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Guidance for parallel consultation

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Abbreviations

| | |
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| AIFA | L'Agenzia italiana del Farmaco, Italy |
| ATMPs | Advanced Therapy Medicinal Products |
| CAT | Committee for Advanced Therapies |
| CHMP | Committee for Medicinal Products for Human Use |
| COMP | Committee for Orphan Medicinal Products |
| EC | European Commission |
| ED | Early Dialogue |
| EDWP | Early Dialogues Working Party |
| EDC | Early Dialogues Committee |
| EU | European Union |
| EMA | European Medicines Agency |
| EUnetHTA | European Network for Health Technology Assessment |
| F2F | Face to face |
| G-BA | Gemeinsamer Bundesausschuss, Germany |
| HAS | Haute Autorité de Santé, France |
| HCP | Health Care Professional |
| HTA | Health Technology Assessment |
| HTABs | Health Technology Assessment Bodies |
| JA | Joint Actions |
| LoI | Letter of Intent |
| NCA | National Competent authority |
| NICE | National Institute for Health and Care Excellence, England |
| NIPN | National Institute of Pharmacy and Nutrition, Hungary |
| PSA | Parallel Scientific Advice |
| PDCO | Paediatric Committee |
| PLEG | Post Licensing Evidence Generation |
| PRAC | Pharmacovigilance Risk Assessment Committee |

| | |
|--------------|--|
| RER | Regione Emilia-Romagna, Italy |
| RIZIV-INANMI | Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité, Belgium |
| SAWP | Scientific Advice Working Party |
| SEED | Shaping European Early Dialogues |
| SME | Small or medium Enterprises |
| TC | Teleconference |
| ZIN | Zorginstituut Nederland, the Netherlands |

1. Introduction

As the first step to market access, a new medicine requires a marketing authorisation from a medicines regulatory agency. Following regulatory approval, Health Technology Assessment (HTA), providing evidence-based information and analysis, takes place at the national level States in accordance with national practices and legislative frameworks¹. Health Technology Assessment is then used to inform subsequent decisions on coverage (reimbursement) and price of an authorised drug at the national level.

Interactions between medicines' developers, Regulators and Health Technology Assessment Bodies (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 stakeholders 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 EU body responsible for coordinating the existing regulatory and scientific resources put at its disposal by EU Member States for the evaluation, supervision and pharmacovigilance of medicinal products, including the provision of Scientific Advice for regulatory purposes.

The European Network for Health technology Assessment (EUnetHTA) was established to create an effective and sustainable network for HTA across Europe – working together to develop reliable, timely, transparent and transferable information to contribute to HTA in European countries, creating a sustainable system of HTA knowledge sharing, and promoting good practice in HTA methods and processes. EUnetHTA Joint Action 3 (JA3) aims to define and implement a sustainable model for the scientific and technical cooperation on HTA in Europe, and is co-funded by the European Commission (EC). Within EUnetHTA JA3, Work Package 5 (WP5) aims at bridging the gaps between patients, caregivers, technology developers, current registry holders, and authorities in the health care sector, HTA producers and HTA users. Its main objective is to help to generate, all along the technology lifecycle, optimal and robust evidence for different stakeholders, bringing benefits for patient access and public health.

HTABs have performed several multi-HTABs Early dialogues (ED) in the framework of EUnetHTA Joint Action 2. Between 2013 and 2015, under the coordination of Haute Autorité de Santé (HAS), France, 14 HTABs took part in the Shaping European Early Dialogues for health technologies (SEED) project. Financed by the EC, the SEED project aimed to perform 10 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 EMA 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 since 2010 and the public consultation, have been taken into account to revise this workflow/process to better meet the needs and objectives of Parallel Scientific Advice/ Early Dialogues.

New EUnetHTA and EMA platform on evidence generation interactions

This new platform comprises enhanced collaboration for Parallel regulatory HTA Scientific Advice/[Early Dialogues](#) (henceforward referred to as Parallel Consultation) between EMA and EUnetHTA. Parallel Consultation provides a single gateway for requests for parallel discussions before the start of pivotal clinical trials on initial evidence generation for Marketing Authorisation Application/Reimbursement,

¹Development 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

and Post Licensing Evidence Generation (PLEG) involving EMA, EUnetHTA and HTA bodies. Partnership of EMA and EUnetHTA also allows for: streamlined logistics, improved HTA coordination through EUnetHTA ED Secretariat, greater participation via the involvement of EUnetHTA HTA Early Dialogue Working Party (EDWP) ², and maximum gain from the parallel procedure by optimising opportunities for mutual understanding and problem solving between Regulators and HTAs. This facilitates optimal and robust evidence generation for different stakeholders bringing benefits for patient access and public health.

For all submitted requests, the EUnetHTA ED Secretariat facilitates centralised HTA recruitment, and selection criteria is applied by the EDWP in order to decide if the ED will follow the Consolidated or Individual pathway. The EDWP selection criteria and process are fully explained below in section 3.3. Other products which are not selected for consolidated advice (Individual Parallel Consultation) follow the same general principles and regulatory - HTAs interaction processes. They also benefit from EUnetHTA ED Secretariat scientific and administrative coordination.

Therefore with immediate effect, all Parallel Scientific Advices will change to this Parallel Consultation Platform.

This guidance replaces the “Best practice guidance” on Parallel EMA-HTA Scientific Advice procedure (EMA/502692/2015) as of the date of publication.

Further updates of this guidance are expected with the advent of sustainable funding mechanisms for HTA early dialogues within JA3, and post JA3 in 2020.

2. Principles

2.1. Roles and remits

This guidance highlights ideal timelines and actions for each party undertaking a Parallel Consultation.

This is a multi-stakeholder procedure with Regulators and HTABs being equal partners. As a multi-stakeholder procedure, collaboration and communication between all stakeholders are important to ensure agreement and clarity on the ownership of different actions, and to deliver on the objectives of the exercise.

From the HTAB side, there are two different pathways that a Parallel Consultation can take: Consolidated and Individual. The primary difference between the two is the mode of participation of HTABs. Consolidated Parallel Consultation (CPC) includes the full participation of the EDWP plus up to 3 additional HTABs whereas in Individual Parallel Consultation (IPC), HTABs participate based on their own national priorities. In both cases, the process on the HTAB side is overseen by the EUnetHTA ED Secretariat.

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

² Composition of the EDWP as of July 4th 2017: France (Haute Autorité de Santé: HAS), Germany (Gemeinsamer Bundesausschuss: G-BA), United Kingdom (National Institute for Health and Care Excellence: NICE), Italy (Italian Medicines Agency: AIFA with alternate Regione Emilia-Romagna: RER), Hungary (National Institute of Pharmacy and Nutrition: NIPN), and a shared seat for The Netherlands/ Belgium (Zorginstituut Nederland: ZIN/ Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité: RIZIV-INANMI)

2.2. Confidentiality

The process is confidential as follows: EMA and associated regulatory experts are bound by EMA code of conduct, and confidentiality agreements, and operate under the EMA policy on access to documents (Policy/0043).

Confidentiality in the Parallel Consultation is a priority for HTA participants. An EUnetHTA Declaration of Interest and Confidentiality Undertaking (DOICU) Form is used in this procedure by participants. Refer to the [EUnetHTA website](#) for further information.

Therefore, commercially confidential information provided to the EMA and EUnetHTA within the context of a Parallel Consultation is not shared with any party preauthorisation outside of the respective Regulator and HTA networks in the absence of a signed confidentiality undertaking or the consent of the sponsor.

2.3. Conflict of interest

EMA: Conflict of interest of regulatory experts, health care professionals (HCP) and patient representatives is handled in line with [Policy 44](#).

EUnetHTA: Please refer to the confidentiality section above.

2.4. Status of Parallel Consultation outputs

The advice provided by each stakeholder is not legally binding. European Medicines' Regulators take the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice/Protocol Assistance provided into consideration during the Marketing Authorisation Application (MAA). The Applicant needs to justify fully any deviations from the advice given. Please see the EMA [Scientific Advice](#) Guidance document for further details.

Advice provided by HTABs reflects state-of-the-art of medical science and national requirements at the time of advice.

3. Actors and scope

The process described herein is only for Parallel Consultation jointly involving EMA and EUnetHTA. For regulatory-only, or HTA-only procedures, please see EMA and EUnetHTA Websites.

3.1. Regulators: actors and scope

The Scientific Advice Working Party (SAWP) is an EMA standing working party with the remit of providing Scientific Advice and Protocol Assistance to Applicants, advising on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products (See "Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP)" - EMEA/CHMP/SAWP/69686/04 Rev 11).

The SAWP Coordinator is a medicines Regulator and a member, or alternate member, of SAWP who is responsible for providing reports further to the Scientific Advice or Protocol Assistance requests, addressing comments from the SAWP, Working Parties, and EMA Committees, drafting the SAWP List of Issues, acting as one of the 2 co-chairs for the face to face meeting, and drafting the final report for further input and consideration by SAWP and EMA Committees.

The EMA Scientific Officer supports the SAWP Coordinators with scientific and administrative coordination. This is the principal EMA contact person to which the Applicant and EUnetHTA should address all matters related to an individual procedure.

The EMA Scientific Advice Secretariat informs the Applicant and EUnetHTA ED Secretariat who has been appointed as EMA Scientific Officer after the receiving the Letter of Intent. EMA sends an EMA contact sheet to the Applicant and the EUnetHTA ED Secretariat including all details for Regulator participants (i.e. SAWP Coordinators, EMA Scientific Officer, assistant and other contacts, if applicable) close to the start of the procedure (evaluation phase).

For the EMA, through the Parallel Consultation, the Scientific Advice or Protocol Assistance provided to the Applicant is substantive, is prepared pursuant to Article 57 (1.n) of Regulation (EC) No 726/2004 and is adopted by CHMP having been elaborated through the SAWP.

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 development plans, broad advice, 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.

3.2. EUnetHTA and HTABs: actors and scope

The EUnetHTA ED Secretariat is responsible for all practical coordination of HTAB participation in a Parallel Consultation. Together with the EMA Scientific Officer, on the regulatory side, the EUnetHTA ED Secretariat acts as the sole HTAB contact point for all Parallel Consultations (Consolidated and Individual). Additionally, the EUnetHTA ED Secretariat is responsible for insuring the acceptability of the Letter of Intent and all project management on the HTABs side.

The Early Dialogues Working Party (EDWP) is a standing committee established by EUnetHTA to ensure robust high-quality HTA outputs. All EDWP members will participate in procedures selected for Consolidated Parallel Consultation.

The Early Dialogue Committee (EDC) is constituted for a specific product and the members will fluctuate to a degree for each Consultation.

In the case of Consolidated Parallel Consultations, all EDWP members and a maximum of 3 other HTA members (from EUnetHTA WP5) will participate. The preferences of the Applicant (indicated in the Letter of Intent) will be taken into account, but participation of those HTABs cannot be guaranteed.

In the case of Individual Parallel Consultations I, HTABs will be recruited to participate in an EDC on a voluntary basis based on their national-level priorities and availability. Preferences of the Applicant (indicated in the Letter of Intent) will be taken into account, but participation of those HTABs is not guaranteed. The EDC will then be formed by the participating HTABs and an EDC Scientific Coordinator will be chosen from one of them.

EDC Scientific Coordinator undertakes scientific coordination on behalf of HTAs. For all procedures, the EDC Scientific Coordinator facilitates discussion between HTABs in advance of meetings, interacts with the EMA and acts as a co-chair for the HTABs for the face to face meeting.

HTAB Rapporteur(s) (only in Consolidated Parallel Consultations) collects and consolidates responses from EDC and presents consolidated HTAB answers during the F2F Meeting. The Rapporteur(s) interacts with the EDC Scientific Coordinator and EMA on scientific matters.

3.3. Pathways for HTA involvement in Parallel Consultation

There is one single procedure for Parallel Consultation; however there are two different pathways the consultation can take. Upon receipt of the Letter of Intent, the ED Secretariat examines the document for its acceptability (ensuring all necessary information is included) and then the document is passed to the EDWP who scrutinise all requests for Parallel Consultation, according to the established EDWP selection criteria (detailed in section 3.3.3). Depending on the outcome of the EDWP evaluation, the pathway is decided.

Once the EDC for the application in question is formed, the EUnetHTA ED Secretariat communicates the outcome of the selection, and final participating HTABs (including any need for direct subsequent unilateral arrangements or contracts between the individual HTAs and Applicant, and contact points for such arrangements) to EMA and to the Applicant according to the process outlined in Table 1.

3.3.1 Consolidated Parallel Consultation

Products selected for this pathway will have an EDC composed of the EDWP members and up to 3 additional HTABs. Once the decision to proceed with a Consolidated Parallel Consultation has been taken, the EUnetHTA ED Secretariat begins the process of recruiting additional HTABs to compose the EDC. The preferences of the Applicant (indicated in the Letter of Intent) are taken into account, but participation of those HTABs cannot be guaranteed.

3.3.2 Individual Parallel Consultation

Individual Parallel Consultations are supported by the EUnetHTA ED Secretariat, thereby benefiting from HTA scientific and administrative coordination with centralised HTA recruitment, consolidated HTA comments and List of Issues, albeit with individual HTA written reports as the final product. Opportunities for closed discussion amongst HTA, and with Regulators, with mutual understanding/problem solving are maximised. HTAB Rapporteur(s) are not appointed in Individual Parallel Consultations.

As with the consolidated pathway, the EUnetHTA ED Secretariat recruits HTABs to participate in the Individual Parallel Consultations pathway in a centralised fashion, thereby replacing the need for Applicants to contact HTABs independently to request participation. The HTAB preferences expressed by the Applicant in their Letter of Intent will be taken into account to the extent possible. However, the Applicant should keep in mind that eligibility criteria and scope of assessment may differ for individual HTABs based on their national/regional regulation and expertise. Applicants should contact the EUnetHTA ED Secretariat for further specific details regarding the HTAB that can take part in this Parallel Consultations where needed.

3.3.3 EDWP selection criteria, scope and coordination

In a context of resource constraints in JA3, there is a limit to the number of products to be selected for Consolidated Parallel Consultation.

The product should aim to bring added benefit to patients i.e. by:

A new mode of action for the indication

AND targeting a life-threatening or chronically debilitating disease

AND responding to unmet need (no treatment or only unsatisfactory treatment available)

EUnetHTA aims for a diverse selection of Consolidated Parallel Consultations and therefore selected EDs should represent a wide array of topics, therapeutic areas etc. (e.g. orphan, ATMPs, antibiotics, oncology). The Applicant's Letter of Intent should provide sufficient information to substantiate the claimed basis of selection and follow the guidance notes provided with the form.

The generation of consolidated HTA outputs through the EDWP involves identifying aspects of development programs for which there is a shared position amongst HTA bodies, discussing and understanding the reasons for divergence between HTABs and attempting to reach consensus amongst HTABs. There is a single written report including: consolidated HTA Early Dialogue written answers for shared positions, and individual HTA answers to those questions for which consensus was not possible. Opportunities for closed discussion with Regulators, with mutual understanding/problem solving are maximised. See Table 1.

3.4. Other stakeholders

From an early stage, the EMA along with HTABs may consider the need for additional clinical experts in a given procedure and F2F meeting. The inclusion of patient representatives is expected on a routine basis.

Regulators' clinical experts are identified through National Competent Authorities (NCA) and SAWP members. A Health Care Professional (HCP) representative may also be invited by the EMA through the EMA HCP Working Party framework, as well as other stakeholders as appropriate.

Individual patient experts are identified through patient organisations under the framework for interaction between the EMA and patients and consumers, and their organisations (EMA/637573/2014).

Where possible, patient representatives are invited to attend all TCs and the F2F meeting; briefing of chairpersons (on the inclusion of a patient representative) and patients (on the aims and nature of the meeting) by EMA Scientific Officer is essential. Any additional time or facilities required by patients should be considered.

EMA exchanges with EUnetHTA ED Secretariat on the participation of clinical experts and/or patient representatives.

EUnetHTA is committed to involving patients in its work – including EDs. Hearing directly from patients about the outcomes that matter to them and how their condition impacts their quality of life are two areas that are important from an HTA perspective. The procedure for how patients will be engaged to share their perspective is currently being developed and European patient organisations will be consulted during this process. EUnetHTA will look to learn from and build on the experience gained during SEED, within national HTAB procedures, and at the EMA. This guidance document will be updated once the EUnetHTA patient involvement in ED procedure is finalised.

4. Process

4.1. Simultaneous Notification

For all Parallel Consultations, the Applicant should simultaneously notify the EMA Scientific Advice Secretariat (scientificadvice@ema.europa.eu) and EUnetHTA ED Secretariat (eunethta-has@has-sante.fr) by means of a Letter of Intent using the available [form](#) for Parallel Consultations. The EMA and EUnetHTA should receive the Letter of Intent prior to the deadline published for the intended procedure start date. This Letter of Intent deadline is approximately 2 months (day-60) before the

formal procedure start date (day 0 or SAWP 1) and 4 months before the intended face to face meeting (day 60 or SAWP 3 meeting).

The EUnetHTA ED Secretariat conducts a check to ensure that all information needed for the assessment of selection criteria by EDWP is provided. The request is sent to the EDWP who decide within 5 working days whether to opt for a Consolidated or Individual output. Following the EDWP decision, the EUnetHTA ED Secretariat contacts other WP5 HTABs to request a response (with a 5 working day deadline) regarding their participation. The final decision on the Parallel Consultation pathway and the final composition of the EDC, Scientific Coordinators and presubmission TC request outcome is communicated to the EMA Scientific Officer, the EMA Scientific Advice Secretariat and the Applicant within 2 further working days.

EMA and EUnetHTA ED Secretariat will then mutually agree the allocation of face to face meeting slots, accommodating any closed HTA meetings, considering the batch of requests for the intended start date. EMA will confirm the date and time of the F2F meeting in writing to EUnetHTA ED Secretariat and the Applicant by approximately day -40.

4.2. Presubmission phase

For all Parallel Consultations, the presubmission phase starts, when the Applicant sends the draft briefing package to the EMA Scientific Officer, the EMA Scientific Advice Secretariat (scientificadvice@ema.europa.eu), and to the EUnetHTA ED Secretariat (eunetha-has@has-sante.fr).

Default without presubmission TC

By default, the presubmission phase is based on written comments on the draft briefing document.

The draft briefing package should be sent **at least 30 days** before the due start date (Day 0 or SAWP1) of the procedure. (See published EMA Scientific Advice [published timetables](#) for a 70 day procedure; SAWP 3 provides the intended face to face meeting date). Please note, the submission of the draft briefing document is requested 1 week earlier than standard EMA Scientific Advice.

In addition to the standard EMA timetables, EMA sets up a timetable in consultation with the EUnetHTA ED Secretariat for each procedure including closed EMA EUnetHTA interactions following receipt of the Letter of Intent from the Applicant and confirmation of EDC selection/participating HTA bodies from EUnetHTA ED Secretariat. EMA sends this timetable to all participants. Calendar meeting requests are sent by EMA to EUnetHTA ED Secretariat and other regulatory participants shortly after a TC or meeting is confirmed.

The Applicant sends Draft Briefing Document directly to the EMA Scientific Officer and EMA Scientific Advice Secretariat (scientificadvice@ema.europa.eu), and the EUnetHTA ED Secretariat (eunetha-has@has-sante.fr) in accordance with the agreed timeline. It is important that the timelines are adhered to so that participants have sufficient time with the draft briefing document 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 EUnetHTA ED Secretariat (collated comments from HTABs) are provided directly to the Applicant by 15 working days, where necessary for the optimisation of the draft submission prior to the start of the procedure.

Comments are shared between EMA Scientific Officer and EUnetHTA ED Secretariat, 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 asked or if

additional questions should be added, and to consider whether the questions are appropriately addressed to HTABs, Regulators or both.

Exceptional with presubmission teleconference (TC)

In certain cases, a presubmission TC and extended presubmission phase may be agreed upon by EMA or EUnetHTA depending on product and Applicant characteristics e.g. inexperienced Applicants or very complex and/or controversial programs and this should be denoted in the Letter of Intent.

For any products requesting a presubmission TC, the Applicant must send the draft briefing document with the Letter of Intent at day-60, 2 months before the intended start date of the procedure. The decision on the need for an exceptional presubmission TC will be taken by the EMA and EUnetHTA ED Secretariat subsequent to the Letter of Intent submission, and EMA will communicate this to the Applicant.

EMA will arrange this TC if agreed upon by EMA and EUnetHTA ED Secretariat. The extended presubmission phase with TC lasts approximately 8 weeks. The TC includes EMA, EUnetHTA ED Secretariat, the Applicant, or other experts as needed. The procedure timetable will be based on the EMA published Scientific Advice timetables for a 70 day procedure with a presubmission meeting.

The presubmission TC will take place around D-30, after the draft briefing document has been received by all parties.

The Applicant circulates the presubmission presentation with numbered slides covering briefly the background, the questions and Applicant's positions, directly to EMA Scientific Officer and EUnetHTA ED Secretariat 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.

Comments reflecting the TC from the EMA and EUnetHTA ED Secretariat (collated comments from HTABs) are provided directly to the Applicant where necessary for the optimisation of the draft submission by 4 working days after the TC.

Finalising the briefing document

The Applicant sends a revised final briefing document with all annexes and references having addressed the EMA comments and EUnetHTA ED Secretariat points of clarification to the EMA Scientific Officer and EMA Scientific Advice Secretariat (scientificadvice@ema.europa.eu) and to EUnetHTA ED Secretariat (euneththa-has@has-sante.fr), at least 2 full working days before the start of the procedure. One version should be in "track changes" mode and the other should be "clean". Both EMA and EUnetHTA ED Secretariat conduct an administrative check to ensure the briefing package is fit for purpose (i.e. that all annexes and references are present and readable, and that any essential changes have been made to the briefing document).

Following confirmation of validation from both EMA and EUnetHTA ED Secretariat, the Applicant sends the final briefing document directly to all EMA contacts in the procedure as instructed and to the EUnetHTA ED Secretariat, via Eudralink, 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 circulation of the final briefing document immediately prior to SAWP 1, as in the published Scientific Advice timelines.

4.3. Evaluation phase

Lists of Issues

For all Parallel Consultations, Lists of Issues facilitate the discussion during the face to face meeting by indicating the focus of Regulators' and HTABs' discussion.

In the regulatory process, the SAWP discusses the first reports (preliminary views) at the SAWP 2 meeting and drafts a Regulators' List of Issues by approximately day 32 of the procedure.

HTABs proceed with their own assessment and discussion in accordance with EDWP internal process, consolidation and national policies. The EUnetHTA ED Secretariat facilitates closed HTAs interactions for discussion of respective HTA body positions and HTA coordination. The EDC Scientific Coordinator consolidates a draft HTA List of Issues by approximately day 32 of the procedure.

EMA and EUnetHTA exchange draft lists of issues where consent has been given by the Applicant.

Pre face to face TCs

The purpose of the pre-face to face TCs 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 at least one development plan, could be discussed in advance of the face to face meeting. The Regulator's chairperson for the F2F meeting should be agreed in the pre-face to face TC.

The EMA arranges a first closed preparatory TC between EMA, Regulators and EUnetHTA (ED Secretariat, Coordinator and Rapporteur), to take place around day 32 of the procedure, focusing on issues identified by Regulators and HTABs. Final versions of List of Issues are sent to the Applicant by the EMA and EUnetHTA ED Secretariat respectively after the TC. They are also exchanged between EMA and EUnetHTA ED Secretariat.

The need for and nature of additional closed regulatory/HTA discussions should be discussed at the first TC with available options including:

- Optional closed TC between Regulators and HTABs between Day 50 and day 59 in the event of complex divergent requirements or major amendments to the development plan as deemed necessary
- SAWP Coordinators may be invited to attend the closed HTA meeting
- Extended closed regulatory HTA interactions immediately prior to Face to face meeting with Applicant.

Preparation for face to face meeting

The Applicant can contact the EMA Scientific Officer and/or EUnetHTA ED Secretariat regarding the format of the face to face meeting. This is to ensure that the meeting fulfils the needs of involved stakeholders. The Applicant should send any written responses, if requested according to EMA or HTAB respective Lists of Issues, ideally 12 working days before the face to face meeting directly to all EMA contacts and EUnetHTA ED Secretariat. There should be no major changes to the development plan compared to the final briefing document, unless the process in topic "Amended development plans" has been followed.

The Applicant should send the final presentation and list of participants directly to all EMA contacts and to EUnetHTA ED Secretariat, 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 "Amended development plans" has been followed.

The EUnetHTA ED secretariat is asked/ to send their final list of attendees to the EMA and to the Applicant also in advance of the meeting (1 week before the F2F). The EMA circulates a final list of all participants 2 days in advance of the face to face meeting. The meeting is hosted at the EMA premises.

Amended development plans triggered by the lists of issues or external factors.

Amended development plans triggered by the Lists of Issues or external factors can be accommodated to some extent during the evaluation 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 plan as early as possible, 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.

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 Regulators on major aspects of trial designs
- To discuss potential solutions that could facilitate one trial design or at least one development plan

The face to face meeting has 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, the maximum length of the meeting is 3 hours.

Before the Applicant enters the room, the Regulators and the HTABs have the opportunity to have a further closed session (between 15 to 45 minutes, the time is determined on a case by case basis in a

pre face to face TC; Applicants will be informed accordingly) in order to interact on any possible changes of position after the Applicant's responses and presentation.

The meeting with the Applicant is interactive, focusing on the issues raised by the Regulator and the HTABs in the Lists of Issues. 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 a follow up Parallel Consultation).

The Applicant is expected to send detailed minutes of the face to face meeting, within 5 working days directly to all EMA contacts and to EUnetHTA ED Secretariat. 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.

| DAYS (calendar days) | Applicant | EMA | HTABs |
|---------------------------------|---|---|---|
| Letter of Intent | | | |
| D -60 | <ul style="list-style-type: none"> ▶▶ The Applicant submits a Letter of Intent, using the provided template, simultaneously to EMA (scientificadvice@ema.europa.eu) and EUnetHTA ED Secretariat (euneththa-has@has-sante.fr) ▶▶ For any products requesting a presubmission TC, the Applicant must send the draft briefing document together with the Letter of Intent | <ul style="list-style-type: none"> ▶▶ Communication of EMA contact point (EMA Scientific Officer) to Applicant and EUnetHTA ED Secretariat | <p>Selection and prioritiation of product by EDWP, General eligibility check by EDWP in 5 working days.</p> <ul style="list-style-type: none"> ▶▶ EDWP decision on eligibility and pathway (CPC or IPC) communicated to EMA and Applicant by EUnetHTA ED Secretariat ▶▶ Parallel Consultations Consolidated and Individual (CPC and IPC) will follow the same steps, unless indicated otherwise ▶▶ Final composition of EDC communicated to EMA and Applicant (max. 5 working days) |
| D≈ -43 | | <ul style="list-style-type: none"> ▶▶ Administrative TC between EMA and EUnetHTA ED Secretariat | |
| Draft Briefing Document | | | |

| | | | |
|--|--|--|---|
| D -30 | <ul style="list-style-type: none"> ▶▶ Applicant submits the Draft Briefing Document, annexes and references simultaneously to the EUnetHTA ED Secretariat and to the EMA via Eudralink³ | <ul style="list-style-type: none"> ▶▶ The Draft Briefing Document is forwarded by the EMA Scientific Advice Secretariat to the SAWP for appointment of 2 SAWP Coordinators and, where appropriate, a SAWP Coordinator for questions relating to significant benefit (only applicable for Protocol Assistance) | <ul style="list-style-type: none"> ▶▶ EUnetHTA ED Secretariat communicates the Draft Briefing Document, annexes and references to EDC |
| | <ul style="list-style-type: none"> ▶▶ Presubmission TC for eligible products with Regulators, HTAs and Sponsors | | |
| Written Request for Clarification and Further Justification of Planned Methods etc. | | | |
| D -15 | | <p>Feedback on Draft</p> <ul style="list-style-type: none"> ▶▶ Where applicable, comments on the Draft Briefing Document are forwarded to Applicant in writing by ~D -15 and copied to EUnetHTA ED Secretariat ▶▶ Additional Experts/patients representative are identification shared with EUnetHTA ED Secretariat | <ul style="list-style-type: none"> ▶▶ EUnetHTA ED Secretariat sends the consolidated EDC request for clarification to EMA and the Applicant with instructions for the preparation of the Final Briefing Document |
| Submission and Validation of Final Briefing Document | | | |
| D -2 D -0 | <p>Submission</p> <ul style="list-style-type: none"> ▶▶ The Applicant sends two versions of the Final Briefing Document simultaneously to EUnetHTA ED Secretariat and the EMA via Eudralink in response to the request for clarification. One version should be in "track changes" mode and the other should be "clean" | <p>Validation of Final Briefing Document</p> <ul style="list-style-type: none"> ▶▶ Positive validation of the Final Briefing Document by EMA Scientific Advice Secretariat to the Applicant and EUnetHTA ED Secretariat at D -2 together with final instructions | <p>Validation of Final Briefing Document</p> <ul style="list-style-type: none"> ▶▶ EUnetHTA ED Secretariat confirms validation to the Applicant and EMA ▶▶ EUnetHTA ED Secretariat shares the Final Briefing Document with EDC members |
| Evaluation Phase | | | |

³ The use of a secure link system (for authorised personnel only) will ensure proper transmission of large files and the confidentiality of sensitive documents.

| | | | |
|--|---|---|--|
| D +30 | | <ul style="list-style-type: none"> » Discussion of the first reports during SAWP meeting focussing on controversial issues followed by production of a draft List of Issues, which outlines the topics of Regulators' interest to be addressed by the Applicant in the F2F meeting | <ul style="list-style-type: none"> » EDC identifies and exchanges List of Issues (e-meeting) » EDC starts to discuss the draft written positions |
| ≈D +32 | | <ul style="list-style-type: none"> » EUnetHTA ED Secretariat and EMA exchange their respective draft Lists of Issues, where consent has been given by the Applicant » EMA and SAWP Coordinators take part in a closed e-meeting (preF2F TC) with EUnetHTA ED Secretariat, EDC Scientific Coordinator and Rapporteur⁴ | |
| | | <ul style="list-style-type: none"> » Finalisation of List of Issues » After the pre-F2F TC EMA sends SAWP List of Issues to the Applicant and EUnetHTA ED Secretariat | <ul style="list-style-type: none"> » Finalisation of List of Issues » After the pre-F2F TC EUnetHTA ED Secretariat sends the List of Issues to the Applicant and the EMA and provides the information on which recommendations will be consolidated⁵ vs. individual ones to the EDC⁶ |
| Applicant's Written Response to List of Issues (optional) | | | |
| D +45 | <ul style="list-style-type: none"> » The Applicant sends their written responses (if applicable) to the List of Issues raised by the EMA and EUnetHTA to EMA and EUnetHTA ED Secretariat (if applicable: notification of amended development plan with changes and justifications) | | <ul style="list-style-type: none"> » EUnetHTA ED Secretariat distributes the Applicant's written response (if applicable) to EDC |
| D ~ +50 | | <p>Optional:</p> <ul style="list-style-type: none"> » TC between EMA and EUnetHTA to discuss late changes from the Applicant | |
| Preparation for Face to Face meeting | | | |

⁴ In the IPC pathway, there is no Rapporteur, thus the List of Issues is consolidated by the EDC Scientific Coordinator

⁵ For products following the CPC pathway

⁶ For the CPC pathway those questions for which there is consensus will receive consolidated answers and those for which there is not will receive individual responses from each of the participating HTABs. For the IPC pathway, responses to all questions will be provided by the individual HTABs without consolidation.

| | | | |
|-----------------------------|---|--|--|
| D +56 | <p>»» Applicant sends power point presentation to EMA and EUnetHTA ED Secretariat, 4 full working days before F2F meeting, addressing the Lists of Issues for both HTABs and Regulators. The Applicant should group related issues together. A list of Applicant's participants should be enclosed also</p> | | |
| Face to face meeting | | | |
| D ~ +60 | | <p>»» The meeting takes place at the EMA premises, and will normally have 2 co-chairs: one from the Regulators and one from the HTABs (the EDC Scientific Coordinator).</p> <p>»» Optional: closed HTA session (2 hours): discussion among EDC (if no EDC e-meeting has occurred at D +55-59). Optionally can also include Regulators.</p> <p>»» Tripartite session: F2F meeting between EDC and EMA with the Applicant. The meeting duration will depend on the range of issues to be discussed and advice format (maximum 3 h), with 15 minutes closed pre, and 15 minutes closed post F2F (EMA and EUnetHTA). Pre-meeting could be extended to 45 minutes if necessary (e.g. late changes to the development plan)</p> <p>The Applicant addresses key issues that were identified by EUnetHTA EDC and EMA. An interactive discussion follows on the key issues</p> | |
| D +70 | | <p>»» The Regulators' Final Advice Letter is adopted by the CHMP (and by the COMP in case of questions on significant benefit for Protocol Assistance) and sent to the Applicant and EUnetHTA ED Secretariat</p> | <p>»» Finalisation of EDC Written Recommendations according to pathway⁷</p> |
| D +75 | | | <p>»» EUnetHTA ED Secretariat sends the Final Written Recommendations to EMA and the Applicant as a final deliverable⁸</p> |

Table 1 Outline of actions for Applicant, EMA and EUnetHTA in all Parallel Consultations

⁷ EUnetHTA recommendations following the CPC pathway, HTABs' individual recommendations for the IPC pathway

⁸ Note: D +70 and D +75 could fluctuate if there are late changes to the development plan by the Applicant

5. Practical Issues

5.1. Fees

The EMA charges fees for this procedure, which are the same as for standard Scientific Advice/Protocol Assistance including the application of any fee incentives. For more information see [Fees payable to the European Medicines Agency](#).

The participation of HTA bodies in the EDs offering consolidated HTA outputs elaborated through EDWP (Consolidated Parallel Consultation) in the frame of the EUnetHTA Joint Action may be partially covered by EUnetHTA JA3 budget. However, some HTABs may charge fees for participation in Consolidated or Individual Parallel Consultation. Information on fees request is available from EUnetHTA ED Secretariat.

Future funding sources: to achieve the quality and sustainability of HTA Early Dialogues, the funding mechanism of these EDs will be adapted, likely by being based on a fee-for-service approach. Mechanisms for the future funding of EDs will be evaluated and decided during the first two years of JA3.

5.2. Contact points

It is preferable to have a principal point of contact (with back-up) for each stakeholder. The points of contact should be confirmed for each procedure.

The EUnetHTA ED Secretariat is the point of EUnetHTA contact in relation to all HTA aspects, unless otherwise indicated.

The EMA Scientific Officer is the principal EMA contact person to which the Applicant and EUnetHTA should address all queries related to an individual procedure. Applicants' are instructed to send their documents to EMA contacts as indicated in the contact sheet.

The Applicant should keep the EMA Scientific Officer and EUnetHTA ED Secretariat up to date with changes in contact details.

5.3. Processing of documents

The Parallel Consultation uses Eudralink - a secure system for sending/receiving documents between all parties.

The Applicant is responsible for sending the briefing documents directly to the EUnetHTA ED Secretariat and EMA contacts. 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. This is in order to guarantee an appropriate time for the revision and the evaluation by Regulators and HTABs.

The Applicant provides consent to document exchange in the Letter of Intent between EMA and EUnetHTA.

5.4. Briefing document for Parallel Consultation

A common briefing document is used; each question can be addressed to the Regulators or the HTABs alone, or to both. Quality and nonclinical questions are possible during a Parallel Consultation procedure, and posed to Regulators only. 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 required ([See published template for Parallel Consultation](#)).

6. Other

6.1. Advice format

The EMA will send the CHMP final Scientific Advice/Protocol Assistance letter to the Applicant in accordance with the [published timelines](#) (i.e. the subsequent CHMP meeting).

IPC: Individual HTABs provide HTABs' Early Dialogue written answers to the questions directly to the Applicant within 15 working days of the face to face meeting.

CPC: In the case of a consolidated HTA output, the EUnetHTA ED Secretariat sends out final validated written answers to Applicant at day 70.

Final outcome letters are exchanged between EMA and EUnetHTA ED Secretariat where the Applicant has provided consent in the Letter of Intent for document exchange.

6.2. Follow up procedures

A follow-up procedure to an earlier Parallel Consultation procedure for the same indication is possible. There is no time window during which this has to be completed. The briefing document should contain a clear table of the changes compared to the previously reviewed development plan with justifications. However, for conflict of interest reasons, HTAB want to avoid collaborative development with Applicant through iterative process.

7. Summary of documents and meeting aims

Table 2. Description of documents

| Documents | Description |
|-------------------------|---|
| Letter of Intent | Formally requests the EMA and EUnetHTA ED Secretariat of the intent to submit a Parallel Consultation. |
| Draft Briefing Document | Draft Briefing Document comprising the questions and Applicant'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, including all annexes and references. |
| SAWP List of Issues | Documents outlining the concerns or |

| Documents | Description |
|--|---|
| EUnetHTA List of Issues | disagreements with the Applicant's proposal. Further justifications, clarification or changes to the Applicant's proposals are requested. |
| Final CHMP Scientific Advice/ Protocol Assistance letter Final Individual HTA Early Dialogue written answers Final Consolidated HTA Early Dialogue 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 (exceptional) | Applicant's draft Briefing Document Applicant's presubmission presentation | <p>The aim of the presubmission TC is:</p> <ul style="list-style-type: none"> 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. <p>The Applicant participates in the TC with the aim of delivering a final Briefing Document that meets the needs of Regulator and HTAB participants.</p> | EMA List of comments on draft briefing document for Regulators EUnetHTA List of comments on draft Briefing Document for HTABs |
| HTAB closed interactions | HTAB Lists of Issues for discussion at face to face meeting- HTABs | <p>The aim of the pre-face to face HTAB only teleconference is:</p> <ul style="list-style-type: none"> To facilitate discussion of respective HTAB positions and coordination. | EUnetHTA List of Issues |
| Pre-face to face teleconference (closed discussion) | Applicant's final briefing document List of Issues (draft) for discussion at face to face meeting for Regulators and HTABs | <p>The aim of the pre-face to face teleconference is:</p> <ul style="list-style-type: none"> 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. | SAWP List of Issues EUnetHTA List of Issues |
| Face to face meeting | Applicant's final Briefing Document Applicant's presentation List of Issues for | <ul style="list-style-type: none"> To discuss issues of concern or disagreement from Regulators and/or HTABs with the Applicant's proposal regarding the major aspects of trial designs. | Final CHMP Scientific Advice/ Protocol Assistance Letter Final HTABs Early |

| Meetings | Input Document | Objective of meeting | Output Document |
|----------|---|---|--------------------------|
| | discussion at face to face meeting for Regulators and HTABs Any written responses from Applicant | <ul style="list-style-type: none"> 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. | Dialogue Written Answers |

8. List of complementary documents

8.1. Letter of Intent template

8.2. Briefing document template