EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Research and Development Support

Best practice guidance for the parallel regulatory - HTA scientific advice procedure

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Abbreviations

AIFA	Agenzia Italiana del Farmaco
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AQUAS	Agency for Health Quality and Assessment of Catalonia
CAT	The Committee for Advanced Therapies
CHMP	Committee for medicinal products for human use
COMP	Committee for Orphan Medicinal Products
EC	European Commission
EMA	European Medicines Agency
EUnetHTA	European Network for Health technology Assessment
FIMEA	Finnish Medicines Agency
G-BA	Gemeinsamer Bundesausschuss
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
HTABs	Health Technology Assessment Bodies
HVB	Hauptverband der österreichischen Sozialversicherungsträger
IQWIG	Institute for Quality and Efficiency in Health Care
LoI	Letter of Intent
NICE	National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
PDCO	The Paediatric Committee
PRAC	The Pharmacovigilance Risk Assessment Committee
PSA	Parallel Scientific Advice
SAWP	Scientific Advice Working Party
SEED	Shaping European Early Dialogues
TC	Teleconference
TLV	Tandvårds- och Läkemedelsförmånsverket
ZIN	Zorginstituut Nederland

1. Process

1.1. Introduction

As the first step to market access, a new medicine requires a marketing authorisation from a medicines regulatory agency. Following regulatory approval, subsequent decisions on coverage (reimbursement) and price of an authorised drug are made at the national level. Health Technology Assessment (HTA) provides evidence-based information and analysis used in this decision making on how to allocate resources on a sustainable level within many EU member states in accordance with national practices and legislative frameworks[i].

Interactions between medicines' developers, regulators and HTABs or other possible stakeholders to discuss the development plan means that evidence can be generated to meet the needs of respective decision-makers as efficiently as possible. Thus, a strong interaction between regulators and HTABs/other relevant institutions is critical to facilitate patients' access to important new medicines and hence for the overall benefit of public health. The European Medicines Agency (EMA) is the European Union body responsible for coordinating the existing regulatory and 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 purposes.

Since 2010, the EMA has initiated a pilot project of parallel HTA-regulatory scientific advice, with the participation of several HTABs that allows developers to receive simultaneous feedback from both regulators and national HTABs on their development plans for new medicines. Further input on this pilot procedure was received during the EMA HTA workshop on parallel scientific advice on the 26 of November 2013. This procedure was designed based on the experience gained since 2010 and with the help of multi-stakeholder working group comprising the European Medicines Agency (EMA), regulatory National Competent Authority delegates from the EMA Scientific Advice Working Party (SAWP), and HTA body representatives from NICE, AIFA, G-BA, TLV as HTA bodies (see Table 1 for full names and member states) most frequently involved in the procedures. Other HTABs have also been consulted, see table below.

A draft of the "Best practice guidance" for this procedure was published for public consultation on the 8 of May 2014. The responses to this consultation have been reviewed with the multi-stakeholder working group.

In addition to this initiative, Health Technology Assessment Bodies (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. Between Q4 2013 to Q2 2015, under the coordination of HAS, 14 HTABs took part in the Shaping European Early Dialogues for health technologies (SEED project. Financed by the EU Commission, the SEED project aimed to perform 10 multi-HTABs early dialogues and explore possible scenarios for conducting early dialogues in the future. Associated with the SEED project, EMA took part in 4 of these dialogues as parallel regulatory SEED advice procedures. Results from the EUnetHTA JA2, the SEED project, as well as the results of the Best Practice parallel regulatory-HTA scientific advice pilot and the public consultation, have been taken into account to a revise this workflow/ process to best meet the objective of early dialogues in the medium term.

Guidance on the parallel procedure is herein provided to further support this activity advice based on the comments received in the public consultation, and experience gained within the pilot and within the

parallel EMA SEED initiative, and agreed with the multi-stakeholder process working group. Other HTABs have also been consulted. (See table 1 for full list of HTABS providing comments on the procedure). It is anticipated that the procedure will evolve further, taking developments in the European Union's HTA cooperation into account under Joint Action 3.

This EMA parallel scientific advice procedure with regulators, HTABs and other relevant stakeholders will continue on an operational basis in the interim.

Table 1. HTABs providing comments

HTABS
AEMPS - Agencia Española de Medicamentos y Productos Sanitarios (Spain)
AIFA - Agenzia Italiana del Farmaco (Italy)
AQuAS - Agency for Health Quality and Assessment of Catalonia (Spain)
FIMEA - Finnish Medicines Agency(Finland)
G-BA - Gemeinsamer Bundesausschuss (Germany)
HAS - Haute Autorité de Santé(France)
HVB - Hauptverband der Österreichischen Sozialversicherungsträger (Austria)
IQWIG - Institute for Quality and Efficiency in Health Care (Germany)
NICE - National Institute for Health and Care Excellence (England)
NOMA - Norwegian Medicines Agency (Norway)
TLV - Tandvårds - och Läkemedelsförmånsverket(Sweden)
ZIN - Zorginstituut Nederland (The Netherlands)

1.2. Principles

This document sets out the best practice for all parties, including HTABs, EMA, regulators and applicants undertaking a parallel regulatory-HTA scientific advice procedure under this guidance. This best practice guidance highlights ideal timelines and actions for each party.

Regulatory-HTA parallel scientific advice is a multi-stakeholder procedure with regulators and HTABs being equal partners. As a multi-stakeholder procedure, collaboration and communication between all stakeholders is important to ensure agreement and clarity on the ownership of different actions, and to deliver on the objectives of the parallel scientific advice exercise.

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

The process is confidential as follows: EMA and associated regulatory experts are bound by EMA code of conduct, and confidentiality agreements, and operate under EMA policy on access to documents. See collated HTABs information for confidentiality frameworks of participating HTABs.

Therefore, commercially confidential Information provided to the EMA within the context of scientific advice will not be shared with any party preauthorisation in the absence of a signed confidentiality undertaking or the consent of the sponsor as per European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use) Policy/0043. Scientific advice or protocol assistance outcomes will not be shared with other applicants.

1.3. Products and indication in scope: EMA and HTABs

EMA provides advice from regulators pertaining to the conduct of the various tests and trials that are needed to demonstrate the quality, safety and efficacy of medicinal products. Applicants may request advice on any 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, and at any stage of the product lifecycle. This may include very early strategic advice, advice on novel or adaptive development plans, early broad advice on a multiple possible development plans, plans for pivotal phase III studies, post-authorisation safety and efficacy studies, advice on the development of registries, or 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) and is adopted by Committee for Medicinal Products for Human Use (CHMP) having been elaborated through the 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.

The eligibility criteria and scope of assessment may differ for individual HTABs based on their national/regional regulation and expertise. Available information has been collated for HTABs participating in parallel regulatory HTA advice. This is available on the EMA and individual HTABs websites . Applicants should contact HTABs for further specific details. Parallel Scientific Advice (PSA) is offered at any stage in the developmental lifecycle of medicines to provide prospective advice before the studies in question have started.

It is acknowledged that for certain medicinal products (e.g. vaccines, or life style products), national advisory bodies other than HTABs can issue advice to payers/healthcare-guidance organisations. In these cases applicants may propose the participation of other relevant national advisory bodies (following their agreement/confirmation of interest) in the PSA procedure, and the same principles as described in this best practice guidance will be applied. References to HTABs in the description of the process shall be understood to include these national advisory bodies.

HTABs will participate in a specific procedure according to their availability and remit.

It should be noted that *some* HTABs may charge fees for participation in scientific advice in addition to those fees charged by the EMA for scientific advice.

A common briefing document is used; each question can be addressed to the regulators or the HTABs alone, or to both. The labelling of questions is a guide, but does not prevent interested bodies answering questions deemed also relevant and of interest. Use of the associated briefing document template is strongly recommended (See published template for parallel advice).

The advice provided by each stakeholder is not legally binding. EMA and Regulators will take the advice provided into consideration during the Marketing Authorisation Application (MAA) and the Applicant will need to carefully and fully justify any deviations from the advice given. Please see the EMA Scientific Advice Guidance Document for further details. Please see the collated HTAB information for the status of the parallel advice and the relationship with final appraisal by HTAB

1.4. Phases of the parallel regulatory-HTA scientific advice process

Parallel regulatory-HTA scientific advice has a pre-notification phase, a presubmission phase and an evaluation phase.

1.4.1. Pre-notification phase (early engagement)

The applicant should pre-notify the EMA scientific advice secretariat in order to secure an available slot for the face to face meeting which is scheduled during the same week as the SAWP meeting. The EMA should be pre-notified approximately 6 weeks prior to the required letter of intent deadline, which is approximately 5 months before the intended date of the face to face meeting if a presubmission teleconference (TC) is planned and 4 months prior, if no presubmission TC is planned. EMA will confirm the date and time of the face to face meeting within 2 working days of a request for a face to face meeting. For such a request, the applicant needs to provide product name/code, the mechanism of action, the indication, the desired date of the face to face meeting, which HTABs will be targeted if known, whether there will be clinical only and/or nonclinical and quality questions, and if a presubmission TC is needed. Nonclinical and quality questions are possible during a parallel advice procedure but these questions are posed to EMA only.

This informal pre-notification phase allows diary preplanning and time for engagement of the HTABs in the procedure. Following confirmation of the date of the face to face meeting, applicants then contact HTABs swiftly to request their availability for the desired face to face meeting date. HTABs may also choose to participate as observers. Alternatively, EMA may make initial contact with HTA bodies to request availability.

The pre-notification phase ends when the applicant sends the letter of intent and draft briefing package to the EMA and to all the participating HTABs. The letter of intent and draft briefing package should be sent in line with the published EMA normal scientific advice timetables for a 70 day procedure (with or without a presubmission meeting). Please see the published timetables.

1.4.2. Communication

It is preferable to have a principal point of contact (with back-up) for each stakeholder. The points of contact will be a scientific officer, appointed by the EMA, the project managers from each HTA body, and a project manager from the applicant.

1.4.3. Coordination

EMA will send a contact sheet for all EMA regulator participants (i.e. SAWP coordinators, and where appointed patient representative(s), The Paediatric Committee (PDCO), The Pharmacovigilance Risk Assessment Committee (PRAC) and The Committee for Advanced Therapies (CAT) experts, and the Committee for Orphan Medicinal Products (COMP) coordinator, or other EMA contacts if included).

The EMA will facilitate administrative and logistical coordination. The applicant should inform EMA about intended and subsequently confirmed participating HTABs; EMA will provide a final table of confirmed participating HTABs to the HTABs.

The applicant should keep the EMA scientific advice officer and the HTABs contacts up to date with any changes/developments. E.g. new HTABs/ changes in contact details.

Regarding regulators' content (scientific) coordination; two coordinators, from National Competent Authorities, who are members of the Regulators' scientific Advice Working Party (SAWP) are appointed to lead their respective assessment teams from the SAWP (regulatory) perspective.

Depending on the number of HTABs involved, a HTABs coordinator for a specific procedure will be nominated by participating HTABs, and agreed after a HTABs discussion. The HTABs coordinator will

coordinate the content (scientific) discussions from the HTABs perspective, facilitate discussion between HTABs in advance of meetings and will act as a co-chair for the HTABs where possible.

From an early stage, the EMA along with HTABs may consider the need for additional clinical experts in a given procedure and face to face meeting. Regulators' clinical experts are identified through national competent authorities and SAWP members. A Health Care Professional (HCP) representative may also be invited by the EMA through the EMA HCP working party framework. Individual patient experts are identified through patient organisations and under the framework for interaction between the EMA and patients and consumers, and their organisations.

Conflict of interest of regulatory experts and patient representatives will be handled in line with standard EMA policies. See collated HTABs information for conflict of interest frameworks of participating HTABs. The applicant will be informed about the participation of clinical experts and/or patient representatives in the draft list of participants.

In addition to the standard EMA timetables, EMA will set up a timetable for each procedure including dates for presubmission, pre-face to face teleconferences, and closed EMA Regulators- HTABs interactions following receipt of the letter of intent and confirmation of participating HTA bodies. EMA will send this timetable to all participants. Calendar meeting requests will be sent by EMA to HTABs, applicants and other regulatory participants shortly after a TC or meeting is confirmed.

EMA uses Eudralink - a secure system for sending /receiving documents between parties in its in-house procedure. The HTABs will be given access to Eudralink for the purpose of the parallel advice procedure. However, the applicant should clarify with HTABs on their preferred method of sending and receiving documents; if an alternative is used, it should be a secure method of document transfer method.

The applicant is responsible for sending the briefing directly documents to the HTABs and EMA and regulator participants. The applicant must ensure that receipt of documents has been acknowledged by all the participants. Document version control, numbering, and adherence to timelines are essential to ensure all parties have the appropriate document at the correct time. It is strongly advised to avoid making significant changes to the documentation/clinical development close to the face to face meeting except where this has been discussed and agreed with participants as in topic 1.3.5.4. This is in order to guarantee an appropriate time for the revision and the evaluation by Regulators and HTABs.

1.4.4. Presubmission phase

The presubmission phase starts when the Applicant sends the letter of intent and draft briefing document to the EMA (scientificadvice@ema.europa.eu), and participating HTABs (contact details as described in the collated HTAB information) as per published EMA Scientific Advice deadlines.

The presubmission phase offers two different options for applicants to consider (with or without a teleconference (TC) including the applicant, the EMA, regulators and HTABs during the presubmission phase). It is up to the applicant to specify which option is preferred when making the notification as in the pre-notification phase 1.3.1 above.

1.4.4.1. Option 1 with presubmission teleconference (TC).

This presubmission phase lasts approximately 7 weeks and includes a presubmission TC with the EMA, regulators, HTABs, the applicant, or other experts as needed. This would be most suitable for inexperienced applicants or very complex and/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 presubmission meeting. The applicant circulates the letter of intent and the draft briefing document directly to all EMA, regulator and HTAB participants according to the agreed timetable.

The presubmission TC will take place approximately between 1-5 weeks after the briefing document has been received by all parties. The EMA will arrange this TC upon receipt of the letter of intent and notification of participating HTABs.

The applicant circulates the presubmission presentation with numbered slides covering briefly the background, the questions and applicant positions, directly to all EMA, regulator and HTAB participants at least 4 working days before the TC, including a list of applicant's participants. The presentation for the presubmission TC should avoid major changes compared to the development plan as explained in the draft briefing document already submitted to all parties.

The aim of the presubmission TC is: to discuss the scope, wording and clarity of the questions, to consider whether the material provided in the briefing package is sufficient to answer the questions posed, to consider whether all the right questions have been added or if additional questions should be added, and to consider whether the questions are appropriately labelled as for HTABs or regulators. Reviewing the choice and number of questions, such as questions on population, comparator, endpoint etc. at an early stage is considered important as it is difficult to expand to new questions at a later date.

After, the presubmission TC, the EMA will send regulators' comments on the package in writing within 2 working days. HTABs' comments made at the TC will be summarised by EMA, circulated to HTABs, and when agreed, sent to the applicant within 2 working days of the presubmission TC. Comments should be shared between regulators and HTABs.

1.4.4.2. Option 2 without presubmission TC.

This presubmission phase lasts approximately 3 weeks. There is no TC. The procedure timetable will be based on the EMA published scientific advice timetables for a 70 day procedure without a presubmission meeting. The applicant sends the letter of intent and draft briefing document directly to all EMA, regulator and HTAB participants in accordance with the agreed timeline. It is important that the timelines are adhered so that that participants have sufficient time with the draft briefing document (at least 5 working days), in order to provide feedback to the applicant, and also such that there is sufficient time for the applicant's revision before the agreed formal start of the procedure. Initial written comments from the EMA and HTABs are provided directly to the applicant where necessary for the optimisation of the draft submission by 7 working days prior to the start of the procedure.

Comments should be shared between regulators and HTABs, and consider: the scope, wording and clarity of the questions, whether the material provided in the briefing package is sufficient to answer the questions posed, whether all the right questions have been added or if additional questions should be added, and to consider whether the questions are appropriately labelled as for HTABs or regulators.

1.4.4.3. Finalising the briefing document

In either option1 or 2, the applicant sends a revised final briefing document with all annexes and references addressing the EMA/regulators' comments and HTABs' points of clarification to the EMA scientific officer, 2 working days before the start of the procedure. 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 and readable).

Following confirmation of validation from the EMA scientific officer, the applicant sends the final briefing document directly, to all HTABs and all EMA contacts in the procedure, via Eudralink (or other agreed method), 1 working day before the start of the procedure. The applicant should ensure that the final briefing document has been received by all participants.

The presubmission phase ends with the submission of the final briefing document which is day 1 of the SAWP meeting 1 (the formal procedure start) in the published EMA Scientific Advice timelines.

Figure 1. Option 1 with presubmission TC - overview of process and actions by each party in parallel.

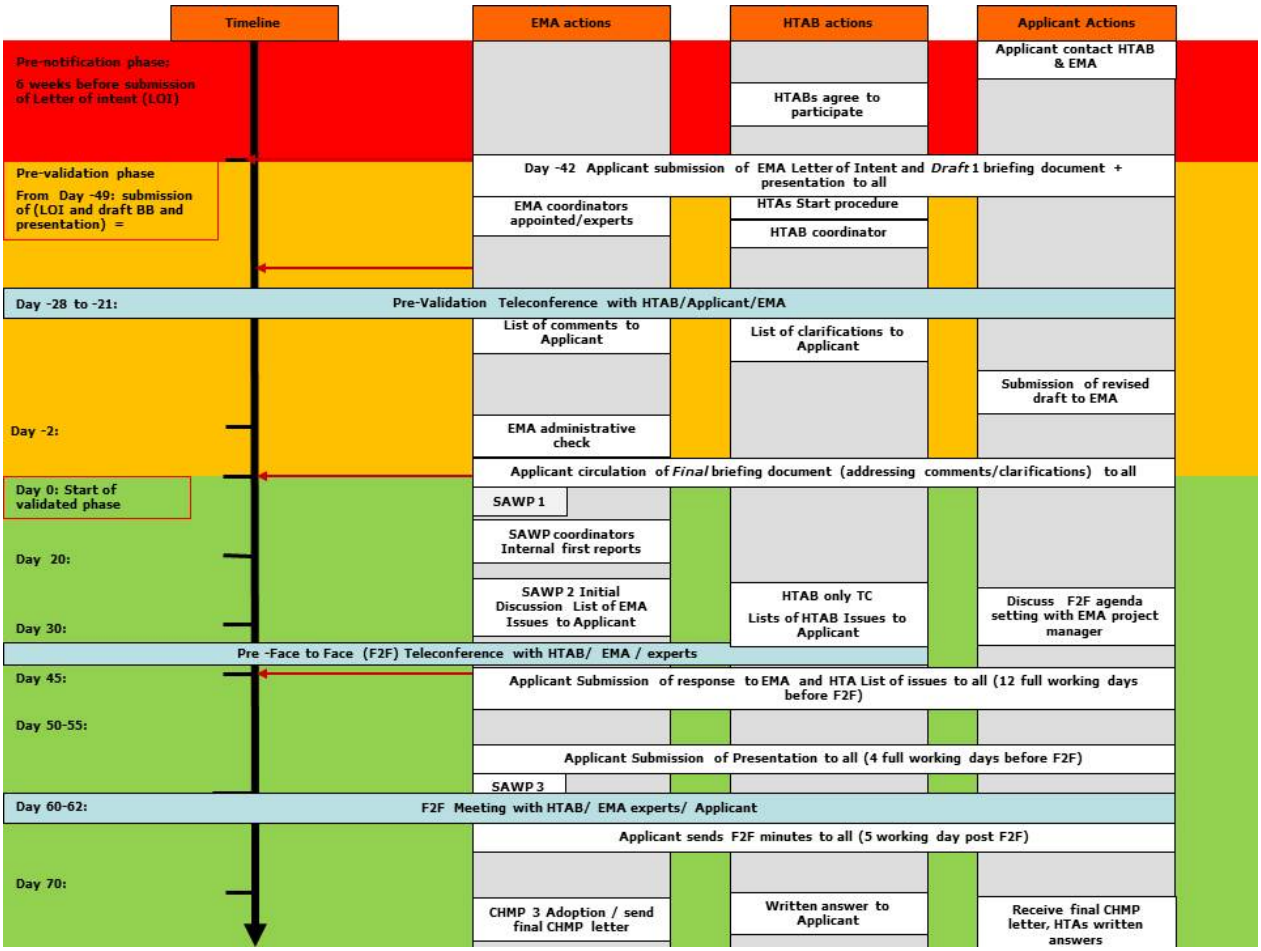
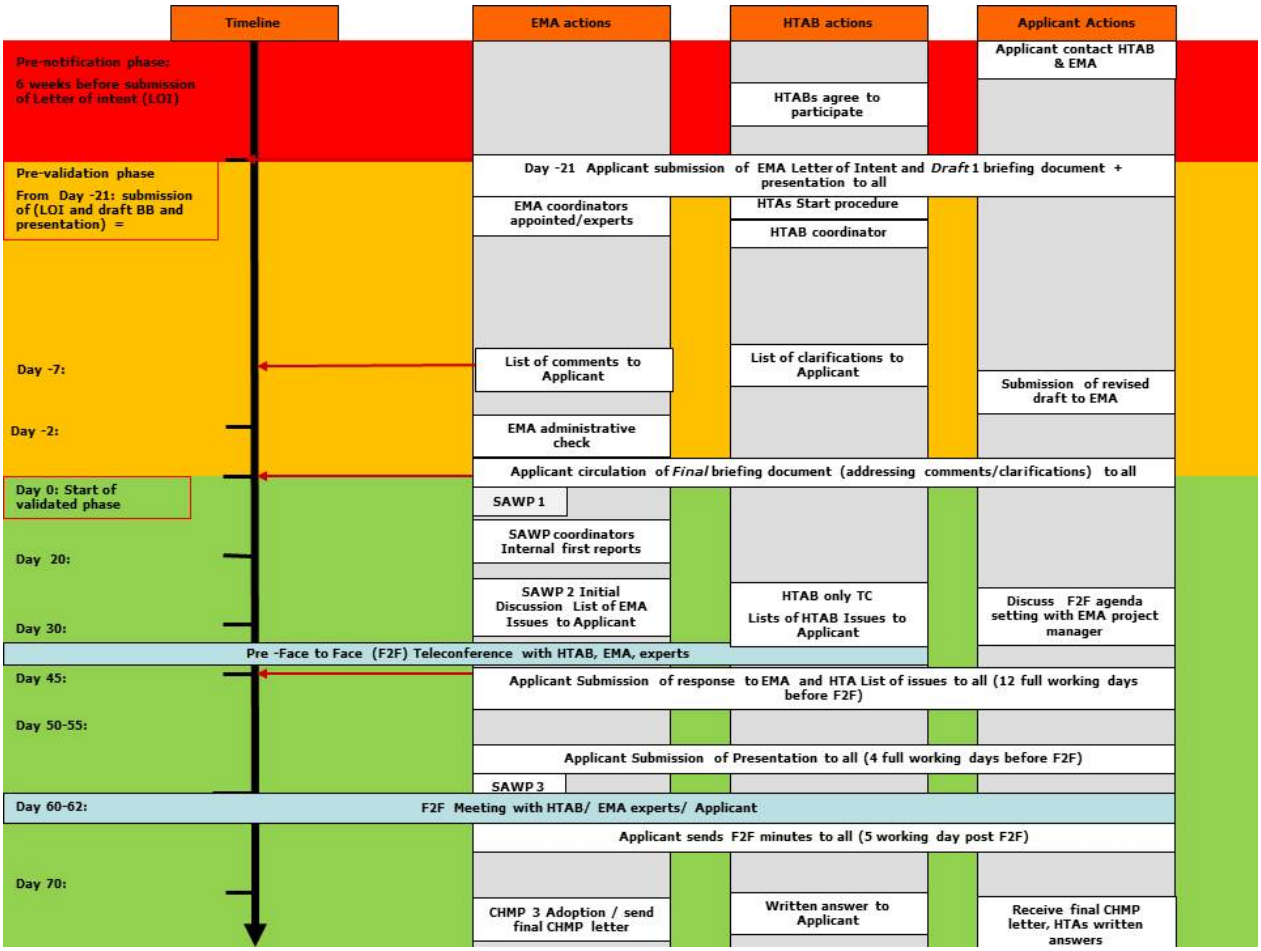


Figure 2. Option 2 without presubmission TC- overview of process and actions by each party in parallel.



1.4.5. Evaluation phase

1.4.5.1. Lists of issues

In the regulator process, the SAWP discusses the first reports (preliminary views) at the SAWP 2 meeting and generates a regulators' List of Issues by approximately day 30 of the procedure. This list of issues outlines the topics of regulators' interest to be addressed by the applicant in the face to face discussion meeting. EMA sends this List of Issues to the applicant and to the HTABs. This will facilitate the discussion during the face to face meeting by indicating the focus of regulators' discussion. The applicant provides consent to document exchange in the letter of intent.

Simultaneously, each HTA body proceeds with their internal assessment and discussion in accordance with national policies and requirements. HTABs will draft a list of issues for targeted discussion which the HTAB coordinator or EMA will collate. EMA will send this to the applicant by approximately day 30 of the procedure.

1.4.5.2. Pre face to face TCs

The EMA will arrange a closed preparatory TC for HTABs only to facilitate discussion of respective HTA body positions and HTA coordination.

The EMA will arrange a closed preparatory TC between regulators and HTABs. These TCs will be arranged to take place between day 35 and day 45 of the procedure.

The purpose of the pre-face to face TC is to exchange upon and understand respective (preliminary) positions of the different regulator and HTAB participants; critical divergences between HTABs and the regulators on the major aspects of trial designs such as population, comparator or endpoints should be identified. Potential solutions that could facilitate one trial or one development plan could be discussed in advance of the face to face meeting. The chairperson for the face to face meeting should be agreed in the pre-face to face TC.

1.4.5.3. Preparation for face to face meeting

The applicant is advised to contact the EMA scientific advice officer regarding the format of the face to face meeting. This is to ensure that the meeting will meet the needs of the stakeholders. 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 applicant should send any written responses, if requested according to EMA or HTAB lists of issues, 12 working days before the face to face meeting directly to all regulator and HTAB participants. There should be no major changes to the development plan compared to the final briefing document, unless the process in topic 1.3.5.4 has been followed.

The applicant should send the final presentation and list of participants directly to all regulator and HTAB participants, 4 working days before the face to face meeting. The presentation can include a very brief introduction, rationale and status of the program. An upper limit of 5 slides for this introduction is recommended to maximise the time available for the questions and discussion. Once sent to the meeting participants, according to the agreed timelines, the presentation should not be amended by the applicant. There should be no major changes to the development plan compared to the final briefing document, unless the process in topic 1.3.5.4 has been followed.

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 regulator participants 2 days in advance of the face to face meeting. The meeting is hosted at the EMA premises.

The inclusion of patient representatives and experts in the procedure is encouraged as routine. Where possible, patient representatives will be invited to attend all TCs and the face to face meeting; briefing of chairpersons (on the inclusion of a patient representative) and patients (on the aims and nature of the meeting) by EMA scientific officers is essential. Any additional time or facilities required by patients should be considered.

1.4.5.4. Amended development plans triggered by the lists 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 an amended development by 3 weeks, at the latest, before the face to face meeting. The amended plan must be received by all parties, at the latest by 12 working days before the face to face meeting, together with 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.

1.4.5.5. Face to face discussion meeting

The aims of the face to face meeting are:

- To discuss issues of concern or disagreement from regulators and/or HTABs with the applicant's proposal regarding major aspects of trial designs
- To discuss critical divergences between HTABs and the regulators on major aspects of trial designs
- To discuss potential solutions that could facilitate one trial or one development plan

The face to face meeting will normally have 2 co-chairs: one from the regulators and one from the HTABs. The meeting duration will depend on the range of issues to be discussed and advice format.

Where all parties provide lists of issues and written answers, it is possible to shorten the face to face meeting, targeting keys issues for discussion as identified based on the EMA and HTABs' lists of issues. If any participating HTA body does not provide both HTA body list of issues and written answers, then all applicant's questions will need to be addressed in the face to face meeting, in order to allow the HTA body to provide advice orally on all questions. It is usual to pause after each question/issue for discussion. During the face to face meeting, the views of each stakeholder should be clearly represented on each issue. Time should be allowed for summing up at the end of the meeting.

Following the face to face meeting, a closed debriefing between HTABs and regulators should be held. This is dedicated to the recap, identification and resolution of any outstanding divergences, where such divergences mean that a single development plan/trial could not be carried out.. There might be situations in which the divergences cannot be resolved due to differences in the regulators' and HTABs' assessment questions and remit. Possible ways to further address these divergences should be considered (e.g. methods for indirect comparisons, multi-stakeholder workshops, broad advice, and qualification procedure or follow up parallel advices).

1.5. Advice format

The applicant is expected to send detailed minutes of the face to face meeting, within 5 working days directly to all participants on the contact sheet. The minutes should reflect the views for each participating stakeholder in the face to face meeting discussion. Areas of agreement and divergence of opinion between regulators and HTABs should be summarised by the applicant. Minutes are regarded as an applicant's record of the meeting and will not, in general, be endorsed by the participating bodies.

The EMA will send the CHMP final advice letter to the applicant in accordance with the published timelines (i.e. the subsequent CHMP meeting). HTABs will provide HTABs' written answers to the questions directly to the applicant within 15 working days of the face to face meeting, or in a format according to the collated HTABs information referred to above. Final advice letters will be exchanged between participants where the Applicant has provided consent in the letter of intent for document exchange.

1.6. Follow up procedures

A follow-up procedure to an earlier parallel regulatory-HTA scientific advice procedure for the same indication is possible. 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 presubmission 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

WITH PRESUBMISSION TC:

Letter of Intent & draft Briefing Document: September 14th
Pre-Submission Teleconference: October 19th
Final Briefing Document: October 28th
Start of Procedure/D0: November 3rd
SAWP List of Issues: December 4th
Pre-Face to Face Teleconference: week commencing Dec 14th
Face to Face Meeting: January 11-14th
Final CHMP Scientific Advice Letter: January 29th

WITHOUT PRESUBMISSION TC:

Letter of Intent & draft Briefing Document: October 12th
Final Briefing Document: October 28th
Start of Procedure/D0: November 3rd
SAWP List of Issues: December 4th
Pre-Face to Face Teleconference: week commencing Dec 14th
Face to Face Meeting: January 11-14th
Final CHMP Scientific Advice Letter: Jan 29th

2. Summary of documents and meeting aims

Table 2. Description of documents

Documents	Description
Letter of intent	Formally notifies the European Medicines Agency of the intent to submit an EMA regulatory HTA Parallel Scientific Advice; brief description of the requested procedure.
Draft briefing document	Draft briefing document comprising the questions and company's positions, as well all the relevant information, annexes and references, important to assess such questions.
Final briefing document	Finalised version of the draft briefing document addressing regulators' comments and HTABs' points of clarification.
Regulators' list of issues HTA list of issues	Documents outlining the concerns or disagreements with the applicant's proposal. Further justifications, clarification or changes to the applicant's proposals are requested.
Final CHMP advice letter Final HTA written answers	Documents with written answers to the applicant's questions.

Table 3. Description of meetings objectives

Meetings	Input Document	Objective of meeting	Output Document
Presubmission teleconference	Applicant's draft briefing document, Applicant's presubmission presentation	The aim of the presubmission teleconference is: • To discuss the scope, wording and clarity of the questions, • To discuss whether the material provided in the draft briefing package is sufficient to answer the questions posed. • To consider whether all the right questions have been added or if additional questions should be added • To consider whether the questions are appropriately labelled as for HTAs or regulators The applicant participates so that the applicant can deliver a final briefing document that meets the needs of regulator and HTAB participants.	List of comments on draft briefing document for regulators and HTABs
HTAB only pre face to face TC	Lists of issues for discussion at face to face meeting- HTABs	The aim of the pre-face to face HTAB only teleconference is: • To facilitate discussion of respective HTAB positions and coordination. • To have an internal discussion on HTAB coordinator role • Selection of HTAB co-chair if not already agreed	
Pre-face to face teleconference (closed discussion)	Applicant's final briefing document List (draft) of issues for discussion at face to face meeting for regulators and HTABs	The aim of the pre-face to face teleconference is: • To exchange upon and understand respective (preliminary) positions of the different regulator and HTAB participants; • To identify commonalities and critical divergences between HTABs and the regulators on the major aspects of trial designs such as population, comparator and endpoint. • To discuss potential solutions that could facilitate one trial, or one development plan in advance of the face to face meeting. • To identify the co-chairs	List of issues for discussion at face to face meeting for regulators and HTABs (if not already finalised)
Face to face meeting	Applicant's final briefing	• To discuss issues of concern or disagreement from regulators and/or	CHMP final advice letter

Meetings	Input Document	Objective of meeting	Output Document
	document, Applicant's presentation List of issues for discussion at face to face meeting for regulators and HTABs (if not already finalised) Any written responses from Applicant	HTABS with the applicant's proposal regarding the major aspects of trial designs • To discuss critical divergences between HTABs and the regulators on major aspects of trial designs • To discuss potential solutions that could facilitate one trial, or one development plan	HTAB written answers*
			* unless HTAB annotates and corrects draft minutes

3. Annex Briefing Document Template

Parallel Regulatory-HTA 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.]

4. 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]

Background information on the disease to be treated

[Outline main features of the disease including relevant epidemiological data, information on natural history of the disease and evolution on treatment should be discussed. 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 all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) together with their labelling status in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development, this information should be included.]

Indication

[Specify the indication(s) intended for the label including product positioning in the treatment pathway: (e.g. 1st line, 2nd line, 3rd line, add-on, monotherapy, 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 should be described as precisely as possible. If any population should not be included in the label, this should be clearly indicated.]

Background information on the product

[Include mode of action, chemical structure and pharmacological classification. Route of administration and the pharmaceutical form of the product should be described. Dose, frequency of administration and the duration of use should be described based on the available evidence at the stage of development and, and any special precautions or recommendations for use of the product (including a possible risk management strategy t.

If the administration of the product is associated with the use of a diagnostic test, a medical device or with a medical procedure, this

information should be stated and adequate information given on the associated test or device]

<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.

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.]

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).]

Product value proposition

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

5. Questions and Applicant'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. For a given development program, it is recommended that clinical question are posed about Population, Comparator and outcome. The intended place in treatment of the intervention should be clear.*

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 Applicant'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.]

<Questions on Chemical, Pharmaceutical and Biological development>

Question 1

{}?

Applicant's position

{}

Question 2

{}?

Applicant's position

{}

<Multidisciplinary Question<s> on Chemical, Pharmaceutical, Biological and Toxico-Pharmacological development>

Question {X}

{}?

Applicant's position

{}

<Questions on Toxico-Pharmacological development>

Question {X}

{}?

Applicant's position

{}

<Multidisciplinary Question<s> on Toxico-Pharmacological and Clinical development>

Questions on Clinical development

< Regulators' questions only>

Question {X}

{}?

Applicant's position

<Regulators' & HTABs' Questions>

Question {X}

{}

Applicant's position

{}

< HTA-only Questions>

Question {X}

{}

Applicant's position

{}

<Questions on Significant Benefit>

[For Protocol Assistance, the questions should be within the scope of the designated orphan indication. See EMA Guidance for Companies requesting Scientific Advice or Protocol Assistance' (EMEA-H-4260-01-Rev.6).]

Question { To the COMP X}

{}

Applicant's position

{}

6. 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 Applicant'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 with cross references in the background information and relevant Applicant Position. The use of tabulated overviews and graphs is encouraged.]

Quality background information

<Active substance>

<Finished product>

Non-clinical background 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 background information

[A tabular overview of all clinical studies (completed, ongoing and planned), including study number, main design features, patient number and characteristics, design, doses and duration of treatment, comparator, results of the trial (or preliminary results of ongoing trials if available)... etc. could be informative, if not provided elsewhere. Detailed information should be available in study reports in

annexes. Cross-links to annexes are recommended. Whilst the focus should be kept on the intended indication, the development in other indications could be briefly summarised, where relevant. Data of early phases are also necessary as they serve as basis of the development plan]

<Clinical pharmacology>

<Pharmacokinetics>

<Pharmacodynamics>

<Clinical efficacy>

Planned clinical trials.

[This section should provide a comprehensive overview of all planned trials with the product in the intended indication. For the trial that is to be the subject of the advice, a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), patient subgroups and stratification (if applicable), line of treatment, comparators, endpoints (primary, secondary, etc.), measures used to assess endpoints, flowchart, follow up, methods of statistical analysis etc. All relevant systematic information should be given at a sufficient level of detail, together with justification for the choice made and a critical discussion of key issues.]

Overview of the clinical development program

[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.]

Information for HTA

<Relative effectiveness>

[Guidance on consideration of relative effectiveness evidence should be brought together in a separate section before the section on economic evaluation plans and is optional. However it is very likely that the generation of evidence on relative effectiveness (based on clinical trial efficacy) will be discussed as part of the consultation. The section could mention (as bullets):

<population,>

<choice of comparator,>

<Study design,>

<Study duration,>

<evidence synthesis (including indirect comparisons/NMA),>

<Trial endpoints (including minimal clinically important differences)

<predictive modelling of effectiveness from surrogate endpoints,>

<transferability of trial data,>

<evidence for sub-groups.>

<Other relevant statistical issues (e.g. stratification),>

<Choice of measures of health-related quality of life could be included in this section.>

[PAES studies are in scope (ll97-98) and therefore plans and study designs for 'real world' evidence generation post-launch (potentially pre-launch) to verify trial-based estimates of effectiveness, whether or not PAES, merit (separate) mention in this briefing document (optional).]

<Economic assessment>

[• The company should state the scope of the planned economic analysis, clearly defining the research questions. Evidence gaps and model assumptions should be described.

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 quality of life

- 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]>

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 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, HTA)

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]

[i]Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. Allen et al. Health Policy 2013, Volume 113, Issue 3, December 2013, Pages 305–312