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Guidance on Parallel EMA/HTA body (HTAb) Scientific Advice for the Interim Period

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Abbreviations

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
EU	European Union
EMA	European Medicines Agency
EUnetHTA 21	European Network for Health Technology Assessment 2021
F2F	Face-to-face meeting
G-BA	Gemeinsamer Bundesausschuss, Germany
HCP	Health Care Professional
HTA	Health Technology Assessment
HTAbs	Health Technology Assessment bodies
HTAR	HTA regulation
HTD	Health technology developer
JSC	Joint Scientific Consultation
MAA	Marketing Authorisation Application
NCA	National Competent authority
PICO	Approach used in evidence-based medicine to define e.g. Population – Intervention – Comparator(s) – Outcome(s)
PLEG	Post Licensing Evidence Generation
SAWP	Scientific Advice Working Party
TC	Teleconference

1 Introduction

Interactions between medicines' developers, Regulators and Health Technology Assessment bodies (HTAbs) or other possible stakeholders to discuss the development plan at an early stage of a medicinal product's clinical development means that robust evidence can be generated during pre-approval studies 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 with added value and hence for the overall benefit of public health.

In order to further facilitate the joint work of EMA and HTAbs in preparation of the joint scientific consultations under Article 16 of the HTA regulation (HTAR), the parties involved agree to offer an interim consultation approach, henceforward referred to as Parallel EMA/HTA body (HTAb) Scientific Advice. Health technology developers (HTDs) are offered the opportunity, from September 2023 onwards, to receive Parallel EMA-HTAb Scientific Advice on a rolling basis until the HTA regulation becomes applicable.

For all submitted requests, the HTAb involvement coordinating body, the G-BA (Gemeinsamer Bundesausschuss / Federal Joint Committee, Germany), which will be referred to as the "HTA Coordination Contact" hereafter, facilitates a centralised HTA recruitment.

Parallel EMA-HTAb Scientific Advice provides a single gateway for requests for parallel discussions during the interim period, facilitating the transition from the completion of EUnetHTA 2021 in September 2023 to the full application of the HTA regulation (HTAR) in January 2025. This interim format ensures the continuation of the fruitful collaboration between Regulators and HTAbs for parallel advice with high scientific quality, further fostering mutual understanding between the entities and providing central coordination for HTAbs. The model facilitates scientific advice before the start of pivotal clinical trials on initial evidence generation for Marketing Authorisation Application/Reimbursement, and Post Licensing Evidence Generation (PLEG, only in conjunction with a request for discussion of pivotal trial design) and promotes optimal and robust evidence generation fit-for-purpose for both Regulators and HTAbs, ultimately benefitting public health with improving access to medicines which are effective to European patients being the ultimate goal.

The European Commission recognizes the value of the close collaboration between the European Medicines Agency (EMA) and Health Technology Assessment (HTA) bodies in Europe, as well as the potential for capacity building of a parallel scientific advice offer between October 2023 and December 2024.

This parallel EMA/HTA body Scientific Advice for the interim period is provided solely on the initiative of individual HTA agencies in preparation for the application from 12 January 2025 of Regulation (EU) 2021/2282 on health technology assessment.

2 Principles

2.1 Roles and remits

This guidance highlights ideal timelines and actions for each party undertaking a Parallel EMA/HTAb Scientific Advice.

This is a multi-stakeholder procedure with EMA 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.

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

2.2 Confidentiality

By submitting a request for a Parallel EMA/HTAb Scientific Advice, the Applicant agrees to the exchange of information between EMA and participating HTAbs.

The Parallel EMA/HTAb Scientific Advice process is confidential.

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

Each HTAb participant and associated expert, e.g. healthcare professionals and patient (representatives), is required to sign a confidentiality agreement according to national rules of the involved HTAb. To actively participate, HTAbs must have national rules and procedures in place to maintain confidentiality. Also, when participating with observer status the maintenance of confidentiality needs to be ensured by the respective HTAb.

Therefore, commercially confidential information provided to the EMA and HTAbs within the context of a Parallel EMA/HTAb Scientific Advice shall not be shared with any party before authorisation outside of the respective EMA and HTAb 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.

HTAbs interested in active participation must have national rules and procedures in place to avoid conflict of interest (COI) situations as this will not be managed centrally but falls within the responsibility of the participation HTAbs.

2.4 Status of Parallel EMA/HTAb Joint Scientific 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 fully justify ~~a~~ny deviations from the advice given. Please, see the EMA Scientific Advice Guidance document for further details.

Advice provided by HTAb partners is based on the documentation provided by the Applicant. The individual recommendations reflect the state-of-the-art of medical science and national requirements at the time of advice.

As an outcome of the parallel EMA-HTAb Scientific Advice procedure, HTDs will receive the EMA Scientific Advice Letter and individual Written Recommendations (non-consolidated) separately by each of the participating national HTAbs.

3 Actors and scope

The process described herein is only for Parallel EMA/HTAb Scientific Advice jointly involving EMA and HTAbs. For regulatory-only Scientific Advice involving only the EMA, please see EMA website. National HTAb advice needs to be requested individually with the respective national body.

The Applicant needs to ensure that the timing of a JSC is reasonable, e.g. a regulatory-only advice procedure shortly before a JSC with the same questions asked to EMA in that recent interaction is not deemed appropriate.

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 14).

The SAWP Rapporteur 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 two co-chairs for the discussion meeting, and drafting the final report for further input and consideration by SAWP and EMA Committees.

The EMA Scientific Officer supports the SAWP Rapporteurs with scientific and administrative coordination. This is the principal EMA contact person to be reached, along with the EMA Procedure Assistant, by the Applicant and HTAbs for matters related to an individual procedure.

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.

3.2 HTAbs: actors and scope

HTAbs aiming to join a Parallel EMA/HTAb Scientific Advice can take two different roles. HTAbs may either actively participate, providing advice on their national requirements, or they can take the role of an observer, following the advisory process and the recommendations of the other participating HTAbs and the EMA.

HTAb may participate in a parallel advice on a voluntary and individual basis with a minimum of two (actively participating) HTAb per advice procedure. The Applicant will not be able to choose the involved HTAbs. Selection criteria of the HTA Regulation will apply and acceptance is dependent on the available resources of the respective HTAb on a case-by-case basis. In case less than two HTAb are available, the request will continue as EMA-only scientific advice.

There is no HTAb Assessor for a Parallel EMA/HTAb Scientific Advice. Each HTAb is responsible for their recommendations and is providing their national position individually.

For all submitted requests, the HTAb involvement coordinating body, the G-BA (Gemeinsamer Bundesausschuss / Federal Joint Committee, Germany) will function as the "HTA Coordination Contact". The HTA Coordination Contact facilitates a centralised HTA recruitment and is responsible for all practical coordination of HTAb participation in a Parallel EMA/HTAb Scientific Advice. The HTA Coordination Contact acts as the sole HTAb contact for all Parallel EMA/HTAb Scientific Advices for EMA and Applicants.

Parallel EMA/HTAb Scientific Advice focusses on advice before the start of pivotal clinical trials, on initial evidence generation for MAA/HTA assessment and on PLEG. However, discussions on PLEG can be facilitated only in conjunction with a request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies.

3.3 HTAb involvement in Parallel EMA/HTAb Scientific Advice

3.3.1 Submissions on a rolling basis

HTDs are offered the opportunity, from September 2023 onwards, to receive parallel EMA-HTAb Scientific Advice on a **rolling basis** until the HTA regulation becomes applicable.

Applicants are invited to flag their interest for such parallel scientific advice by sending an email to G-BA (Gemeinsamer Bundesausschuss/Federal Joint Committee, Germany) as the HTA Coordination Contact copying EMA.

In order to apply for a Parallel EMA/HTAb Scientific Advice, health technologies developers (HTD) should complete the application form available on the EMA/EUnetHTA 21 websites or upon request (interimadvice.hta@g-ba.de) and submit their application and annexes (if applicable) via Eudralink to the HTA Coordination Contact (interimadvice.hta@g-ba.de). The Applicant's request for a Parallel EMA/HTA Scientific Advice should provide sufficient information to substantiate the claimed basis for selection and follow the guidance notes provided with the form. Health technology developers should submit this application three months earlier than the standard submission deadline for applications (e.g., application before 05-Mar for a start of HTA-EMA Scientific Advice procedure on 03-Jul).

The selection criteria of the HTA Regulation will apply (see 3.3.2) and acceptance of a request is dependent on the available resources of the respective HTAb on a case-by-case basis. In case less than two HTAb are available, the request will continue as EMA-only scientific advice.

There is no option for a follow-up consultation for Parallel EMA/HTAb Scientific Advice. All relevant questions should be submitted in a single application.

The HTA Coordination Contact facilitates a centralised HTA recruitment and communicates the outcome of the selection to Applicants and EMA within four weeks after having received the Application form. Information will be provided regarding the participating HTAbs to the Applicant and EMA according to the Parallel EMA/HTAb Scientific Advice process outlined in Table 2.

Details in terms of HTAb requesting fees for their involvement will be communicated by the HTA Coordination Contact to the Applicant after the information on acceptance.

Other products which are not selected for a parallel EMA/HTAb Scientific Advice can pursue a regular Scientific Advice procedure with EMA and may be eligible for national advice from some HTAbs.

3.3.2 Selection criteria

HTAbs will apply the same selection criteria as defined in the HTAR. A prerequisite for a Parallel EMA/HTAb Scientific Advice is that the pivotal clinical trial (pivotal phase II/ or III) has not yet started. Discussions on PLEG can be facilitated only in conjunction with a request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies.

Promising candidates have to meet the following criteria to be considered:

a) Unmet medical need (no treatment or only unsatisfactory treatment available);
b) First in class;
c) Potential impact on patients, public health, or healthcare systems;
d) Significant cross-border dimension;
e) Major Union-wide added value; or
f) Union clinical research priorities.

Oncology products and/or ATMPs and indications for which there is no established guidance for clinical development (i.e. in absence of recent HTA evaluation in a similar indication) are also given preferred consideration.

In the application form the HTD should elaborate on the selection criteria respectively and provide an explanation why the criteria are met and the product is eligible for an advice procedure, at the time of the application.

3.3.3 Parallel EMA/HTA Scientific Advice format and outcome

There is one single procedure for Parallel EMA/HTAb Scientific Advices; the consultations take place in a discussion meeting format allowing for a direct exchange between the participating HTAbs, EMA and the Applicant. All Parallel EMA/HTAb Scientific Advices are supported by the HTA Coordination Contact, thereby benefiting from HTA scientific and administrative coordination.

The entire procedure will be approximately 3,5-4,5 months in duration starting from reception of the draft briefing package. The Parallel EMA/HTAb Scientific Advice with a discussion meeting allows for a direct exchange between the participating HTAbs, EMA and the Applicant. The discussion meeting is hosted by EMA and is held virtually at the moment. However, this may change through the course of the interim period and face-to-face (F2F) meetings in person might be applicable.

The HTAb recommendations will not be consolidated, but an attempt is made to establish mutual understanding and ideally consensus. As an outcome of the parallel EMA-HTAb Scientific Advice procedure, HTDs will receive individual Written Recommendations (non-consolidated) separately by each of the participating national HTAb as well as the EMA Scientific Advice Letter. The full procedure is detailed in Table 2.

3.4 Other stakeholders

EMA along with HTAbs may consider an involvement of patient (representatives) and clinical experts in the given procedure. However, expert involvement on the HTA side can only take place on a national level by the participating HTAbs.

EMA

Regulators' clinical experts are identified through National Competent Authorities (NCA) and SAWP members. An 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 the discussion 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.

HTAbs

HTAbs are committed to involving patients (representatives) and HCP experts in their work. Hearing directly from patients about the outcomes that matter to them and how their condition impacts their quality of life and hearing directly from HCP about natural disease history and current disease management are areas that are important from an HTA perspective.

For Parallel EMA/HTAb Scientific Advices this will be facilitated by the participating HTAbs in accordance with their national procedures. The experts involved at national level will not attend the discussion meeting.

4 Process

4.1 Simultaneous notification

For all Parallel EMA/HTAb Scientific Advices, the Applicants who received a notification of selection should notify the EMA Scientific Advice secretariat by means of an application submitted via the IRIS platform. The EMA and HTA Coordination Contact should simultaneously receive the draft briefing package by the published deadline for the intended procedure start date (for submission details, please refer to 4.2 "default without presubmission TC").

This IRIS submission deadline is approximately 1 month (30 days) before the formal procedure start date (day 0 or SAWP 1) and 3 months before the intended discussion meeting (day 60 or SAWP 3 meeting). For accurate submission deadlines, please refer to the relevant 2023 and 2024 submission deadlines on the EMA website.

EMA and the HTA Coordination Contact will then mutually agree the allocation of discussion meeting slots. EMA will confirm the date and time of the discussion meeting to the HTA Coordination Contact and the Applicant by approximately day - 40.

4.2 Presubmission phase

For all Parallel EMA/HTAb Scientific Advices, the presubmission phase starts when the Applicant submits the request to the EMA through IRIS and sends the draft briefing package to the HTA Coordination Contact via Eudralink (https://eudralink.ema.europa.eu/).

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 submitted at least 30 days before the due start date (day 0 or SAWP1) of the procedure. (See EMA Scientific Advice published timetables for a 70 day procedure; SAWP 3 provides the intended discussion meeting date).

In addition to the standard EMA timetables, EMA sets up a timetable in consultation with the HTA Coordination Contact for each procedure including closed EMA/HTAb interactions. Calendar meeting requests are sent by EMA to the HTA Coordination Contact and other regulatory participants shortly after a meeting is confirmed.

The Applicant simultaneously submits the request through IRIS and sends the draft briefing document to the HTA Coordination Contact[1] in accordance with the agreed timeline. It is important that the timelines are adhered to to allow for the participants to have sufficient time with the draft briefing document in order to provide feedback to the Applicant, and it is also important 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 HTA Coordination Contact 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. However, HTAbs reserve the right to contact the Applicant in order to request further clarification at any time within the procedure, if needed.

Comments are shared with the Applicant by the EMA Scientific Officer and HTA Coordination Contact (if applicable) in terms of a check for completeness: 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. Both EMA and HTAB reserve the right to answer selected questions that have been directed to the other entity if deemed appropriate.

[1] The submission to the HTA Secretariat must be done via Eudralink (https://eudralink.ema.europa.eu/) which will allow for the confidential exchange of information.

Finalising the briefing document

The Applicant submits a revised final briefing document with all annexes and references having addressed the EMA comments and HTAbs' points of clarification (if any) through IRIS at least 5 full working days before the start of the procedure. One version should be in "track changes" mode and the other should be "clean". EMA conducts an administrative check to ensure the briefing package is fit for purpose (e.g., that all annexes and references are present and readable, and that essential changes have been made to the briefing document).

Following confirmation of validation from EMA, the Applicant submits the final briefing document through IRIS and sends this also to the HTA Coordination Contact via Eudralink (https://eudralink.ema.europa.eu/), according to the shared timeline. One version should be in "track changes" mode and the other one should be "clean". There is no formal confirmation of the validation by the HTA Coordination Contact but applicants are contacted proactively if files are identified to be missing. The Applicant should ensure that the final briefing document has been received by both parties.

The presubmission phase ends with the circulation of the final briefing document prior to SAWP 1 (Wednesday before start of SAWP; SAWP1 defined according to the published timelines).

There is no option for a follow-up consultation with EUnetHTA 21 during the project phase. All relevant questions must be submitted in the briefing package for the JSC.

4.3 Evaluation phase

Lists of Issues

For all Parallel EMA/HTAb Scientific Advices, a Lists of Issues (LoI) facilitates the discussion during the discussion 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 40 of the procedure.

In the HTA process, HTAbs participating in the advice share one consolidated List of Issues (following PICO (Population, Intervention, Comparator, Outcome)) collected through an exchange between the participating HTAb and will be shared with the HTD around day +35 of the procedure.

Exchange between EMA and HTAbs

EMA and HTAb LoI are also exchanged between EMA and HTA Coordination Contact.

The EMA arranges a closed preparatory virtual meeting between EMA and HTAbs (including HTA Coordination Contact), to take place around one week prior to the discussion meeting, focusing on the issues identified by Regulators and HTAbs.

The purpose of this virtual meeting is to exchange and understand respective (preliminary) positions of the different Regulator and HTAb participants on the major aspects of the trial designs. Potential solutions that could facilitate one single trial, or a common development plan, could be discussed in advance of the discussion meeting. The Regulator's and the HTAb's chairperson for the discussion meeting should be agreed on during the exchange.

Preparation for discussion meeting

The Applicant can contact the EMA Scientific Officer and/or HTA Coordination Contact regarding the format of the discussion meeting. This is to ensure that the meeting fulfils the needs of the involved stakeholders. The Applicant should send any written responses to the HTAbs' List of Issues 12 working days before the discussion meeting directly to the HTA Coordination Contact. For EMA's List of Issues, the Applicants' written response is expected 5 working days before the start of the discussion meeting week (SAWP3 meeting week, according to the published timelines).

The Applicant should submit the final presentation and list of participants via IRIS and to the HTA Coordination Contact, 2 working days before the end of the week preceding the discussion meeting week (SAWP3 meeting week, according to the published timelines). Any changes to the presentation after this date will not be accepted. Thus, once shared with the meeting participants, according to the agreed timelines, the presentation should not be amended by the Applicant. 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. 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 HTA Coordination Contact is asked to send their final list of attendees to the EMA also in advance of the meeting (1 week before the discussion meeting). Applicants may have up to 12 representatives which can be increased to 14 in case of Applicants between collaborating companies. The EMA circulates a preliminary list of all participants 2 days in advance of the discussion meeting. The meeting is hosted by EMA and is held virtually.

Amended development plans triggered by the Lists of Issues/written response to List of Issues or external factors

Amended development plans triggered by the LoI 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 discussion meeting. The amended plan must be received by all parties together with a clear comparative table of changes in the plans and justification for the changes.

For HTAbs, the written response to LoI and, if applicable, necessary information regarding the amended development plan must be received at the latest by 12 working days before the discussion meeting. Any substantial changes to the development plan submitted past this date cannot be addressed within the discussion meeting or reflected in the minutes.

For EMAs LoI, the Applicants' written response and, if applicable, necessary information regarding the amended development plan is expected 5 working days before the start of the discussion meeting week (SAWP3 meeting week, according to the published timelines).

Discussion meeting

The meeting is hosted by EMA and is held virtually at the moment. However, this may change through the course of the interim period and face-to-face (F2F) meetings in person might be applicable.

The aims of the discussion meeting are:

- To discuss issues of concern or disagreement from EMA and/or HTAbs with the Applicant's proposal regarding major aspects of trial designs.
- To get a mutual understanding of each body's constraints as it has to be acknowledged that Regulators and HTAbs are operating within distinct remits (benefit/risk evaluation vs. added value or cost-effectiveness evaluation). Possible resulting divergences between Regulators' and HTAbs' positions on major aspects of the trial design will be discussed.
- To share and discuss preliminary positions on major aspects of trial designs from HTAbs with all participants.
- To discuss potential solutions that could facilitate one trial design or at least one development plan.

The discussion meeting has 2 co-chairs: one from EMA and one from the HTAbs. The meeting duration will depend on the range of issues to be discussed, the maximum length of the meeting is 3 hours. If it is agreed between the EMA and the HTAbs prior to the discussion meeting that the content of the

discussion is limited, the meeting can be set at 1.5 hours. The Applicant will be informed about the length of the discussion meeting in due time.

Before the Applicant enters the room, the Regulators and the HTAbs have the opportunity to have a closed session in order to exchange on organisational items and to interact on any possible changes of position after the Applicant's responses and presentation. This pre-meeting could be extended if necessary (e.g. late changes to the development plan).

The meeting with the Applicant is interactive, focusing on the issues raised by the Regulator and the HTAbs in the LoI. Wherever possible the issues of both Regulators and HTAbs should be grouped together and structured following PICO (Population, Intervention, Comparator, Outcome) to enable for a joint discussion of the stakeholders. During the discussion meeting, the views of each stakeholder should be clearly presented on each issue. It is usual to pause after each question/issue for discussion. Time should be allowed for summing up at the end of the meeting.

The Applicant is expected to provide detailed minutes of the discussion meeting, within 5 working days directly to EMA. The minutes should reflect the views for each participating stakeholder in the discussion meeting. Areas of agreement and divergence of opinion between Regulators and HTAbs can 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 minutes should be sent also to the HTA Coordination Contact for information. The minutes will not be commented by HTAbs.

Table 1: Outline of actions for Applicant, EMA and HTAbs in Parallel EMA/HTAb Scientific Advices

Day	Applicant	EMA	HTAbs
Submission of draft briefing package			
D - 30	➢ **Applicant** submits the draft briefing document with annexes and references simultaneously to the **HTA Coordination Contact** via Eudralink[2] and to the **EMA** via IRIS.	**IRIS** automatically confirms receipt Communication of EMA contact point (EMA Scientific Officer) to Applicant and HTA Coordination Contact. IRIS submission triggers **appointment of 2 SAWP Rapporteurs** and, where appropriate, a SAWP Rapporteur for questions relating to significant benefit (only applicable for protocol assistance) by the SAWP.	**Main contact for all HTA matters: HTA Coordination Contact** ➢ **HTA Coordination Contact** confirms receipt to the Applicant. ➢ **HTA Coordination Contact** communicates the draft briefing document, annexes and references to **involved HTAbs (active participants and observers).** ➢ HTAbs can request any necessary clarifications to the Applicant at any time.
D - 15		**Feedback on draft** ➢ Where applicable, comments on the draft briefing document are sent to Applicant through IRIS by ~D -15 and also sent to the **HTA Coordination Contact**: ➢ Additional Experts/patients representative are identified and shared with **HTA Coordination Contact.**	➢ External experts are involved at national level to provide input for the respective national positions of the participating HTAbs.
D - 10		Administrative meeting between EMA and HTA Coordination Contact.	

[2] https://eudralink.ema.europa.eu/

Day	Applicant	EMA	HTAbs
Validation/reception of briefing package			
D - 5	**Submission** The **Applicant** submits the briefing package together with annexes and references in response to the request(s) for clarification to the EMA via IRIS and to HTAs via Eudralink. One version of briefing document should be in "track changes" mode and the other should be "clean".	**Validation of Final briefing document** Notification of positive validation of the final briefing document by EMA Scientific Advice secretariat to the Applicant via IRIS and information of the HTA Coordination Contact thereof at D -2 together with final instructions.	**Reception of final briefing document**: ➢ There is no formal confirmation of the validation by the HTA Coordination Contact but a proactive reach out if files are identified to be missing.
Submission of final briefing package			
D -2	The **Applicant** submits final briefing package including annexes and references to the **EMA** via IRIS **and to the HTA Coordination Contact** via Eudralink.		➢ **HTA Coordination Contact** shares the final briefing document with **HTAbs (active participants and observers).**
Evaluation Phase			
		➢ Discussion of the first reports during SAWP meeting focusing 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 discussion meeting.	➢ Preliminary discussion (virtual meeting) on HTAbs` issues and positions on main topics (PICO) of the development **Production of a HTAb List of Issues, which outlines the topics of HTAbs interest to be addressed by the Applicant in the discussion meeting.**

Day	Applicant	EMA	HTAbs
~D + 35-40		**HTA Coordination Contact** and EMA exchange their respective draft Lists of Issues and send the lists to the **Applicant.**	
Applicant's written response to List of Issues			
D + 45-50	➢ **Applicant** sends their written responses to the List of Issues raised by HTAbs via Eudralink to the **HTA Coordination Contact** (if applicable: including notification of amended development plan with changes and justifications). ➢ **Applicant** sends their written responses (if applicable) to the List of Issues raised by the **EMA** via IRIS.		➢ **HTA Coordination Contact** distributes the Applicant's written response and any notification of an amended development plan with changes and justification (if applicable) to the **HTAbs (active participants and observers).**
Preparation for discussion meeting			
~D + 55	➢ **Applicant** submits power point presentation to **EMA via IRIS and HTA Coordination Contact via Eudralink**, at least 2 full working days before the week preceding the discussion meeting week (SAWP3 meeting week),	➢ EMA and SAWP Rapporteurs take part in a closed virtual meeting (pre-discussion meeting) with HTA Coordination Contact and participating HTAbs: The EMA arranges a closed preparatory virtual meeting between EMA and HTAbs (including HTA Coordination Contact) to take place around one week prior to the discussion meeting, focusing on the issues identified by Regulators and HTAbs. This facilitates a meaningful exchange of the respective views in preparation of the meeting with the HTD. Regulators and the HTAbs have the opportunity to have a closed session in order to interact on any possible changes of position after the Applicant's responses and presentation (e.g. late changes to the development plan).	

Day	Applicant	EMA	HTAbs
	addressing the Lists of Issues for both HTAbs and Regulators. The Applicant should group related issues together. Further changes after this date will not be accepted. ➢ Applicant submits list of participants.		
Discussion meeting			
D + 60	➢ The meeting is hosted by EMA (virtually or face-to-face (F2F)). ➢ The meeting will normally have 2 co-chairs: one from the Regulators and one from the HTAbs. **Tripartite session: Discussion meeting between EMA and HTAbs with the Applicant.** The meeting duration will depend on the range of issues to be discussed (maximum 3 h), with 15 minutes closed pre-, and 15 minutes closed post-discussion meeting (EMA and HTAbs). This pre-meeting could be extended if necessary (e.g. late changes to the development plan). The **Applicant** addresses key issues that were identified by **EMA and HTAbs**. An interactive discussion follows on the key issues.		
D + 70		➢ The Regulators' **Final Advice Letter** is adopted by the CHMP (and by the COMP in case of questions on significant benefit for Protocol Assistance), made available to Applicant via IRIS and sent to the **HTA Coordination Contact.**	➢ **Finalisation of HTAbs' individual Written Recommendations**.
D + 75-80			➢ **HTAbs' Individual Written Recommendations sent to Applicant and EMA.**

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 charging of fees by the HTAb side depends on the HTAbs participating and their national rules on whether fees are payable for their involvement. The Applicant will be informed about occurring fees by the HTA Coordination Contact as soon as HTAb participation is confirmed.

5.2 Contact points

The HTA Coordination Contact is the single point of HTA contact in relation to all HTA aspects, unless otherwise indicated.

The EMA point of contact (with back-up) is identified in IRIS. The Applicant should keep the HTA Coordination Contact up to date with changes in contact details. Changes in contacts should also be implemented by Applicants directly in IRIS to inform the regulatory side.

5.3 Processing of documents

The Parallel EMA/HTAb Scientific Advice uses Eudralink for exchanging documents between the Applicant and the HTA Coordination Contact. Document exchange between the Applicant and EMA takes place through the IRIS platform.

The Applicant is responsible for sending all relevant documents directly to the HTA Coordination Contact and EMA in a simultaneous manner. The Applicant must ensure that receipt of documents has been confirmed 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 discussion 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 between EMA and HTAbs in the Application Form.

5.4 Briefing document for Parallel EMA/HTAb Scientific Advice

A common briefing document template 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 EMA/HTAb Scientific Advice procedure and should be posed as regulatory questions. In the same manner questions related to health economics are possible and should be directed to HTAbs. The labelling of questions is a guide but does not prevent interested bodies answering questions deemed also relevant and of interest although originally raised to the other entity.

Applicants are encouraged to submit detailed information concerning the choice of patient reported outcomes and any substantiated PLEG plans (if applicable) already with the draft briefing document. However, Applicants are to acknowledge that PLEG can only be discussed in conjunction with a request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies. Use of the associated briefing document template is required.

6 Other

6.1 Advice format

The EMA will provide via IRIS the CHMP final Scientific Advice/Protocol Assistance letter to the Applicant in accordance with the published timelines

The HTA Coordination Contact sends out individual Written Recommendations documents conducted by the participation HTAb separately, around day +75-80.

Final outcome letters are exchanged between EMA and the HTA Coordination Contact.

6.2 Follow up procedures

Due to the limited timeframe to conduct Parallel EMA/HTAb Scientific Advice, a follow-up procedure to an earlier procedure for the same indication cannot be a priority when selecting the advice procedures and most likely will not be possible.

7 Summary of documents

Table 4. Description of documents

Documents	Description
Application form	Application form for the formal expression of interest by an Applicant, available on the EMA/HTAb websites or upon request via email. Email contact points: EMA central contact email address scientificadvice@ema.europa.eu and HTA central contact email address interimadvice.hta@g-ba.de (hosted by G-BA).
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 - with adaptations in text and reference list highlighted.
SAWP List of Issues HTAb 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 Scientific Advice/ Protocol Assistance letter HTAbs individual Written Recommendation documents	Documents with written answers to the Applicant's questions.