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# 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

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# 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

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# 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, taking into account the experience gained so far.

# 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 Commission 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 the 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.

When references in this guideline are made to the assessment activities conducted by the CHMP, for advanced therapy medicinal product they should be read as referring also to the assessment conducted by the Committee for Advanced Therapies.

# 2. Scope

This guideline addresses the granting and renewal of conditional marketing authorisations, as well as the subsequent granting of marketing authorisations not subject to specific obligations following their completion.

# 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 submission of the application for marketing authorisation.

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 of Commission Regulation (EC) No 507/2006) and that the requirements for conditional marketing authorisation are fulfilled (Article 4 of Commission Regulation (EC) No 507/2006), 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 that an application for a conditional marketing authorisation has been submitted (Article 3 of Commission Regulation (EC) No 507/2006).

### 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 a conditional marketing authorisation. The categories of medicinal products that fall within the scope of the conditional marketing authorisation 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 European Union (Decision of the European Parliament and of the Council No. 1082/2013/EU on serious cross-border threats to health[1]). A reference to the relevant WHO Resolution or Decision, or to the measures adopted by the Commission in the framework of the Decision of the European Parliament and of the Council No. 1082/2013/EU on serious cross-border threats to health should be provided.

3. Orphan medicinal products

   A copy of the Commission Decision on the designation as an orphan medicinal product should be provided.

[1] Repealing Decision No. 2119/98/EC

## 4.1.2. Fulfilment of the requirements for conditional marketing authorisation

The requirements for a conditional marketing authorisation 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 its opinion each of these requirements are expected to be met:

**(a) The benefit-risk[2] balance of the product is positive**

Article 4 (a) of Commission Regulation (EC) No. 507/2006 states that one of the criteria for granting a conditional marketing authorisation is that the benefit-risk balance of the medicinal product is positive, as defined in Article 1(28a) of Directive 2001/83/EC.

In general for any marketing authorisation application, the demonstration of a positive benefit-risk balance should be based on (comprehensive) scientific evidence, in particular evidence from clinical trials (usually randomised controlled trials) that can provide the most convincing evidence to support assessment of therapeutic efficacy, safety and hence benefit-risk balance.

The data requirements laid down in Annex I of Directive 2001/83/EC, are also applicable for products granted conditional marketing authorisation. However, in the case of conditional marketing authorisation the evidence at the time of initial authorisation may be less comprehensive than normally required. For the demonstration of a positive benefit-risk balance the available evidence should be sufficient to demonstrate the benefits of the medicinal 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).

The uncertainties related to the absence of comprehensive clinical data in a conditional marketing authorisation generally require that uncertainties 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 and only the clinical data could be less comprehensive than is normally the case.

However, products to be used in emergency situations, 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 medicinal product.

The safety profile of the medicinal product should be adequately defined and appropriate to justify a positive benefit-risk balance.

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

- results on longer-term, clinically most relevant efficacy endpoint (when using an intermediate endpoint at time of authorisation), e.g. survival data vs. overall response rate,

[2] The term "benefit-risk balance" (used in this guideline) should be regarded as interchangeable with the term "risk-benefit balance" (used in Regulation (EC) No 507/2006).

- safety and efficacy results from a larger database or for longer duration, with the same endpoint(s) and in the 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,
- vaccine effectiveness data, having used e.g. immunogenicity data for authorisation,
- 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. The granting of a conditional marketing authorisation could be appropriate when an intermediate endpoint shows benefits that outweigh the uncertainties about the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required. It also has to be clarified that in cases when the used intermediate endpoint is a fully validated surrogate endpoint (e.g. as confirmed with a CHMP qualification opinion in the framework of scientific advice) 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 the available data would require to be complemented by additional data (e.g. with longer duration, larger database or additional endpoints) in order to be considered comprehensive, 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 medicinal product.

The limitations in the extent of safety data available contribute to the uncertainties and are to be taken into account in the evaluation of the benefit-risk balance. The acceptability of safety of the medicinal product has to be assessed on a case-by-case basis, based on the available safety data and taking into account the demonstrated benefits of the medicinal 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 those normally expected for confirmatory studies in the particular indication for respective type of the medicinal product. However, it has to be substantiated that the benefits demonstrated by 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, the beneficial effects observed will have to be expected to translate into compelling clinical benefits, therefore indicating a particularly promising medicinal product that might bring considerable added value.

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

- Positive benefit-risk 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 provide comprehensive clinical data confirming that the benefit-risk 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 with 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 medicinal product.

The specific obligations imposed should aim to obtain evidence to confirm the positive benefit-risk balance in the approved indication and to achieve a comprehensive dossier on the medicinal 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. Specific obligations typically include, but are not limited to randomised clinical trials.

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 are addressed within an appropriate timeframe.

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 being, or to be, performed as specific obligations to avoid potential difficulties after granting a conditional marketing authorisation, for instance difficulties in recruitment of subjects, 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 particularly 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 a marketing authorisation application (e.g. in a scientific advice procedure) the overall development plan and design of studies that, on one hand, are planned to be completed before authorisation and, on the other hand, will be conducted as specific obligations following the granting of a conditional marketing authorisation. When discussing the 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 the 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, including:

- 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)
  - Study population and the number of subjects to be included with corresponding justification
  - 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 of the Article specifies that unmet medical needs mean a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union 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, outweighing not only 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 satisfactory methods exist, or that it is necessary to provide a major improvement over 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).

In order to support the claim that unmet medical needs will be fulfilled, the applicant shall 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

Special considerations apply in cases when comparison with authorised methods involves already conditionally authorised medicines, and for orphan medicines, when orphan designation is based on significant benefit.

At the time of recommending a conditional marketing authorisation it must be established that unmet medical needs can be addressed by the product in question, while the extent to which those needs will be addressed over time is gradually confirmed after authorisation through completion of specific obligations. For the demonstration of fulfilment of unmet medical needs by a second or subsequent product, the accumulated clinical data and residual uncertainties concerning the effects of an already conditionally authorised medicine(s) should be taken into account. While the specific obligations are not yet fully completed, it is not possible to confirm the full benefit of a conditionally authorised product, therefore another medicinal product could potentially address the same unmet medical needs, provided it is expected, based on appropriate scientific data, that such a product addresses the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product. A second (or subsequent) medicinal product could in such case be recommended for a conditional marketing authorisation. This is without prejudice to any market exclusivity rights of orphan medicinal products under Regulation (EC) No 141/2000, which may prevent the granting of a marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product.

As advantages over existing treatments might also be relevant for confirmation of orphan designation by the Committee for Orphan Medicinal Products (COMP) for medicinal products where the orphan designation is based on significant benefit, the CHMP and COMP will cooperate during their assessment of such applications as necessary (e.g. by sharing the CHMP assessment reports with COMP as they become available). The applicants should bear in mind that provisions on conditional marketing authorisations differ in their nature from provisions on orphan medicinal products. Orphan medicinal products benefit from market exclusivity, the protection of which requires a strict interpretation. Recommending a conditional marketing authorisation by the CHMP does not imply a confirmation of significant benefit (to be assessed by the COMP).

**(d) 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 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 of the medicinal product
- 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 Agency's 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 4.1.2.(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 are also encouraged to engage with Health Technology Assessment bodies during the development, e.g. through a parallel scientific advice.

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 avoiding delays in assessment procedure, and is especially important in cases when accelerated assessment is undertaken. As medicinal products addressing unmet medicinal needs are expected to be of major interest from the point of view of public health, Applicants are encouraged to duly consider the appropriateness of seeking accelerated assessment for medicinal products suitable for a conditional marketing authorisation.

## *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 4.1.2.

The proposal should be made as early as possible, in order to allow sufficient time for reaching an agreement with the Applicant on the details of the specific obligations and their timeframe. 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[3]. 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 Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation and that the requirements of its Article 4 have been met. Such assessment will be reflected in the relevant assessment reports in the course of the procedure 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 Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation and if the requirements of its Article 4 have been met. The assessment will be reflected in the relevant assessment reports in the course of the procedure 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 is 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.

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 (EC) 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

[3] Please refer to the EMA pre-authorisation guidance document published on the EMA website for further details on the steps of the assessment procedure for initial marketing authorisation applications.

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) No 726/2004 a conditional marketing authorisation is valid for one year. Thereafter, following Article 6 (1) of Commission Regulation (EC) No 507/2006, the conditional marketing authorisation may be renewed annually.

Following Article 6 (2) of Commission Regulation (EC) 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 benefit-risk 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 CHMP will conduct the assessment in a 60 day procedure, with an additional 30 day procedure for assessment of responses to a List of Outstanding issues, if necessary.

Modification of specific obligations or the due dates for their completion imposed at the time of granting marketing authorisation may be accepted only based on an appropriate justification and for reasons that could not be expected at the time of authorisation. Any foreseeable delays with fulfilment of specific obligations that become apparent after authorisation and their impact on the benefit-risk balance should be reported promptly. Extension to the due date for completion of a specific obligation may be granted only if the evidence provided in the interim report(s) indicates that the benefits for patients from the availability of the product on the market still outweigh the risks inherent in the remaining uncertainty related to the additional data that are still required.

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

The renewal of the marketing authorisation will be conducted annually, while the authorisation remains conditional. Once the specific obligations are fulfilled and a marketing authorisation not subject to specific obligations is issued (as defined in Article 7 of Commission Regulation (EC) No 507/2006), the marketing authorisation will be valid for 5 years, in accordance with Article 14(1) of Regulation (EC) No 726/2004.

## *5.1. Documents to be submitted*

### 5.1.1. General requirements

In order to allow the CHMP to confirm the benefit-risk 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[4]:

[4] 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

a. A chronological list of specific obligations and other conditions to the MA submitted since the granting of the 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 4.1.2(b)).

d. A clinical expert statement addressing the current benefit-risk balance 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.g. if important new non-clinical of pharmaceutical data is available.

e. Data related to specific obligations, where the due date for submission of such data coincides with the renewal application and where the data have not already been submitted separately.

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.

## 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 and an assessment of the fulfilment of the specific obligations. It 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 general structure shown below 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 already during the initial marketing authorisation application 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

When the specific obligations have been fulfilled, the CHMP may, in accordance with Article 7 of Commission Regulation (EC) No 507/2006, adopt an opinion recommending the 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

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| 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