EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 23 July 2015
2 EMA/CHMP/509951/2006, Rev.1
3 Committee for Medicinal Products for Human Use

4 Guideline on the scientific application and the practical 5 arrangements necessary to implement Commission 6 Regulation (EC) No 507/2006 on the conditional 7 marketing authorisation for medicinal products for human 8 use falling within the scope of Regulation (EC) No 9 726/2004

10 Draft

CHMP discussion	July 2006
Adopted by CHMP for release for consultation	14 December 2006
End of consultation (deadline for comments)	31 March 2007
Consultation with PRAC, CAT, COMP, PDCO	June 2015
Adopted by CHMP for release for public consultation	23 July 2015
Start of public consultation	27 July 2015
End of consultation (deadline for comments)	30 September 2015
Date for coming into effect	To be confirmed

11

12

This guideline draft has been updated in order to reflect the experience accumulated with Conditional Marketing authorisations and is therefore released for repeated public consultation.

Comments should be provided using this template. The completed comments form should be sent to CMA_guideline@ema.europa.eu.

13

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

Table of contents

Executive summary

This guideline has been developed in order to provide advice on the scientific application and the practical arrangements necessary to implement the legal provisions on the conditional marketing authorisation.

1. Introduction (background)

According to Article 14(7) of Regulation (EC) No 726/2004, following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible. By way of derogation, such authorisation shall be valid for one year, on a renewable basis.

This provision for a conditional marketing authorisation is further defined in Regulation (EC) No. 507/2006.

Conditional marketing authorisation, in line with the defined scope and criteria and in the interest of public health, is usually appropriate for products where benefit-risk balance is such that the immediate availability outweighs the limitations of less comprehensive data than normally required, i.e. medicines with an established potential to address an unmet medical need.

2. Scope

This guideline addresses granting and renewing a conditional marketing authorization, as well as granting of a marketing authorisation not subject to specific obligations following their completion. This guideline should be followed unless otherwise justified.

3. Legal basis

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.

4. Granting of a conditional marketing authorisation

4.1. 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 EMA about its intention to request a conditional marketing authorisation as part of the "letter of intent" to be sent to the EMA 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 and, if applicable, also specific proposals for 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 EMA will inform the Commission.

4.1.1. 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 and life expectancy, justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. For a disease to be considered seriously debilitating it would need to have a well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages. 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, i.e. affect an important portion of the target population.

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.

4.1.2. 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

Article 4 (a) of Commission Regulation (EC) No. 507/2006 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.

The demonstration of a positive benefit-risk balance should be based on scientific evidence, in particular evidence from clinical trials. The available evidence should be sufficient to demonstrate the

benefits of the product to a degree that allows them to be assessed against the risks identified in the studies conducted and the risks related to the absence of some of the data (see also requirement (d) below).

Products to be used in emergency situation, in response to recognised health threats, may provide particularly important benefits, therefore higher risks related to the absence of some data may be acceptable. Article 4(1) states that in such cases a conditional marketing authorisation can be granted also if preclinical or pharmaceutical data are not comprehensive. Such applications will be assessed on a case-by-case basis, taking into account the respective health threats and effects of the product. For other categories within the scope of Article 2 only the clinical data can be less comprehensive than is normally the case.

The elements of the comprehensive data that are not available at the time of authorisation should be discussed by the applicant and their acceptability justified based on the strength of available results and taking into account the requirement for a positive benefit-risk balance. If justified, such elements could include:

- results on longer-term, clinically most relevant efficacy endpoint (having used an intermediate endpoint at time of authorisation), e.g. overall survival vs. progression-free survival,
- safety and efficacy results from a larger database or for longer duration, with the same endpoint(s) and in same population, e.g. response rate at a later time cut-off,
- further data on additional endpoints / specific issues identified, e.g. effects on metastases, hepatic disorders,
- further data in important sub-populations, e.g. patients with resistance or a particular biomarker that may be important,
- further data on impact of other medication, e.g., efficacy data with other co-medication for combination therapies.

The establishment of beneficial effects at the time of authorisation could potentially be based on intermediate endpoints that are reasonably likely to translate into clinical benefit, but do not directly measure the clinical benefit. If such approach is proposed, the suitability of the intermediate endpoint should be discussed, and its ability to establish or predict the clinical benefit justified based on the available evidence. In particular, the applicant should discuss the level of certainty with which the intermediate endpoint predicts clinical benefit, and why any remaining uncertainties would be acceptable. Conditional marketing authorisation could be appropriate when an intermediate endpoint shows benefits that outweigh any uncertainties about the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required. It has to be also clarified that in cases when the used intermediate endpoint is a fully validated surrogate endpoint and further data on actual clinical benefits are not required, a marketing authorisation not subject to specific obligations might be appropriate.

Scenarios of establishing a positive benefit-risk balance with less than comprehensive data include also situations when comprehensive data would require other additional data (e.g. with longer duration or more data on particular subgroups), but the benefits demonstrated with the available data outweigh the risks and it would be disproportionate from the public health perspective to delay the approval of the product.

The limitations in the extent of safety data available contribute to the uncertainties and are to be taken into account in the benefit-risk balance. The acceptability of safety of the product has to be assessed

on a case by case basis, based on the safety data available and taking into account the demonstrated benefits of the product.

In summary, for a conditional marketing authorisation it might be acceptable that studies are smaller in size and/or with a shorter duration and/or different endpoints than normally expected for confirmatory studies in the particular indication for respective type of the product. However, it has to be substantiated that the benefits demonstrated with the available data outweigh the risks, also considering the increased uncertainties around the benefits and risks that are related to the less comprehensive nature of the data. Since the risks related to limitations of data are unlikely to be estimated precisely, it is expected that beneficial effects observed are particularly strong for the respective endpoint in the light of the totality of evidence available, therefore indicating a particularly promising 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.
- 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 providing comprehensive clinical data and 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, providing information on clinically most relevant (long term) endpoints, investigating the effect duration, providing larger safety database, and generally providing a better understanding 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 and to achieve a comprehensive dossier on the product. 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 will result in a resolution of 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 how 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. Granting of a marketing authorisation 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 renewal. Specific obligations may be imposed also 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.

The applicant is strongly encouraged to discuss in advance of the submission of marketing authorisation application (e.g. in a scientific advice procedure) the overall development plan and design of studies that are planned to be completed before authorisation and conducted as specific obligations following the granting of a conditional marketing authorisation. When discussing development programme for a conditional marketing authorisation it is recommended to include prospective scenario building for the potential marketing authorisation, planning the impact of future outcomes on next steps in the development programme (including on proposed specific obligations).

The applicant for an orphan medicinal product for which the designation is based on significant benefit over existing therapies, when preparing and discussing the development programme, is encouraged to consider also suitability of the data to be generated for confirmation of the orphan designation at the time of 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 should 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 critical 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.

Fulfilment of an unmet medical need is a major feature of products suitable for conditional marketing authorisation and indicates the particular value that the product is expected to bring, which also allows outweighing not just the risks clearly identified at the time of authorisation, but also the risks related to less comprehensive data than would be normally the case.

To address this requirement, applicants should justify that there exists an unmet medical need and that it is necessary to introduce new methods 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 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. In exceptional cases, also major improvements to patient care could provide a major therapeutic advantage, e.g. if the new treatment is expected to address serious existing issues with treatment compliance or if the treatment allows ambulatory treatment instead of treatment in hospital only.

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).

As advantages over existing treatments are relevant also for confirmation of orphan designation by the Committee for Orphan Medicinal Products (COMP) for products where the designation is based on significant benefit, the CHMP and COMP will cooperate in their assessments of such applications as necessary (e.g. by sharing the CHMP assessment reports with COMP).

In order to support the claim that unmet medical needs will be fulfilled, the applicant is 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 will address 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 (see also requirement (a) above).

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)

4.2. 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"). Please see also section 1.2.(b) above regarding the scientific advice on development programme for products intended for conditional marketing authorisation and the recommended approach of prospective scenario building. Applicants may also consider requesting parallel scientific advice with Health Technology Assessment bodies.

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 EMA and rapporteurs.

The applicants are reminded that prospective planning of conditional authorisations is important for ensuring swift assessment procedure, and is especially important in cases when accelerated assessment is requested.

4.3. 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. During the consultation, the applicant will be requested to provide their position on the possible granting of a conditional marketing authorisation and, in case of an agreement also their justification regarding 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 the response should address the elements set out in section 1.2.

The proposal should be made as early as possible, in order to allow sufficient time for agreement on the details of the specific obligations. Normally, the proposal will be made 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. The reasons for proposing a conditional marketing authorisation will be detailed in the CHMP assessment report.

4.4. 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 requirements for granting of a marketing authorisation not subject to specific obligations are also not met, 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 to the Commission Decision), and will be made publicly available by the Agency as part of the European Public Assessment Report.

4.5. 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).

4.6. 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. The requirements for PSUR submission will be reflected in the EURD list and referred to in Annex II to the marketing authorisation.

5. 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.

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 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 and whether the marketing authorisation should be maintained, varied, suspended or revoked.

The marketing authorisation holders are reminded that specific obligations are imposed with an aim to confirm that the benefit-risk balance is positive, therefore in case of a non-compliance with specific

obligations the CHMP may consider that the positive benefit-risk balance is not confirmed and recommend appropriate regulatory action.

In order to ensure that medicinal products are not removed from the market except for reasons related to public health, based on Article 6 (4) of Regulation (EC) 507/2006 the conditional marketing authorisation will remain valid until the European Commission adopts a decision following the renewal assessment procedure, provided that the renewal application has been submitted on time.

The renewal of the marketing authorisation will continue to be conducted annually, while the authorisation remains conditional. When the specific obligations will be completed and a marketing authorisation not subject to specific obligations issued (as defined in Article 7 of Regulation (EC) 507/2006), it will be valid for 5 years.

5.1. Documents to be submitted

5.1.1. 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 application[1]:

a. A chronological list of specific obligations and other conditions to the MA 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

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 data generated in Specific Obligations and taking into account any other safety (including PSUR) 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 specific obligations, where the due date for submission of such data coincides with the renewal application.

If the data included in the renewal submission warrants an update of the product information or risk management plan, such proposed changes can be included as part of the renewal procedure.

Data included in other submissions, but relevant to the benefit-risk balance of the product should be taken into account in preparation of the renewal application. However, the renewal should not replace other required submissions (e.g. variations) and submission of such data should not be postponed to the next renewal.

Practical details on the presentation and submission of renewal applications are given in the EMA post-authorisation guidance document on the EMA website.

[1] These requirements apply to annual renewal of conditional marketing authorisations only, which are outside the scope of "Guideline on the processing of renewals in the centralised procedure" EMEA/CHMP/2990/00

5.1.2. 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 impact of available data on benefit-risk balance, 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 reports. 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 these reports on fulfilment of specific obligations should be sought during the assessment procedure.

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

   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. Study 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, CPMP/ICH/137/95).

6. Marketing authorisation not subject to specific obligations

At any time, when the specific obligations have been fulfilled, the CHMP may adopt an opinion pursuant to Article 7 of Regulation (EC) No 507/2006 recommending granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations'). This can be done at the time of renewal of the conditional marketing authorisation or at the time of assessment of the data submitted to fulfil the last remaining specific obligation. 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.

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.

Abbreviations

CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CTD	Common Technical Document (an agreed format for documentation)
EMA	European Medicines Agency
EURD list	List of EU reference dates and frequency of submission of PSURs
PDCO	Paediatric Committee
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
WHO	World Health Organisation

References

1. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended
2. Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council