after having consulted with the applicant, the CHMP may also propose a conditional marketing authorisation. This proposal has to be accompanied by explanatory reasons that address fulfilment of the requirements for conditional marketing authorisation set out in Article 4 of Commission Regulation (EC) No. 507/2006. To ensure consistency of application these explanatory reasons will address the elements set out in section 1.2. The aim is that the proposal is made as early as possible, to allow for sufficient time for agreement on the details of the specific obligations. Normally, the proposal and explanatory reasons will be given to the applicant in the day 120 list of questions, or exceptionally later, in the day 150 joint assessment report and day 180 list of outstanding issues. The applicant may be asked to provide any relevant additional information to substantiate the fulfilment of the requirements for conditional marketing authorisation, as necessary. There may be a need for a meeting with the rapporteurs and the EMEA to discuss the details of the specific obligations. The reasons for proposing a conditional marketing authorisation will also be detailed in the CHMP assessment report.

4. CHMP assessment of a request for conditional marketing authorisation

The acceptability of the applicant’s request for a conditional marketing authorisation will be part of the scientific review. The CHMP shall summarise its assessment of the request for conditional marketing authorisation, and particularly the claims that the medicinal product falls within the scope of the regulation for conditional marketing authorisation and that the requirements of Article 4 have been met. The assessment will be reflected in the relevant assessment reports and in the final CHMP assessment report. Similarly, in case of CHMP proposal for a conditional marketing authorisation after having consulted with the applicant, the CHMP will assess if the medicinal product falls into the scope of the regulation for conditional marketing authorisation and if the requirements of Article 4 have been met. The assessment will be reflected in the relevant assessment reports and in the final CHMP assessment report.

In case the CHMP is of the opinion that any of the requirements for the granting of a conditional marketing authorisation are not fulfilled, and where the data provided in the application are considered insufficient to establish a positive benefit-risk balance, this would lead to the adoption of a negative opinion on the granting of a marketing authorisation.

Upon granting of a conditional marketing authorisation, the specific obligations and the timeframe for their completion will be clearly specified in the conditional marketing authorisation (Annex II.C to the Commission Decision), and will be made publicly available by the Agency as part of the EPAR.

5. Information included in the summary of product characteristics and package leaflet

Enhanced transparency regarding the assessment of such applications and clear information should be provided to patients and healthcare professionals on the conditional nature of the authorisations.

The summary of product characteristics and package leaflet will mention that a conditional marketing authorisation has been granted subject to certain specific obligations to be reviewed annually (see Guideline on summary of product characteristics and Quality Review of Documents product information templates).

6. Periodic safety update reports

Article 9 of Commission Regulation No. 507/2006 states that the periodic safety update reports shall be submitted to the Agency and Member States immediately upon request or at least every six months following the granting or renewal of a conditional marketing authorisation. Such requirement will be included in Annex II.B to the Commission Decision.

B. Renewal of a conditional marketing authorisation

Based on Article 14 (7) of Regulation (EC) 726/2004 a conditional marketing authorisation is valid for one year. Thereafter, following Article 6 (1) of Commission Regulation 507/2006, the conditional marketing authorisation may be renewed annually.

1. Date for renewal

Following Article 6 (2) of Commission Regulation 507/2006, the marketing authorisation holder shall apply for its renewal at least six months before its expiry and shall provide the Agency with an interim report on the fulfilment of the specific obligations to which it is subject.

The holder of the marketing authorisation shall submit the renewal application at the latest by the recommended submission dates published on the EMEA website.

2. Timetable

The EMEA will acknowledge receipt of a valid renewal application and shall start the procedure in accordance with the starting dates published on the EMEA website. The holder of the marketing authorisation will be informed of the adopted timetable at the start of the procedure.

The CHMP will assess the renewal application on the basis of the risk-benefit balance and formulate an opinion whether the specific obligations or their timeframes need to be retained or modified, within 90 days after receipt of a valid renewal application. That opinion shall be made publicly available.

The following timetable will apply:

Day 1	Start of evaluation
Day 40	Rapporteur's assessment report sent to co-rapporteur
Day 50	Joint rapporteur and co-rapporteur assessment report
Day 60	First discussion at CHMP: day 60. <ul style="list-style-type: none">➤ If no outstanding issues: adoption of CHMP opinion➤ If outstanding issues: adoption of list of outstanding issues + decision on possible oral explanation by the marketing authorisation holder.
Day 70	Answers from the marketing authorisation holder on outstanding issues
Day 80	Revised rapporteur and co-rapporteur assessment report
Day 90	Oral explanation by the marketing authorization holder (if applicable) Adoption of CHMP opinion

3. Documents to be submitted

3.1 General requirements

In order to allow the CHMP to confirm the risk-benefit balance of the medicinal product and to review the specific obligations and their timeframes for completion, the marketing authorisation holder should provide at least the following information in their renewal application¹:

- a) A chronological list of follow-up measures and specific obligations submitted since grant of marketing authorisation indicating scope, status, date of submission and date when issue has been resolved (where applicable).
- b) Summary of product characteristics, Annex II, labelling and package leaflet (one relevant example)
- c) An interim report on the fulfilment of the specific obligations, including details for each specific obligation. The aim of this report is to inform about the status of the data that is the subject of a specific obligation, to provide interim data as appropriate and agreed, and to inform about the likelihood that the applicant will be able to provide the data (see also section 3.2).
- d) A clinical expert statement addressing the current benefit-risk of the product on the basis of periodic safety update report data and safety or efficacy data accumulated since the granting of the marketing authorisation. In exceptional cases, a non-clinical or quality expert statement may also be required.
- e) Data related to a specific obligation and/or periodic safety update report, where the due date for submission of such data coincides with the renewal application.

Practical details on the presentation of renewal applications are given² in the EMEA post-authorisation guidance document on the EMEA website .

At the occasion of a possible fifth annual renewal of the conditional marketing authorisation, marketing authorisation holders should provide all the information listed in Annex 2 of the Notice To Applicants “Guideline on the processing of renewals in the centralised procedure” together with the interim report on the fulfilment of the specific obligations.

3.2 Requirements for the interim report on the specific obligations

One report should be submitted for the product including all specific obligations. The structure and contents of the interim report will vary depending on the type of study, and available data. The purpose of the information to be submitted for each study is to allow an assessment of the fulfilment of the specific obligations, and should provide sufficient information to allow an assessment of whether such obligations and their timeframes should be retained or modified. In the typical situation where the specific obligations refer to data collected from clinical trials, the following general structure is suggested for interim reporting. It is understood that even for clinical studies, depending e.g., on the design and blinding of trial, one or more subheadings may not be applicable and other data may be required. Agreement on the key elements of the interim reports should be sought during the assessment procedure. Marketing authorisation holders may seek additional guidance from the rapporteurs about the optimal format for submitting an interim report.

Within the interim report for a product, for each specific obligation consisting of a clinical study, it is recommended to provide the following items:

- a) Title page and synopsis

For each of the ongoing or new studies that is part of a specific obligation, a short description (limited to one page or less) should be provided. The description should address the expected overall study plan and design.

- b) Introduction

¹ These requirements apply to annual renewal of conditional marketing authorisations only, replacing the requirements of Annex 2 of the Notice To Applicants “Guideline on the processing of renewals in the centralised procedure”.

² EMEA post-authorisation guidance document will be updated to reflect conditional MA renewal in due time.

Describe the status of development of the study, any issues that are still outstanding or that have a significant impact on the feasibility of the study, expected delays, etc.

c) Accrual

Describe enrolment, accrual over time, accrual by centre, country, and region, accrual by treatment group, information on data availability and follow-up status, and duration of follow-up. Include analyses of issues such as assumptions about accrual, event rates, implications for study power, evaluation of changes in characteristics of enrolled patients over time; conditional power calculations, implications for timing of final analysis.

d) Baseline Characteristics

Display baseline variables by treatment group, eligibility. Describe any issues with screening criteria, impact of exclusion criteria, and issues of generalisability.

e) Adverse Events

Describe adverse events by treatment and severity, at the body system level and at the level of preferred term, and describe the occurrence of serious adverse events.

f) Primary Endpoint Analysis

Describe the expected timing and, to the extent that this can be published based on the protocol and operating procedures, the outcome, of interim analyses or of final analyses, or other available data, as appropriate.

g) Study conduct and compliance

Describe treatment compliance, compliance with efficacy and safety assessments, significant changes in the conduct of the study or planned analyses, important protocol deviations, dropout and missing data, critical quality assurance and quality control findings.

Final reporting of clinical trials should follow the conventional format of study reports (see ICH Topic E3 Note for guidance on structure and content of clinical study reports, CHMP/ICH/137/95).

3.3 CHMP Assessment and Opinion

The CHMP will assess the renewal application, in order to confirm the benefit-risk balance of the medicinal product and whether the specific obligations or their timeframes need to be retained or modified (as detailed in the Annex II).

In order to ensure that medicinal products are not removed from the market except for reasons related to public health, the conditional marketing authorisation will remain valid until the Commission reaches a decision based on the renewal assessment procedure. Therefore, following adoption of a positive opinion, the renewal decision will refer to the expiry date of the preceding marketing authorisation so that the renewed authorisation will be valid for 1 year from the date of the previous expiry.

C. Marketing authorisation not subject to specific obligations

At any time, when the specific obligations have been fulfilled, the CHMP may adopt an opinion in the meaning of Article 14 of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations'). Therefore, the CHMP may recommend the granting of a 'marketing authorisation not subject to specific obligations' at the time of renewal of the conditional marketing authorisation (i.e. in its renewal opinion) or at the time of assessment of the data submitted to fulfil the last remaining specific obligation (i.e. in a CHMP opinion according to Article 7 of Regulation (EC) No 507/2006). The scope of such an Article 7 opinion will have to be judged on a case by case basis, however, where the submission of the results of specific obligations leads to the need to update product information, this will be included in the same Article 7 opinion. In contrast, other changes, i.e., changes not directly linked to the submission of the results of specific obligations should ideally be submitted as variations to the marketing authorisation.

When submitting the last specific obligation data and in view of a possible change to a 'marketing authorisation not subject to specific obligations', the marketing authorisation holder should address this in their submission and provide updated product information and a clinical expert statement in support of the possible granting of a 'marketing authorisation not subject to specific obligations'.

The reasons for proposing the granting of a 'marketing authorisation not subject to specific obligations' will be detailed in the CHMP assessment report.