EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice procedures

For consultation

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Abbreviations

AIFA	Agenzia Italiana del Farmaco
AQUAS	Agency for Health Quality and Assessment of Catalonia
CHMP	Committee for medicinal products for human use
EC	European Commission
EMA	European Medicines Agency
EUnetHTA	European Network for Health technology Assessment
G-Bba	Gemeinsamer Bundesausschuss
HTA	Health Technology Assessment
HAS	Haute Autorité de Santé
HVB	Hauptverband der österreichischen Sozialversicherungsträger
HTABs	Health Technology Assessment Bodies
LOI	Letter of Intent
NICE	National Institute for Health and Care Excellence
SAWP	Scientific Advice Working Party
SEED	Shaping European Early Dialogues
TC	Teleconference
TLV	Tandvårds- och Läkemedelsförmånsverket

1. Draft Process

1.1. Introduction

As the first step to market access, a new medicine requires a marketing authorisation from a medicines regulatory agency. The second step prior to enabling patient access to a new therapeutic option increasingly involves the assessment of its usefulness to the healthcare system that lies with a payer or healthcare-guidance organisation, and the Health Technology Assessment Bodies (HTABs) that advise them.

A strong interaction between regulators and HTABs is critical to enable innovation to reach patients, and ultimately for the benefit of public health. There is a clear need to initiate early dialogue between medicines developers, regulators and HTABs to discuss and agree on a development plan that generates data that both parties can use to determine a medicine's benefit-risk balance and value. For this document, and the purposes of Parallel Scientific Advice, the European Medicines Agency (EMA) is the European Union body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products, including the provision of scientific advice for regulatory ends.

The HTABs operate at a local or national level under specific local or national rules. See below for Products and indication in scope for participating HTABs.

The following process has been drafted based on the experience to date since 2010 with the help of multi-stakeholder working group comprising the European Medicines Agency (EMA) and regulatory National Competent Authority delegates from the EMA Scientific Advice Working Party (SAWP), with HTA representatives from NICE, AIFA, G-Ba, TLV, as the HTAs who have undertaken such procedures most frequently. Other HTABs who have undertaken EMA HTA Parallel Scientific Advice procedures have also been consulted including AQUAS, HAS, and HVB.

Since 2010, the EMA has put in place a pilot project of Parallel Scientific Advice with the participation of the above mentioned HTA bodies that allows developers to receive simultaneous feedback from both regulators and national HTA bodies on their development plans for new medicines. Further input on the draft process was received during the EMA HTA workshop on Parallel Scientific Advice 26th November 2013.

In addition to this initiative, HTABs have performed several multi-HTABs early dialogues in the framework of the EUnetHTA Joint Actions (JA) 1 and 2, and EMA was invited to participate as observer in the multi-HTABs early dialogues of EUnetHTA JA2. In addition, since September 2013, under the coordination by HAS, 14 HTABs have initiated the SEED (Shaping European Early Dialogues for health technologies) project, financed by the EU Commission, to perform 10 additional multi-HTABs early dialogues and explore possible scenarios for conducting early dialogues in the future. EMA is associated to the SEED project and will take part in three of these dialogues as EMA SEED parallel advice procedures. Both the results of EUnetHTA JA2, the SEED project as well as the results of EMA HTA Parallel Scientific Advice pilot (the draft process under consideration in this document) and the public consultation will be carefully taken into account and assessed to lead possibly to a revised workflow/ process to best meet the objective of the Early Dialogue exercise in the medium term.

1.2. Principles

This Parallel Scientific Advice with EMA and HTABs will continue as a pilot project. This document sets out the best practice for all parties, including HTABs, EMA and Applicants undertaking an EMA HTA Parallel Scientific Advice procedure under this pilot. This best practice guide highlights ideal timelines and actions for each party.

EMA HTA Parallel Scientific Advice is a multi-stakeholder procedure. As a multi-stakeholder procedure, communication between project managers of all stakeholders is important to ensure agreement and clarity on ownership of different actions.

Each participating body adheres to the roles and responsibilities under their respective remit.

The process is confidential.

Products and indication in scope; EMA

No restriction in indications is foreseen from the EMA perspective beyond those products should be in scope for standard EMA scientific advice, qualification advice, qualification opinions or Broad advice on non-product specific areas. Advice may be requested for all medicinal products for use in humans, (as defined in Directive 2001/83 (as amended)), irrespective of the medicinal product's eligibility for the centralised procedure, including advice on the design of studies and trials to support quality, safety and efficacy of a medicinal product at all stages of the product lifecycle. This may include post-authorisation safety and efficacy studies and risk management planning incorporating risk minimisation measures. For the EMA, the Scientific Advice or Protocol Assistance is provided pursuant to Article 57 (1.n) of Regulation (EC) No 726/2004). The scientific advice provided by the EMA is adopted by Committee for Medicinal Products for Human Use (CHMP) having been elaborated through the Scientific

Advice Working Party (SAWP). SAWP members may be CHMP members or European experts from regulatory authorities or academia, and are supported by the EMA secretariat. See the published EMA Scientific advice Guidance document for further details.

Products and indication in scope; HTABs

Applicants should familiarise themselves with the scope, prerequisites and activities of participating HTABs. Available information has been collated by HTAs participating in the pilot, and is available on demand from EMA Scientific Advice Office. It should be noted that *some* HTA agencies may charge fees for participation in Scientific Advice in addition to those fees charged by the EMA Scientific Advice. It is the choice of the Applicant which HTABs to select and approach. If considering more than 5 HTABs, additional discussion with an EMA Scientific Advice Officer is recommended. There is no obligation for invited HTABs to participate in a specific procedure.

A common briefing document is used; each question can be addressed to the EMA, or the HTABs alone, or to both. Use of the associated briefing document template is strongly recommended. See Annex.

The advice provided by each stakeholder is not legally binding and provided in line with their usual practice.

1.3. Phases of the EMA HTA Parallel Scientific Advice process

Scientific advice with HTABs and the EMA has a pre-notification phase, a pre-validation phase and a meeting phase. See Figure 1 below for the overview and actions by each party in parallel.

1.3.1. Pre-notification phase

It is strongly recommended that Applicants engage early in informal discussions with HTABs and EMA to pre-notify their intention for procedure, the product, timescale, and which stakeholders are expected to participate well in advance of sending a formal Letter of Intent to the EMA.

When the preferred date of the face to face meeting is known by the Applicant, the Applicant requests a confirmation from the EMA regarding the agreed date, time and place of the Face to Face meeting.

It is recommended to pre-notify the EMA approximately 6 months before the intended Face to Face meeting in the event a pre-validation phase with a TC is anticipated. However, 4 months could be an adequate period for pre-notification where a shortened pre-validation phase is anticipated. The Applicant is responsible for sending this EMA date confirmation to the HTABs they wish to invite.

The EMA date confirmation should be received by the HTABs at the latest 3 months in advance of the Face to Face meeting for organisational purposes.

Additional HTABs are able to join the procedure in later phases if they are agreeable.

HTABs may also participate as observers only following invitation by the Applicant.

EMA can brief participants on the expected process.

The EMA can provide contact details of the HTABs to the Applicant.

The pre-notification phase ends when the Applicant sends the Letter of Intent to the EMA once all parties have confirmed their participation. The Letter should be sent in line with published EMA scientific advice timetables for a 70 day procedure (with or without a pre-submission meeting).

Communication and coordination during a procedure

It is preferable to have one principal point of contact (with a backup) for all stakeholders. The Letter of Intent should be sent to EMA with the email and phone contact details of all participating stakeholders.

The EMA Scientific Advice Officers and HTAB project managers should be kept up to date with any changes/developments. E.g. new HTABs/ contact changes.

At an early stage, HTABs and EMA may consider the clinical experts required for participation in the procedure and Face to Face meeting. Two Co-ordinators who are members of the EMA Scientific Advice Working Party (SAWP), from national regulatory agencies are appointed to lead their respective assessment teams for the SAWP. For the EMA, conflict of interest of experts and patient representatives will be handled in line with standard EMA policies.

Project managers (EMA, HTABs and Applicant) will consult early on a draft timetable (EMA will provide a first draft) to be agreed for key dates in the parallel procedure (see example of draft time table of dates below). This should be communicated as early as possible to all stakeholders to facilitate work planning and co-ordination.

Calendar meeting requests will be sent by EMA to HTABs and other regulatory participants.

EMA uses Eudralink - a secure system for sending /receiving documents between parties in its in house procedure. The Applicant should clarify with HTABs on their preferred method of sending and receiving documents.

The Applicant is responsible for sending any Applicant documents to the HTABs and to the EMA parties.

Whilst there is some flexibility in arranging deadlines, it is advisable to adhere to timelines to ensure the optimum time is available to assessors and reviewers of documents.

Document version control and numbering is essential to ensure all parties have the appropriate document at the correct time.

1.3.2. Pre-validation Phase

There are different options for Applicants to consider which will allows some flexibility in the pre-validation phase.

Option 1: 60-80 day pre-validation phase allows a possible teleconference (TC) between HTABs, EMA and the Applicant. This would be most suitable for inexperienced Applicants or very complex or controversial programs. Invited HTABs reserve the option to participate in the TC or comment via email, further to review of the draft briefing document. The procedure timetable will be based on the EMA published scientific advice timetables for a 70 day procedure with a pre-submission meeting.

Option 2: ~45 day pre-validation phase with no TC, but with written comments from EMA and HTABs where necessary for the optimisation of the draft submission. The procedure timetable will be based on the EMA published scientific advice timetables for a 70 day procedure without a pre-submission meeting.

In case of option 1 and 2, the first draft of the briefing book should be sent to the EMA in line with the agreed timetable for the procedure.

For option 1: A pre-validation teleconference (TC) will take place approximately 2-3 weeks after the briefing book has been received by all parties; involving the EMA, HTABs and Applicant. The EMA will arrange this TC upon agreement of the timetable and send TC details to all parties.

The Applicant circulates the pre-validation presentation with numbered slides covering briefly the background, the questions and Applicant positions, to all participants at least 48 hours before the TC including a list of Applicant's participants.

The aim of the pre-validation TC is to discuss the scope, wording and clarity of the questions, and whether the material provided in the briefing package is sufficient to answer the questions posed. Reviewing the choice of questions, such as questions on population, comparator etc at an early stage is considered important as the procedure will not be able to expand to add new questions at a later date.

After, the pre-validation TC, the EMA will send their regulatory comments on the package in writing within 2 days. HTABs may send comments on the package/seek clarifications individually to the Applicant after the pre-validation TC according to their usual practice. It is considered helpful if comments are shared among participants.

For Option 2: comments from the EMA and HTABs will be provided in writing as needed allowing sufficient time to revise the draft document, and in line with the agreed procedural timetable.

In either option, the Applicant sends a revised final briefing document, addressing the EMA comments and HTAB points of clarification in the agreed time frame to the EMA contacts, and to the HTABs in the manner agreed.

The pre-validation phase ends with the submission of the final document. This is timed to coincide with the SAWP meeting 1 (the formal procedure start) in standard EMA scientific advice. The EMA will conduct an administrative check to ensure the briefing pack is fit for purpose i.e. that all annexes and references are present.

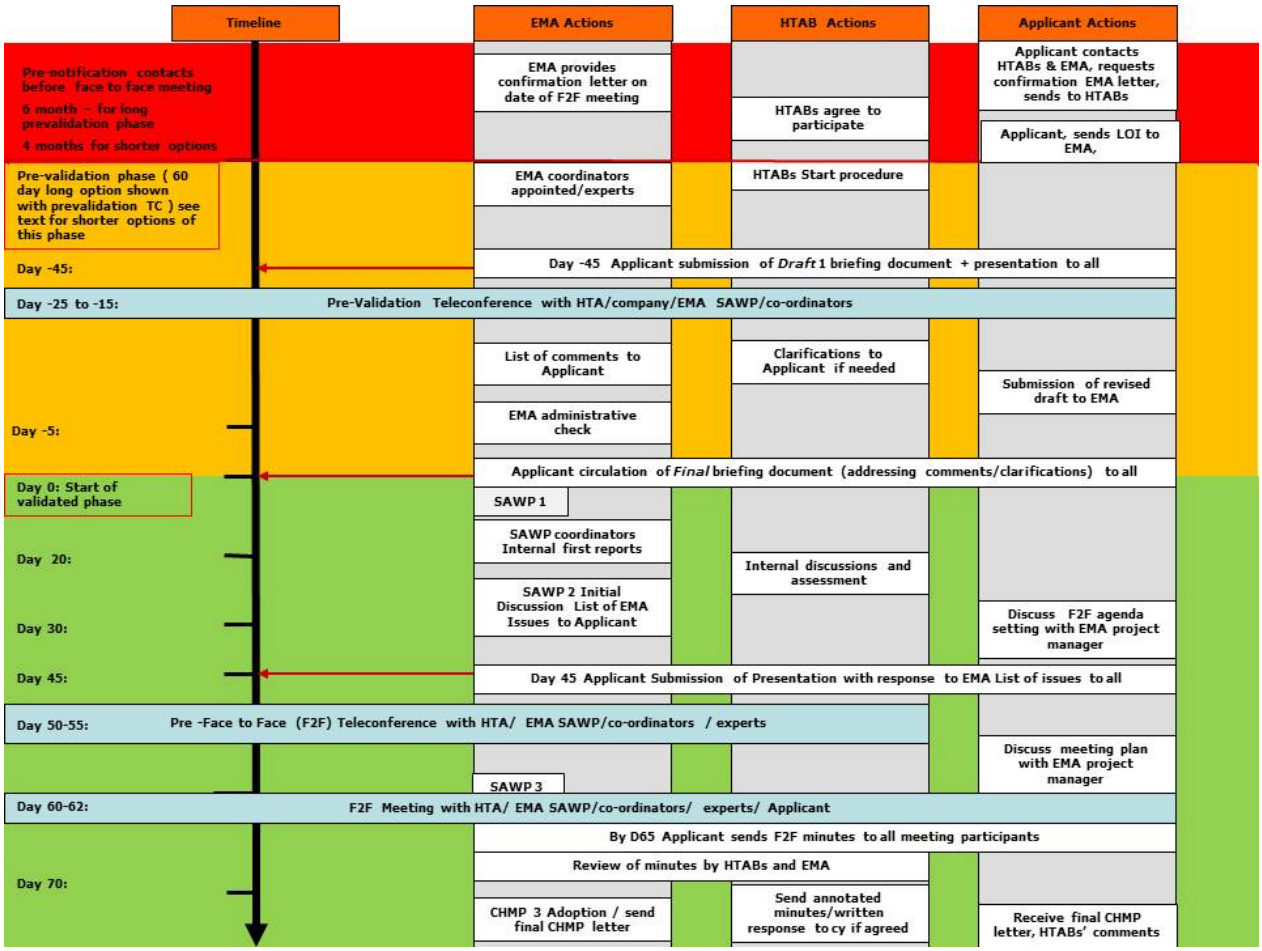

Figure 1 Overview of process and actions by each party in parallel showing the longer pre-validation phase.

1.3.3. Meeting Phase

In the EMA regulatory process, the scientific advice working party (SAWP) discusses the first reports (preliminary views) at the SAWP 2 meeting and generates a List of Issues by the end of SAWP 2. EMA sends this List of Issues to the Applicant. The Applicant is strongly recommended to send the EMA List of Issues to the HTABs. HTABs consider it very helpful to receive this document. This will facilitate the discussion during the Face to Face meeting indicating the focus of regulators' discussion.

HTABs' in-house processes: each HTAB proceeds with their internal assessment and discussion in accordance with national policies and requirements.

The Applicant is advised to contact the EMA Scientific Advice Officer to discuss the format of the Face to Face meeting.

The Applicant should send the presentation for the Face to Face meeting within 2 weeks of receipt of the List of Issues - to the EMA and to the HTABs, together with any written responses if these are requested.

The presentation can include a very brief introduction, rationale and status of the program; all the briefing document questions and key points of the Applicant can be addressed. Tables and figures are useful. The issues raised by the EMA can be intercalated into the presentation with the relevant question but this can be discussed with the EMA scientific officer. The introduction, rationale and status of the program section should be very brief to maximise the time for the questions and discussion. It is usual to pause after each question/issue for discussion. Once sent to the meeting participants, according to the agreed timelines, the presentation should not be substantially amended by the Applicant.

Amended development plans triggered by the EMA List of Issues or external factors.

These can be accommodated during the meeting phase. However, to facilitate sufficient time for review of the amended development plan, it is stressed that the Applicant should advise all parties of their intention to submit it as soon as this is decided. The plan must be received by all parties, at the latest, by 2.5 weeks before the Face to Face meeting together with: the presentation for the Face to Face meeting, a clear comparative table of changes in the plans, and justification for the changes. Any substantial changes to the development plan submitted past this date cannot be addressed within the Face to Face meeting or minutes, at least by some HTAs.

The EMA will arrange a closed preparatory TC with the HTABs. This will be arranged to take place after the Applicant sends the responses to the List of Issues/presentation in order to review respective preliminary positions. The purpose of the Pre-Face to Face TC is to identify critical divergences between HTABs and the EMA on the proposed development plan. Feedback on possible divergences will be communicated to the Applicant in advance of the Face to Face meeting by the EMA Scientific Advice Officer to facilitate preparation for the meeting, with the caveat that important divergences may also be discerned during the Face to Face meeting, and that this feedback does not prejudge the Face to Face meeting.

The Face to Face meeting will normally have 2 co-chairs: one from EMA/SAWP and one from the HTABs. Regarding the choice of HTAB chair, this will rotate amongst the HTABs and will be agreed between the HTABs, on a case by case basis. The EMA Scientific Advice Officer will liaise with participating HTABs, and the chair should be agreed 4 weeks in advance of the Face to Face meeting.

The Meeting time is approximately 4 hours including a short break. The Applicant can prepare the agenda allocating time according to priorities, sending this with the presentation and list of Applicant attendees. Hard copies are not required.

HTABs are asked to send their final list of attendees to the EMA also in advance of the meeting. The EMA will circulate a final list of regulatory participants 2 days in advance of the Face to Face meeting. The meeting is hosted at EMA premises.

The inclusion of patient representatives in the Face to Face meeting is encouraged; briefing of chairs, and patients regarding the purpose and role of the meeting and of patient representation is essential. Additional time or facilities required by patients should be considered in these cases.

During the Face to Face meeting; the views of each stakeholder should be clearly represented on each issue.

1.4. Advice format

The Applicant is expected to send detailed minutes of the Face to Face meeting, attributing individual views to the respective stakeholder, within 5 days to all participants who will review these. In this respect, minutes should reflect the views for each HTAB participating to the Face to Face meeting discussion.

The EMA final advice letter contains CHMP regulatory advice only. HTAB feedback is provided directly to companies during the Face to Face meeting, according to HTAB normal practice or by annotating the Applicant's minutes, or by providing written answers. For some countries, minutes do not replace the national advice protocol for official purposes. See the collated HTAB information referred to above.

1.5. Amendments to development plans

See above in meeting phase.

1.6. Follow up procedures

A procedure can be a follow-up to an earlier Parallel Scientific Advice procedure for the same indication. There is no time window during which this has to be completed. It would be expected that follow up procedures are shorter, omitting the need for a TC in the Pre-validation phase. The briefing document should contain a clear table of the changes compared to the previously reviewed development plan with justifications.

1.7. Example of procedural Timetable

Date (example)	Step description
11 Dec	The Applicant sends the LOI to EMA
	Engagement with intended HTABS
05 Feb	The Applicant sends the briefing package to all parties
10 Feb	The Applicant sends the pre-validation TC presentation to all parties
13 Feb	Pre-validation TC all parties
28 Feb	The Applicant sends the revised briefing package to EMA administrative check
03 Mar	Start of the validated procedure (SAWP 1) Applicant sends Final briefing package to all parties
04 April	The SAWP secretariat circulates to the Applicant the List of Issues. This list can be shared by the Applicant to the HTABs (strongly recommended)

15 April	The Applicant sends the presentation and any requests responses for the F2F meeting considering the comments and clarifications received in the EMA List of Issues.
24 April	Pre-F2F TC together with the HTABs not including The Applicant
07 May	F2F meeting
15 May	The Applicant sends the minutes of the meeting to EMA and HTABs
23 May	EMA sends to the Applicant the final advice letter endorsed by the CHMP.
23 May	HTABs send comments on minutes/written responses depending on HTA practice

2. Questions for public consultation on the Process for EMA-HTA Parallel Scientific Advice

Please see the following link for questions for consultation.

Closing date for responses: **14th July 2014.**

https://adobeformscentral.com/?f=WIJldoXFmz7BsTWjUwOiDA

(**Software required to fill out form:** - Any web browser on desktop, mobile, tablet)

3. Annex Briefing Document Template

Rev. 0

EMA -HTA <Parallel Scientific Advice/Protocol Assistance>

Briefing Document Template

[Standard headings in the template should be used whenever possible; if it is considered necessary to deviate from the pre-specified headings to accommodate product-specific requirements, alternative or additional headings/sections may be considered.

This annotated template should be read in conjunction with the relevant guidelines that can be found on the website of the European Medicines Agency: 'EMA Guidance for Companies requesting Scientific Advice or Protocol Assistance' (EMEA-H-4260-01-Rev.6).

Bracketing convention: {text}: Information that is required to be filled in; <text>: Text to be selected or deleted as appropriate.

[Text] is for explanation and guidance.

Formatting convention: Verdana 9 pt, single space, justified.

References convention:

- For citation of literature references, footnotes are preferred, alternatively the format (first author <et al.>, publication year) is recommended.]

Invented Name:	{}
Active substance:	{}
Pharmaco-therapeutic group:	{}
Intended indication(s):	{}
Company:	{}
Co-ordinators:	{} *[to be completed at the time of final submission of the scientific advice/ protocol assistance briefing document]*
Agencies:	{} *[list here all agencies providing advice]*
Version:	{}
Date:	{DD/MM/YYYY}

Table of Contents

List of Figures

List of Tables

List of Abbreviations

[Any acronyms or abbreviations used should also be defined the first time they appear in the text.]

I. Summary

[It is strongly recommended to address all elements outlined below (whenever applicable) for any advice request, regardless of the scope of the questions. This summary will inform the background information section of the final advice letter. An upper limit of 3 pages for the summary is recommended]

Rationale for seeking advice

[Describe the scope of the questions and the rationale for the advice request (e.g. clinical/non-clinical/quality/significant benefit/similarity/conditional approval/exceptional circumstances).]

II. Product value proposition

[Describe value propositions and how the trial evidence will be used to support these]

III. Background information

[This section should give a comprehensive scientific overview of the product development program, providing relevant systematic information in sufficient detail, together with a critical discussion. However, it should be kept in mind that any information essential for the justification of a given question should also be sufficiently discussed in the corresponding Company's position. The proposed list of subsections is neither meant to be exhaustive nor mandatory, since the relevance or applicability of each subsection may vary depending on the scope of the advice request. In this respect, the potential direct or indirect relevance of the information covered in relation to the questions posed should be considered. Additional details can be included in study protocols, study reports, investigators' brochure provided as annexes. The use of tabulated overviews and graphs is encouraged.]

Disease to be treated

[Outline main features of the disease and current standard therapy (referencing relevant guidelines and variations between the countries), referring to relevant publications as well as any current unmet need(s). For reimbursement decisions, the availability of treatment alternatives is a critical issue. Thus a solid discussion of treatment and treatment alternatives including national treatment guidelines and treatment algorithms is warranted]

Indication

[Specify the intended indication(s). Specify product positioning in the treatment pathway: (e.g. 1st line, 2nd line, 3rd line, screening pre-treatment, monitoring during treatment, etc.). Describe if it is a combination or monotherapy. Aim of treatment (preventive, curative, palliative, symptomatic, disease modifying).Target population]

Description of the product

[Include mode of action, chemical structure, pharmacological classification, proposed dosing regimen, route of administration and details of any additional diagnostic tests, medical devices or medical procedures that the use of the new product will incorporate.

Please specify the proposed wording for the intended indication, posology, and any special precautions or recommendations for use of the product (including a possible risk management strategy)]

Quality information on the product

<Active substance>

<Finished product>

Non-clinical information

[It is recommended to include a tabulated overview of all non-clinical studies (completed, ongoing and planned), including study number, main design features and GLP status. Main findings and safety margins may be described in the narrative.]

<Pharmacology>

<Pharmacokinetics>

<Pharmacodynamics>

<Toxicology>

Clinical information

[A tabular overview of all clinical studies (completed, ongoing and planned), should be included. Please try to include study number, protocol synopsis, location(s), trial objectives, trial design, randomisation, blinding, intervention, patient population, inclusion/exclusion criteria, identified subgroups, comparators, endpoints, HRQL, duration/follow-up and methods of analyses where applicable. Whilst the focus should be kept on the intended indication, the development in other indications could be briefly summarised, where relevant.]

<Clinical pharmacology>

<Pharmacokinetics>

<Pharmacodynamics>

<Clinical efficacy>

[A general overview of the clinical development program should be based on a comprehensive discussion of e.g. the main clinical results so far, dose-response, exploratory trials, special populations, supportive and pivotal clinical studies, and any analyses performed across trials (pooled and meta-analysis). The discussion should identify the most important findings and challenges in the clinical development program, and its compliance with legal requirements, relevant clinical guidelines, previous scientific advice (sufficiently justifying any deviations), etc.

Information on the geographical distribution of centres participating in the pivotal clinical studies can be reflected in this section.]

<Clinical safety>

[A general overview of the safety profile of the product should be based on a comprehensive discussion of e.g. patient exposure (safety database), adverse events observed so far, serious adverse events and deaths, laboratory findings, safety-related discontinuations, specific safety findings, immunological events, safety in special populations, etc.]

<*Quality development*>
[Relevance, and level of detail included may vary depending on the scope of the request. Special pharmaceutical aspects, if any, e.g. novel delivery system, etc.]

<*Non-clinical development*>
[Relevance, and level of detail included may vary depending on the scope of the request. Proof-of-concept and main toxicological findings could be informative.]

Clinical development
[Introduce and describe the status of the clinical development programme. A tabulated summary of completed, ongoing and planned clinical trials could be informative.

Include schematic(s) of the pivotal trial(s).

Include schematic of the development plan including the timing of MAA and the reimbursement application.

Briefly summarise the following aspects:

If scientific advice has been previously requested from the CHMP, national or non-EU (e.g. FDA)

Indicate if relevant CHMP guidance/CHMP advice has been followed or if any deviations have been made or proposed.

Indicate applicability and status of the Paediatric Investigation Plan (with or without deferral or waiver). Indicate availability and need for development in other special populations such as the elderly, male/female and ethnic minorities.]

Regulatory status

[Describe the worldwide regulatory status of the product (e.g. any existing MA, or planned MAA timelines), indicating planned type and timelines of marketing authorisation application (MAA) (e.g. full/mixed dossier; advanced therapy, biosimilar, generic/hybrid/ product) or variation.

If the product has received Orphan Drug Designation (ODD) related to the intended indication, state the orphan indication, the criteria on which the ODD was based

and, if applicable, the development plan to support similarity or clinical superiority.]

Economic evaluation plans

[This section is optional if no questions on economic evaluation are submitted.

If plans for the economic evaluation are provided, these should include to the extent possible:

- *Description of the proposed model (diagram, modelling approach, time horizon, perspective)*
- *Data collection plans to inform the model:*
  - *Evidence synthesis/meta-analysis – sources of evidence*
  - *Comparators – MTC and indirect comparisons and evidence available*
  - *Trial endpoints used to derive health outcomes in the model*
  - *Quality of life – source and methods, tools used to measure QoL*
  - *Incorporation of adverse effects*
  - *Resource use – sources and methods, tools used to measure resource utilisation*
- *Methodological Approaches:*
  - *Extrapolation – assumptions and data sources*
  - *Continuation rules*
  - *Use of surrogate outcomes*
  - *Planned sensitivity analyses*

Evidence gaps and model assumptions should be described.]

IV. Questions and Company's positions

*[**Questions** should conform to the **scope** of the Scientific Advice/Protocol Assistance procedure (EMEA-H-4260-01-Rev.6). It is recommended that questions are phrased in a way to allow for an unambiguous understanding of the question. The scope should be carefully considered in order to avoid too broad or too narrow questions.*

The wording of the question should be clear and concise, avoiding extended reference to the justifications (which should be discussed in the Company position) and starting with e.g. "Does the CHMP agree that/with …?").

Questions should be ordered in the corresponding section according to the expertise (also multidisciplinary) required for the assessment, and numbered sequentially.

IMPORTANT INFORMATION

Each question should be followed by a corresponding, separate Company's position including a comprehensive justification of the chosen approach.

All key information about the topic should be sufficiently discussed, so that the Company position can function as a 'stand-alone' argument. Issues to be covered could include the following: context and proposal, other options (potentially) considered together with a critical discussion on the relative merits and drawbacks of various approaches, possible consequences and eventual measures to ameliorate these. In general, an extension of 1 to 3 pages for each Company position is recommended.

Cross-references to the relevant parts of the briefing document or annexes can be included if additional detail is needed to support the argument.]

<A. EMA-only Questions

Question 1

{}

Company's position

{}

Question 2

{}

Company's position

{}

<B. EMA & HTA Questions

Question {X}

{}

Company's position

{}

<C. HTA-only Questions

Question {X}

{}

Company's position

{}

List of References

[In general, any potentially relevant publications included in the list of references should be annexed (in .pdf format, either collated as a single document or if provided as single files, clearly identified and whenever possible compiled in one or more compressed files, for convenience). In case a relevant publication is not included at the time of validation, it should be ensured that it can be made available upon request.]

List of Annexes

[Annexes should be submitted as separate documents and should include any information potentially relevant to the questions, e.g.

Investigators' brochure

Study protocols (final, draft or outline/synopsis)

Study reports (final/draft/synopses)

Previous scientific advice received (e.g. CHMP Scientific advice/Protocol Assistance, any relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities)

Relevant guidelines (non-EMA)

Documents related to Orphan Drug Designation (e.g. COMP summary report)

Documents relating to Marketing Authorisation Application e.g. Day 120 List of Questions, Letter of undertaking.

Documents related to Paediatric Investigation Plans (e.g. PDCO summary report, opinion)

Contract/agreement consultant/CRO - sponsor

Literature references]