30 March 2023
EMA/150060/2023
Human Medicines Division

European Medicines Agency guidance to support the preparation of the PRIME Kick-off meeting and submission readiness meeting

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1. Background

The objective of this document is to provide guidance on the key meetings within the PRIME scheme to facilitate enhanced regulatory and scientific support: the Kick-off meeting (KOM) and submission readiness meeting (SRM). This document provides practical information to plan, organise and execute effective and productive meetings. It should be read in conjunction with the European Medicines Agency Questions and Answers for applicants seeking access to PRIME scheme for general information on the two meetings.

2. PRIME Kick-off meeting

The PRIME Kick-off meeting is a multidisciplinary scientific and regulatory meeting with the CHMP/CAT Rapporteur, their assessment team and a multidisciplinary group of experts from the relevant EMA scientific committees and working parties (e.g. SAWP, COMP, PDCO, and PRAC) as well as the EMA product team.

It will take place after the appointment of the CHMP/CAT Rapporteur and usually within 3-4 months after PRIME designation has been granted.

2.1. Objectives

This meeting initiates the interaction between the applicant, experts from the EU regulatory network and the Agency.

It **familiarises** the expert team with the product, enabling them to obtain insight into the product development planning (timelines and planned regulatory strategy) and its challenges.

It aims to **identify potential (major) hurdles** of the development program and is also an opportunity to discuss next steps on how best to address and overcome these issues and bottlenecks.

Therefore, the Kick-off meeting establishes a discussion platform to the tailored development support for PRIME products with a view to defining and planning technical and scientific assistance through scientific advice and/or other interactions with EU regulators.

The tabular overview hereafter presents the scope and objectives of the kick-off meeting.

Scope	Objectives
• Briefly outline the main product characteristics	• Familiarising the assessment team with the product
• Present the intended product development programme with detailed timelines for generation of the quality, non-clinical and clinical data, including paediatric development, orphan related aspects, etc., as applicable	• Discussion to seek clarifications and reach mutual understanding of the proposed plan
• Discuss the planning and timing of the next regulatory steps/actions such as scientific advice (SA) with its scope, PIP/Waiver	• Share a tailored plan (regulatory roadmap) for the sequence of interactions with EMA

Scope	Objectives
request, Orphan drug designation application, ATMP certification	• Consider involvement of relevant stakeholders (e.g. HTA bodies, patients) • Identify whether specialised expertise in the EU network will need to be involved in the subsequent consultations
• Highlight potential difficult/controversial issues already identified within the product development and points for which support and input from the regulators and experts might be sought (or has already been received)	• Ensure that important aspects of the development programme are brought to the attention of the regulators and identify additional issues to be tackled, through formal scientific advice (SA) procedures or other relevant interactions (e.g. paediatric development, orphan requirements) • Identify areas requiring cross-committee/working party collaboration
• Introduce the proposed regulatory strategy including type of marketing authorisation application (e.g., full versus conditional MAA or MAA under exceptional circumstances)	• Applicant to receive feedback on regulatory questions and to have better awareness of regulatory requirements to be considered for their regulatory strategy
• Introduce the plans for interactions with Health Technology Assessment (HTA) bodies	• Raise awareness on the importance of planning of such interactions for timely access to patients • Identify potential opportunities for parallel consultation with EMA and HTA bodies
• Present plan for data proposed to be collected post-authorisation, in view of the proposed type of marketing authorisation (e.g., specific obligations for conditional marketing authorisation or marketing authorisation under exceptional circumstances and/or PASS, PAES and additional risk minimisation measures)	• Applicant to receive initial considerations on proposed post-authorisation planning

2.2. Supporting documentation

2.2.1. Briefing document

In advance of the PRIME Kick-off meeting, the applicant should provide a short and focused briefing document. While information from previous submissions (e.g. justification for PRIME eligibility request or scientific advice briefing document) can be included, this document should be self-standing and provide a clear overview of the product development conducted so far, with a focus on plans for further

data generation and interactions with regulators (see also below 'regulatory roadmap and development tracker').

The structure of the briefing book for the Kick-off meeting is based on the CHMP Scientific Advice Briefing Document Template.

The briefing document should provide a summary of:

- The product (e.g. finished product, its mechanism(s) of action, target indication, posology)
- The product development programme (quality, non-clinical and clinical) including detailed planning and timelines. A schematic overview (e.g. GANTT chart) should be included in the briefing document.
  - If scientific advice has been previously requested, the applicant should include an overview of the implementation of the advice(s) and recommendations received.
  - Whilst the focus should be kept on the intended indication, the development in other indications could be briefly mentioned.
- Plan, timelines and scope for:
  - scientific advice/protocol assistance request(s) (e.g. clinical/non-clinical/quality/significant benefit/similarity/conditional approval/exceptional circumstances).
  - paediatric investigational plan/PDCO interactions, orphan drug designation, ATMP classification, ATMP certification for SMEs, etc.
  - interactions with HTA: The applicant is strongly encouraged to consider and discuss request for parallel EMA/HTA consultation as part of the series of scientific advice envisaged.
- The planned regulatory submission strategy.
- The difficult/complex issues related to the product development (quality, non-clinical and clinical) and points on which support and input from the regulators and experts might be sought.

Please refer to Annex 1 hereafter listing aspects expected to be addressed, as relevant.

To prepare a relevant summary of the regulatory, quality, non-clinical and clinical aspects, the applicant is advised to refer to Annex 1 which lists a number of points to consider. The relevance and level of details to be included will vary depending on the type of product, therapeutic area, development stage and issues to be specifically tackled.

Additional documents may be provided in the Kick-off meeting package such as previously received scientific advice (e.g. CHMP Scientific advice/Protocol Assistance, any relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities), minutes of early EMA contacts (e.g. SME, ITF, Orphan and/or paediatric interactions, etc.), ATMP classification, ATMP certification, orphan drug designation, Paediatric Investigation Plans/Waiver.

2.2.2. Regulatory roadmap and development tracker

The development progress of products entering the PRIME scheme is monitored through the submission and maintenance of the PRIME Regulatory Roadmap and Product Development Tracker. For general guidance please see the European Medicines Agency Questions and Answers for applicants seeking access to PRIME scheme (question 13).

This roadmap should take into account any feedback already received from regulators and include plans for scientific advice/protocol assistance requests and other regulatory interactions. The format (GANTT chart or similar) is at the developer's discretion.

In preparation for the Kick-off meeting, the development tracker should also be drafted, aligning the table with the specific topics proposed for discussion in the Kick-off meeting agenda/briefing document, as well as aspects/questions proposed for subsequent scientific advice. The development tracker should be updated based on the Kick-off meeting discussion, and the finalised document should be submitted with the meeting minutes.

3. PRIME submission readiness meeting

Please see the European Medicines Agency Questions and Answers for applicants seeking access to PRIME scheme for broader guidance on the submission readiness meeting.

Approximately 12-15 months prior to the filing of the expected MAA, applicants should contact the PRIME Scientific Coordinator in order to organise a submission readiness meeting with the Rapporteur and the assessment team, relevant national experts as well as the EMA product team.

The meeting is expected to take place 9-12 months prior to the MAA submission; flexibility is expected based on the specific development as well as the applicant's and Rapporteur's preferences.

3.1. Objectives

While the meeting format and participation are the same as for the Kick-off meeting, its purpose is to provide an opportunity at a time point closer to the MAA filing date to discuss the status of the development.

The meeting should also reflect on the implementation of previous scientific and regulatory advice for key development areas and the maturity of the overall data package intended to support the MAA. In this context, applicants should consider that, insofar as possible, the dossier should include all relevant data needed to support the intended MAA. This should take into account that the level of evidence may be less comprehensive for applications for conditional marketing authorisations or marketing authorisations under exceptional circumstances. At this point in time, applicants would also be expected to present mature plans for post-marketing evidence generation, as applicable.

Pre-submission meetings with the CHMP/CAT Co-Rapporteur and PRAC Rapporteur may still be organised and applicants are encouraged to make use of the pre-submission interactions with the Agency, although in some cases the submission readiness meeting can replace the pre-submission meeting.

For details on the routine pre-submission interactions with the Agency, please see Pre-authorisation guidance | European Medicines Agency (europa.eu).

The tabular overview hereafter presents the scope and objectives of the submission readiness meeting.

Scope	Objectives
• Review the development status	• Review overall development and the main areas of the product identified at the Kick-off meeting and discussed in the context of scientific advice

Scope	Objectives
• Present and discuss the implementation of Scientific Advice and the status of key development discussions	• Facilitate knowledge-sharing, identify outstanding risks, and strengthen the upcoming MAA assessment
• Present the submission strategy and the expected data package to support MAA	• Review the submission readiness, discuss the level of data maturity to support an accelerated MAA assessment
• Present plan for data proposed to be collected post-authorisation, in view of the proposed type of marketing authorisation	• Applicant to receive initial considerations on proposed post-authorisation planning
• Discuss and address regulatory issues (e.g. ODD maintenance, PIP compliance, GMP/GCP inspection status and planning), highlight outstanding risks ahead of the MAA submission	• Identify risks and with sufficient time to address/mitigate in advance of the MAA submission

3.2. Supporting documentation

The documentation to support the submission readiness meeting balances the need to support effective discussion with the need to limit administrative burden on applicants; thus the PRIME Regulatory Roadmap and Product Development Tracker maintained since the Kick-off meeting serves as a key document to support the meeting. Applicants are encouraged to proactively identify key topics for discussion and therefore the briefing book submitted for the Kick-off meeting, updated with relevant topics, can be used to support this meeting as well.

Additional documents may be provided, such as:

- Previous scientific advice received (e.g. CHMP Scientific advice/Protocol Assistance, relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities)
- draft accelerated assessment request
- draft report on maintenance of the orphan designation
- draft risk-management plan/overview.

4. Kick-off and submission readiness meetings: preparation and organisational aspects

The key preparatory and organisational steps for the Kick-off meeting and submission readiness meeting are mostly the same and are outlined below with differences for the respective meeting specified where applicable.

Following the granting of PRIME status, the EMA PRIME team will liaise with the company to arrange an introductory call where the next steps for the Kick-off meeting will be explained and the company can ask questions related to this meeting.

EARLY PREPARATION STAGE (2-4 months before KOM/SRM)

Preparation of the supporting documentation and draft agenda

The supporting documents should be prepared ahead of the submission which is expected approximately 4 weeks in advance of the KOM/SRM date (the exact submission deadline will be confirmed by the PRIME Assistant once your Kick-off meeting is scheduled).

The draft agenda should be prepared and sent to EMA together with the supporting documents, highlighting the points the applicant wishes to discuss. To this end, the EMA PRIME team will provide applicants with an agenda template. The applicant should make sure that the supporting documents cover the items indicated in the agenda template and provide relevant background information needed to inform the discussion at the KOM/SRM.

Scheduling

Consider **when** you envisage the meeting being held; to allow maximum regulators attendance, the KOM and SRM are held outside of EMA Committee meeting dates.

For the **KOM** there needs to be at least 2 months lead time from PRIME designation (most applicants settle on a meeting approx. 3-4 months away), however a Kick-off meeting further away than this is also possible depending on development stage, other interactions etc. Please indicate what month would suit (based on upcoming Scientific Advice, other planned regulatory interactions, stage of development, etc).

For the **SRM** a 3-month lead time is recommended, with the meeting itself taking place 9-12 months ahead of the MAA submission. Flexibility is foreseen, and the date should depend on the specific development as well as the applicant's and Rapporteur's preferences.

Consider the need for an afternoon slot to facilitate attendees from different time zones.

Meeting logistics

Currently Kick-off meetings are held as virtual meetings only, via WebEx.

For a smooth conduct of the meeting, it is **important to read the WebEx guidance** that will be provided to you in advance of the Kick-off meeting.

Dial-in details with the URL link for connecting to the meeting will be provided after receipt of the presentation, the date of which will be agreed.

The meeting will last a maximum of 2 hours.

(Approximately) 4 to 1 weeks prior to KOM/SRM date

The supporting documentation should be sent to the dedicated PRIME mailbox (prime@ema.europa.eu) as well as to the PRIME scientific coordinator approximately 4 weeks before the agreed meeting date. EMA will notify the applicant of the exact deadline. Upon receipt, the EMA, the Rapporteur's team and relevant experts will review the document and identify points to be added to the agenda of the kick-off meeting.

Final agenda

The documentation is reviewed in an internal meeting between EMA and the Rapporteur's team. Any additional points for discussion emerging from this meeting will supplement the agenda for the KOM/SRM. The final agenda will contain the issues proposed both by the applicant and by EMA.

The agenda for the KOM/SRM is finalised following the internal EMA meeting: the final agenda consolidating the applicant's and regulators' points for discussion will be provided to the applicant 2 weeks in advance of the meeting.

A teleconference (debriefing meeting) with the company and the EMA PRIME coordinator will take place shortly after the internal meeting, to give the applicant an opportunity to clarify any outstanding points.

Slide deck

The applicant should provide slides on the final points for discussion 1 week (5 working days) in advance of the Kick-off meeting.

Logistical aspects of meeting

Before the meeting we will require a complete **list of participants**, along with details on who will present each section of the slides. This is for security reasons (only identified participants will be admitted), minimises the time spent in introductions at the start of the meeting, and facilitates providing technical assistance to the appropriate speaker, if necessary. You could either provide this in the form of a list by email, or note the presenters on each slide.

At the KOM/SRM

Security

Only identified participants will be allowed to join the meeting: participants should ensure that on attempting to enter the WebEx call they follow the request to enter their name, putting the company name followed by their full name, e.g. "EMA – Joe Bloggs". Also, we will not accept applicant participants into the call before the indicated time and we ask that you and your colleagues do not attempt to join prior to this time as there is an internal pre-meeting taking place.

To maximise use of time, participants introduction will be via the first slide (for the company) and the regulatory speakers will introduce themselves prior to intervening (you will receive a list of the regulatory participants and their affiliation in advance of the meeting).

Experience has shown that the meeting proceeds more smoothly if EMA controls the slides: EMA will request the presentation in advance and we will control the movement through the slides from our end on the applicant's cue.

It is recommended to go through the presentation section by section, pausing after each agenda point for discussion and clarifications.

Meeting minutes

The Minutes of the meeting should be prepared by the applicant and provided to the EMA within 2 weeks after the meeting. Alongside the minutes, the applicant should provide an updated regulatory roadmap, taking into consideration the recommendations made during the meeting.

Other reference links:

https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

Annex 1. Points to consider for the preparation of the briefing document and kick-off meeting

Regulatory information

The applicant should describe the worldwide regulatory status of the product (e.g. any existing MA, or planned MAA timelines) and the planned regulatory strategy for the application through the centralised procedure providing information such as:

- Type of intended marketing authorisation (e.g. full dossier, conditional approval or approval under exceptional circumstances).

  If the applicant intends to seek conditional approval or approval under exceptional circumstances, a brief rationale should be presented, including planning with respect to specific obligations or other key post-authorisation studies.

- Choice of the planned legal basis, such as full (mixed) application, hybrid application (new indication).

- Compassionate use

  If the product is already available or there is an intent to make it available through named patient programmes or cohort of patients in some EU Member States, this can be highlighted in order to discuss suitability of a CHMP opinion on compassionate use.

- Paediatric requirement

  The regulatory planning should highlight the applicability and/or status of the Paediatric Investigation Plan (with or without deferral or waiver)/full product waiver.

- Orphan Drug Designation

  If orphan designation has been applied for this medicinal product or there is any intent to apply for it, the document should include information on the Orphan Drug Designation (ODD), the condition and the criteria on which the ODD was based. Particularly, if ODD was based on 'significant benefit' criteria, the development plan should address how the applicant intends to support significant benefit. In addition, the applicant is encouraged to consider also suitability of the data to be generated for confirmation of the orphan designation at the time of the conditional marketing authorisation.

- Similarity/derogation

  If any medicinal product has been designated and authorised as an orphan medicinal product for a condition relating to the proposed therapeutic indication, the applicant should start to consider whether issues with respect to similarity/derogation claim(s) could be anticipated.

- Medical devices (integral or as delivery device or companion diagnostic device)

  If use of a medical device is associated to the product, a high-level description can be included, particularly highlighting any need to seek CE marking and name of the notified body.

- New active substance status

Provide rationale for the New Active Substance claim only if controversial, and if applicable, highlight the basis for claim of new active substance status with regards to significant differences in safety and/or efficacy.

- Data exclusivity/market protection

  If applicable, discuss any intent to claim for (additional) data exclusivity/market protection.

Quality

Applicants should consider the EMA Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME, which addresses common challenges with meeting quality and manufacturing data requirements during development and at the time of EU marketing authorisation application. When preparing the document, the applicant should consider key pharmaceutical aspects in relation to the active substance and finished product that need to be highlighted to support the discussion during the meeting. Examples of such aspects/issues are included below:

- Active substance (presented as a synthetic scheme with starting materials labelled, as applicable)
- Cell line development and cell banking strategy, as applicable
- Novel/non-standard processes/novel expression system/testing methodology, purification methods, viral removal steps, bioassay
- Product characterisation, including critical quality attributes and biological potency
- Issues or changes foreseen to the formulation development (and bridging data if relevant); novel/innovative formulation
- Manufacturing process development including process changes and upscaling plan for commercial purposes and timing in relation to clinical data generation/launch (discuss any issues and bridging data in case of different manufacturing sites)
- Detail any expected evolution of control strategy or prospective change management protocols
- Quality by Design elements/Design Space, Real Time Release Testing
- Process control strategy (including proposed In process controls and specifications, where defined)
- Validation of analytical methods
- Stability strategy and proposed shelf-life
- Process validation strategy
- Comparability issues, in case comparability data need to be generated (indicate source of the reference medicinal product to conduct the trials/studies)
- Viral, microbiological control and sterility
- The anticipated market demand at launch
- Good Manufacturing Practice (GMP)

Please indicate any potential issues with the GMP status of the different manufacturing sites involved in the manufacture of the finished product and active substance and as relevant, specify planning for inspection readiness to support discussions on inspections by National Competent Authorities.

- Specific aspects such as Active Substance Master File (ASMF), Vaccine Antigen Master File (VAMF), Plasma Master File (PMF), Genetically Modified Organisms (GMO), Materials of animal and/or human origin (TSE)
- Quality aspects related to medical devices/combination devices/in vitro diagnostics, only if applicable.

Non-clinical

The document can include a brief summary on proof-of-principle studies, with justification on the relevance of the chosen models in relation to the disease to be treated.

Regarding non-clinical safety and biodistribution studies, the applicant should provide a tabulated overview of all completed, ongoing and planned non-clinical studies (including study number, main design features and GLP status). This should be accompanied by a description of the rationale for the non-clinical development strategy. A review of the main toxicological findings (and corresponding safety margins), with focus on human relevance and, if possible, how these are to be followed-up in the clinical development, should also be provided.

Clinical

The document can include a general overview of the clinical development programme. This can be presented as tabulated summary of all completed, ongoing and planned clinical trials (including study number, main design features, patient number and characteristics, GCP status, etc.), and adequate discussion, if applicable, covering all aspects of clinical development:

- Clinical pharmacology (PK, interaction, special population e.g. renal and hepatic impairment) studies
- Dosing information from PD studies
- Proposals for PK and PK/PD modelling and simulation analyses, if applicable
- Exploratory trials
- Supportive and pivotal clinical studies, if any
- Any analyses, as currently planned, to be performed to evaluate the study results
- Availability and need for development in other special populations such as the elderly, paediatric, male/female and ethnic minorities.

When preparing the briefing document, the applicant can proactively consider challenges that may be anticipated during the clinical development programme, statistical analysis and its appropriateness with legal requirements, relevant clinical guidelines and previous scientific advice.

The applicant should explain which data are planned to be provided or collected post-authorisation in view of the proposed type of marketing authorisation (e.g., specific obligations for conditional marketing authorisation or marketing authorisation under exceptional circumstances and/or PASS,

PAES and additional risk minimisation measures) and future pricing and reimbursement discussions with HTA.

The applicant should also consider risk management planning, based on the known and expected safety profile depending on the product's molecular structure, other products in the class and any identified and potential risks identified in non-clinical and early clinical studies and how these will be further elucidated in the proposed clinical development programme.