



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

## European Medicines Agency Guidance on interactions in the context of PRIME

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# 1. Background

The objective of this document is to provide guidance on interactions between the applicant, the EMA and the Rapporteur further to eligibility to PRIME. This covers guidance for the preparation and conduct of the kick-off meeting and interactions during the development up to the submission of the marketing authorisation application.

## 2. PRIME kick-off meeting

The PRIME kick-off meeting is a multidisciplinary meeting with the CHMP/CAT Rapporteur, their assessment team and a multidisciplinary group of experts from the relevant EMA scientific committees and working parties (SAWP, COMP, PDCO and CAT in case of ATMP) and Agency staff.

It will take place within 2-3 months following the CHMP/CAT Rapporteur has been appointed.

### 2.1. Objectives

This meeting aims at initiating the interaction between the applicant, experts from the EU regulatory network and the Agency and also at familiarising the expert team with the product, its development programme, timelines and planned regulatory strategy. This should enable the expert team to get a good insight of the product development planning and challenges.

This 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.

It is crucial to bear in mind that the ultimate goal of PRIME is to promote earlier patients' access to promising medicines and thus to ensure that all elements for the initial marketing authorisation application (MAA) are in place to facilitate accelerated assessment, through prospective planning of studies planned to be completed before authorisation and studies and measures proposed to be conducted post-authorisation.

While the participants will not engage into detailed scientific and technical discussions around the identified topics, during the kick-off meeting, the aim is to agree on the next steps on how best to address any identified issues or to identify potential additional issues.

As such, the enhanced scientific support to optimise the development programme will be channelled through scientific advice by the SAWP where the applicant will be able to discuss the details of the development plan, the design of pivotal studies and post-authorisation activities.

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

Scope	Objectives
<ul style="list-style-type: none"> <li>Outline the main product characteristics</li> </ul>	<ul style="list-style-type: none"> <li>Familiarising the assessment team with the product</li> </ul>
<ul style="list-style-type: none"> <li>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</li> </ul>	<ul style="list-style-type: none"> <li>Discussion to seek clarifications and reach mutual understanding of the proposed plan</li> </ul>
<ul style="list-style-type: none"> <li>Discuss the planning and timing of the next regulatory steps/actions such as scientific advice (SA) with its scope, PIP/Waiver request, Orphan drug designation application, ATMP certification</li> </ul>	<ul style="list-style-type: none"> <li>Elaborate a tailored plan for the sequence of interactions with regulators.</li> <li>Consider involvement of relevant stakeholders (e.g. HTA, Patients).</li> <li>Identify whether specialised expertise in the EU network will need to be involved in the subsequent consultations.</li> </ul>
<ul style="list-style-type: none"> <li>Highlight potential difficult/controversial issues already identified with the product development and points on which support and input from the regulators and experts might be sought</li> </ul>	<ul style="list-style-type: none"> <li>Ensure that important aspects of the development programme are brought to attention of the regulators and identifying additional issues to be tackled, through formal scientific advice procedures (SA) or other relevant interactions (e.g. paediatric development, orphan requirements) with a view.</li> <li>Identify areas requiring cross-committee collaboration</li> </ul>
<ul style="list-style-type: none"> <li>Introduce the proposed regulatory strategy</li> </ul>	<ul style="list-style-type: none"> <li>Applicant to receive feedback on regulatory questions and to have better awareness of regulatory requirements to be considered for their regulatory strategy.</li> </ul>
<ul style="list-style-type: none"> <li>Introduce the plans for interactions with Health and Technology Assessment (HTA) bodies</li> </ul>	<ul style="list-style-type: none"> <li>Raise awareness on the importance of planning of such interactions for timely access to patients</li> <li>Identify potential opportunities for parallel consultation with EMA and HTA</li> </ul>
<ul style="list-style-type: none"> <li>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)</li> </ul>	<ul style="list-style-type: none"> <li>Applicant to receive initial considerations on proposed post-authorisation planning.</li> </ul>

## **2.2. Background information**

In advance of the PRIME kick-off meeting, the applicant should provide a short and focused briefing document. This latter should complement the PRIME eligibility justification document or any scientific advice briefing document previously submitted. This document should provide a clear overview of product development conducted so far but most importantly with a focus on plans for further data generation and interactions with regulators.

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 SME, 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 strategy. Please refer to Annex 1 hereafter listing aspects expected to be addressed, as relevant.
- The potential difficult/controversial 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.

To prepare a relevant summary of the quality, non-clinical and clinical aspects, the applicant is advised to refer to Annex 1 hereafter 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 such as previous scientific advices received (e.g. CHMP Scientific advice/Protocol Assistance, any relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities), minutes of early EMA contacts (e.g. SME, ITF, Orphan and/or paediatric advices, etc.), ATMP classification, ATMP certification, Orphan Drug Designation, Paediatric Investigation Plans/Waiver.

### **2.3. Organisational aspects**

In general, the kick-off meeting will be held at EMA premises, unless the applicant favours organisation of a teleconference. The kick-off meeting will last a maximum of 2 hours.

Upon nomination of the CAT/CHMP Rapporteur, you should liaise with your EMA contact point in order to agree on a meeting date in the next 2-3 months. Dates will be identified to facilitate face-to-face attendance of the CAT/CHMP Rapporteur (i.e. during CAT plenary, Monday morning of the CHMP week or during SAWP plenary). On a case by case basis, timelines of other ongoing procedures/meetings at the Agency may be considered

It is recommended that a maximum of 10 participants from the applicant attend the meeting. Additional participants may join by teleconference.

The background information should be provided to the EMA contact point and [prime@ema.europa.eu](mailto:prime@ema.europa.eu) at the latest 3 weeks before the agreed meeting date. Upon receipt, the EMA, Rapporteur's team and relevant experts will review the document and identify points to be added on the agenda of the meeting. The agenda and list of participants will be shared with the applicant prior to the meeting. The applicant will be requested to provide a presentation according to the agenda during the week before the meeting.

The minutes of the meeting should be prepared by the applicant and provided to the EMA within 2 weeks after the meeting. In the minutes, the applicant should include an action plan, taking into consideration the recommendations made during the meeting. The template included in Annex 2 may be used for that purpose.

## **3. Interactions and updates during the development**

After the kick-off meeting, the Applicant should keep the EMA dedicated contact point informed of submission of procedures to the Agency. In case the applicant identifies a topic warranting further discussion with regulators, they should contact the EMA who will advise on the suitable way to address the matter. Where appropriate, the Agency can support interactions with the CHMP/CAT Rapporteur (e.g. ad hoc teleconferences) with a view to resolve minor issues or for the applicant to provide updates on their development.

Overall, it is expected that the applicant keeps the EMA and Rapporteur informed on the implementation of the scientific advices received and on the progress made or hurdles encountered on the development programme. To this effect, the applicant is encouraged to provide regular (at least once a year) updates to the action plan to marketing authorisation. The template in Annex 2 may be used to this effect.

In addition the Applicant should inform the rapporteur and EMA on interactions with competent authorities from the Union or third countries and share minutes of these interactions as soon as they become available.

Once the applicant sends its letter of intent to submit a marketing authorisation application (6-7 months prior to submission), the Co-Rapporteur, peer reviewer and PRAC Rapporteur will be appointed. Relevant members of the EMA product team will also be appointed and informed by the EMA PRIME contact point on previous interactions. At that stage, the steps prior to submitting an application as described in the [EMA pre-authorisation guidance](#) should be followed.

Over the course of drug development, it can be expected that some products granted PRIME support will no longer meet the eligibility criteria of major public health interest as defined in Section 3 (e.g.

further to data derived from confirmatory study or availability of other therapies fulfilling the unmet medical need). In these situations, the applicant/sponsor will be requested to provide a justification on whether the criteria for eligibility to PRIME are still met; this will be assessed by the SAWP/CHMP<sup>1</sup>. PRIME support may be withdrawn if emerging data were to show that the eligibility criteria are no longer met.

Furthermore, the Agency should be informed when the applicant no longer intends to pursue the development of an eligible PRIME medicine.

#### **4. Presubmission stage**

Once the applicant sends its letter of intent to submit a marketing authorisation application (6-7 months prior to submission), the Co-Rapporteur, peer reviewer and PRAC Rapporteur will be appointed. Relevant members of the EMA product team will also be appointed and informed by the EMA PRIME contact point on previous interactions.

At that stage, the steps prior to submitting an application as described in the [EMA pre-authorisation guidance](#) should be followed, in particular presubmission meetings, respectively with the EMA, Rapporteur and co-Rapporteur can be organised.

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<sup>1</sup> And CAT in case of ATMP.

# 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 the 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 any intent to make it available through named patient programmes or cohort of patients in some Member States 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 any intent to apply for, the document should include information on the Orphan Drug Designation (ODD), the condition, 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 medical device is associated to the product, high level description can be included, particularly highlighting any need to seek CE mark 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**

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
- GMP

Please indicate whether 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.

- 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)
- Medical device (CE marked) or structural component to be indicated, 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 consider whether challenges are 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 based 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.

## Annex 2

### PRIME action plan to marketing authorisation

Product name – H000XXXX

Updated on:

### Regulatory activities

In this table, the applicant should list all activities planned up to MAA. It may be useful to also list some activities which may have been completed prior to the PRIME kick-off meetings (eg PIP, orphan designation, SA).

Activity	Status (planned on/ ongoing/completed on)	Comments
e.g		
Scientific advice on A		
Scientific advice on B		
Parallel EMA/HTA scientific advice		
HTA advice		
Parallel EMA/FDA scientific advice		
PIP submission		
PIP modification		
Orphan designation request		
ATMP classification		
ATMP certification		
Invented name request to NRG <sup>2</sup>		
Submission of letter of intent <sup>3</sup>		
Presubmission meeting with Rapporteur		
Presubmission meeting with CoRapporteur		
Presubmission meeting with EMA <sup>4</sup>		
PIP compliance check <sup>5</sup>		

<sup>2</sup> The proposed (invented) name(s) should be requested at the earliest 18 months and preferably 4-6 months prior to the planned MAA.

<sup>3</sup> Letter of intent should be sent 7 months before the intended MAA. This will trigger the appointment of the Co-Rapporteur, peer reviewer and PRAC (Co)Rapporteurs.

<sup>4</sup> Presubmission meeting with EMA should be planned 6-7 months before submission.

<sup>5</sup> To prevent delays at the time of validation of a Regulatory Application, applicants are encouraged to request compliance check by the PDCO at least 2 months prior to the planned submission.

Activity	Status (planned on/ ongoing/completed on)	Comments
Request for accelerated assessment <sup>6</sup>		
MAA submission		

## Update on main clinical trials

Study number	Study title	Status update
		Start date: Enrolment status: Planned completion date:
		Start date: Enrolment status: Planned completion date:

## Update on CMC/manufacturing sites aspects

Eg information on comparability plans, transfer of manufacturing sites as appropriate, validation?

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<sup>6</sup> Request for accelerated assessment should be made as early as possible before the actual submission of the marketing authorisation application (and at least 2-3 months before the actual submission).