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Human Medicines Division

European Medicines Agency Guidance for applicants seeking access to PRIME scheme

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This document provides guidance to prospective applicants to the PRIME (Priority MEdicines) scheme, including relevant templates.

It should be read in conjunction with:

Guidance on accelerated assessment

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

European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance

Toolbox guidance for robust CMC data packages

If you require additional information not covered by this document, please contact prime@ema.europa.eu.

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1. What is PRIME?

The development of promising new medicines to address unmet medical needs is challenging from the scientific and regulatory point of view. Early consultation and scientific advice between applicants and regulators, as well as other healthcare decision-makers, is key to ensuring that data are generated to the standards required for regulatory approval and market access.

The PRIority MEdicines (PRIME) scheme was launched in 2016, to provide the opportunity for an early, proactive dialogue between the applicants and the EU regulatory network. The main aim of this scheme is to reinforce continuous and strengthened scientific and regulatory support in order to ensure generation of a robust data package designed to address marketing authorisation application (MAA) requirements and enable accelerated assessment of new medicines of major public interest targeting an unmet medical need.

The scheme also aims to advise applicants on the best use of existing tools (e.g. parallel EMA/HTA advice, conditional marketing authorisation) relevant to their development programme.

The scheme is voluntary and subject to an application justifying that the eligibility criteria are met. To enter the scheme, requests must be based on adequate data to justify a potential major public health interest. Applicants will be informed in writing of the acceptance or refusal of their eligibility request.

Support provided through the scheme will be tailored to meet the needs of development at different stages.

2. What are the benefits of entry to the PRIME scheme?

With PRIME, products will benefit from support tailored to the stage of development, which will not only be provided through scientific advice, but also through:

- **Early appointment of a Rapporteur** from EMA's Committee for Medicinal Products for Human Use (CHMP) or the Committee for Advanced Therapies (CAT). The early appointment of the CHMP/CAT Rapporteur is a key feature of the scheme that enables continuity in a life-cycle approach. The Rapporteur and its assessment team will discuss preparatory aspects of the MAA from both a technical and scientific viewpoint, ensuring that important aspects of the development programme are brought to discussion at CHMP through scientific advice or protocol assistance in a timely and comprehensive manner. This engagement also provides the possibility for greater regulatory preparedness to support scientific opinions at the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), the Pharmacovigilance Risk Assessment Committee (PRAC) and CHMP/CAT at the time of MAA;
- **An initial kick-off meeting** with the CHMP/CAT Rapporteur and a multidisciplinary group of experts from relevant EMA scientific committees and working parties and EMA staff to (1) provide preliminary guidance on the overall development plan, (2) discuss key development steps subject of future scientific advice and (3) open the discussion on the recommended regulatory strategy;
- **EMA dedicated contact point**, i.e. the PRIME Scientific Coordinator who will coordinate the support offered throughout the scheme.

- **Iterative scientific advice** on the overall development plans, at major development milestones and on key issues, with possibility to involve additional stakeholders [e.g. health technology assessment (HTA) bodies, patients, the US Food and Drug Administration (FDA)].
- Access to **expedited follow-up scientific advice** under certain criteria, with shortened timelines for receiving the adopted CHMP advice.
- A **submission readiness meeting** approximately 1 year ahead of the MAA filing date to discuss the status of the development for key development areas and the maturity of the dossier in view of planned type of MAA (e.g. conditional MAA), including plans for post-marketing evidence generation and any expected regulatory challenges.
- Confirmation of the potential for accelerated assessment at the time of an application for marketing authorisation.
- A dedicated **toolbox** to support the quality data package development.

SMEs and applicants from the academic sector may be granted **Early Entry PRIME** status following demonstration of **proof of principle**, which confers the following benefits:

- Introductory meeting: Raising awareness of regulatory requirements early in the development by providing scientific and regulatory advice on the overall development plan and at major development milestones, with the possibility to involve multiple stakeholders [e.g. HTA bodies, patients, FDA].
- SMEs and applicants from the academic sector[1] located in the EEA, are eligible to a full fee waiver for scientific advice requests.
- The EMA product team will be appointed at the time of Early Entry PRIME designation and provide advice on the applicant's plans for generation of **proof of concept** data. These data are required to confirm transition to full PRIME eligibility, which triggers the appointment of the CHMP/CAT Rapporteur.

3. What are the eligibility criteria for PRIME?

The PRIME scheme is limited to medicines under development which are not authorised in the EU and for which the applicant intends to apply for an initial MAA through the centralised procedure.

The eligibility criteria for PRIME are identical to EMA's MAA accelerated assessment criteria but are applied at an early stage of development with a higher degree of uncertainty compared to the time of accelerated assessment requests. The criteria target medicinal products of **major public health interest**, in particular from the viewpoint of therapeutic innovation.

Products eligible to PRIME support shall:

- Target conditions where there is an **unmet medical need**, i.e. for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a

[1] Applicant established in the EEA and fulfilling the definition of public or private higher education establishments awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, or international European interest organisations as set out in Commission Regulation (EU) No 1290/2013 of 11 December 2013. Applicants should not be financed or managed by private profit organisations in the pharmaceutical sector ("PPO"), nor should have they concluded any operating agreements with any PPO concerning their sponsorship or participation to the specific research project for which a fee exemption is sought for scientific advice under the PRIME scheme.

method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected;

- Demonstrate the **potential to address the unmet medical need** to a significant extent, for example, by introducing new methods of therapy or improving existing ones.
- The available data should support the claim that the product has the potential to **bring a major therapeutic advantage to patients** in a given indication, through a clinically meaningful improvement of outcomes, such as having an impact on the prevention, onset and duration of the condition, or improving the morbidity or mortality of the disease.

The appropriateness for access to the PRIME scheme depends on both the magnitude of the treatment effect, which could include duration of the effect, and the relevance of the observed clinical outcome. Relevant clinical outcomes generally refer to an endpoint that predicts an effect on associated morbidity, mortality or progression of the underlying disease.

Consequently, entry to the scheme for the majority of products is expected to be supported by evidence of clinical response in patients (i.e. generated in exploratory clinical studies) adequately substantiating the product's potential to address to a significant extent the unmet medical need by providing a clinically relevant advantage for patients (see question 4).

For all PRIME eligibility requests, applicants should elaborate on the expected benefits of PRIME taking into account the planned development and post-authorisation activities; this is particularly relevant in the case where a product is already advanced in its development programme (e.g. pivotal trial ongoing and for which scientific advice has been received).

4. At which phase of development can I apply for PRIME?

Any sponsor engaged in the exploratory clinical trial phase of development can submit a request to enter the PRIME scheme, based on the availability of preliminary clinical evidence to demonstrate the promising activity of the medicinal product and its potential to address to a significant extent an unmet medical need (**proof of concept**).

Applicants from the academic sector[2] and micro-, small-and medium-sized-enterprises (SME) applicants may submit an eligibility request at an earlier stage of development if:

- compelling non-clinical data in a relevant model provide early evidence of promising activity (**proof of principle**) and
- first-in-human studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.

This would result in **Early Entry PRIME designation**. Submission of further data is expected to support granting of full PRIME designation.

SMEs should register with the Agency's SME office in advance of submitting an eligibility request. Applicants who consider they meet the definition of academic sector should contact the Agency prior to submitting an eligibility request.

[2] Applicant established in the EEA and fulfilling the definition of public or private higher education establishments awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, or international European interest organisations as set out in Commission Regulation (EU) No 1290/2013 of 11 December 2013. Applicants should not be financed or managed by private profit organisations in the pharmaceutical sector ("PPO"), nor should they have concluded any operating agreements with any PPO concerning their sponsorship or participation to the specific research project for which a fee exemption is sought for scientific advice under the PRIME scheme.

PRIME is not the right support tool for you if:

- Your product is already advanced in its development programme (e.g. pivotal trial ongoing and/or for which scientific advice has been received) and where there is no more scope for enhanced regulatory support or where such scope is very limited.
- You are already in the MAA pre-submission phase (i.e. you have submitted a letter of intent for a MAA). In this case, you should consider alternative tools (e.g. pre-submission meeting request, request for accelerated assessment).
- You are seeking support for development in a new indication for an already authorised product for which you are the marketing authorisation holder. In this case, you should consider alternative tools (e.g. scientific advice, pre-submission meeting with EMA and the Rapporteur).

5. How do I prepare and submit my application?

You should submit a request for eligibility to PRIME via the IRIS platform, by choosing the PRIME eligibility process type. This platform provides a single space for applicants to submit requests, communicate, share information with EMA and deliver documents concerning the PRIME eligibility request procedure.

On the IRIS platform starting site, applicants can also find guidance documents on how to register, as well as a more detailed user guidance which helps to create and submit scientific applications for industry and individual applicants.

Applications for PRIME eligibility should include the following documents submitted through the IRIS portal:

- The Applicant's justification based on the template (this should be submitted in MS Word format),
- Literature references cited in the justification (this should be appended in a zip file),

in accordance with submission deadlines, as published on our website.

Prior to submitting a request, unless you have already done so, you should register for access to the IRIS platform and request a research product identifier (RPI) for your product. The process is the same as for Scientific Advice.

Users should complete the registration steps below before using the IRIS platform. The *Quick interactive guide to IRIS registration process* *provides* a summary to ensure that:

- you have an active EMA account;
- your organisation is registered in EMA's Organisation Management Services (OMS). It can take from five to ten working days to update or register a new organisation;
- you have the appropriate user access role and affiliation to an organisation. IRIS user roles are requested in the EMA Account Management portal.

If a request for an RPI also requires registration of an active substance in EMA's public list of substances, this may take up to five working days.

EMA's revised IRIS guide to registration explains the registration steps in more detail.

There is no fee payable for submission of a request to enter the PRIME scheme.

The justification should be presented as a short but comprehensive document (not more than 30 pages in length), using the template provide. The request should be duly substantiated and justify the expectation that the medicinal product is of major public health interest.

The overarching objective of the document is to justify that the PRIME eligibility criteria are met. Detailed guidance on the justification to be submitted by applicants aiming to be part of the scheme is provided in the justification template. The decision trees in Annex I of this document outline the CHMP approach to the assessment of PRIME applications and may assist applicants in formulating their justification.

Information included in the application will be used to confirm automatic eligibility to the centralised procedure should your product be granted eligibility to PRIME (see also question 9).

6. Can I request pre-submission support for my PRIME eligibility request?

EMA provides pre-submission support to applicants planning a PRIME application, including the possibility of a virtual pre-submission meeting to discuss the eligibility of their development to PRIME. Applicants wishing to avail of pre-submission support should submit a request via the IRIS platform, by choosing the PRIME meeting request process type. More detailed information on the submission is available in the IRIS Guidance for Applicants.

To support a pre-submission meeting request, applicants should submit a summary of the justification for PRIME eligibility (2-3 pages **maximum**) including:

- information on the product and its stage of development
- an overview of the rationale on meeting the criteria for unmet medical need
- high level summary of relevant clinical and non-clinical data considered to support the product's potential to address the unmet medical need.

The EMA PRIME team will review the request before confirming with the applicant that either the virtual meeting will be granted, or that written feedback on the request will be provided. Further information on the technical aspect of the meeting organisation is available in the European Medicines Agency guidance to support the preparation of PRIME meetings.

7. How will my request for eligibility to PRIME be reviewed?

Once EMA has received your application, the Agency will confirm whether it is within the scope of the scheme (see question 3) and that the format and content are adequate to support the review of the request.

If deemed acceptable, one Scientific Advice Working Party (SAWP) reviewer and one EMA scientific officer will be appointed. You will be informed of the start of the procedure and expected timelines.

Review of PRIME eligibility requests will be conducted through the SAWP. The reports will be forwarded for comments to the SAWP (Day 30) and CHMP, prior to final adoption by CHMP (Day 40). If you develop an advanced-therapy medicinal product (ATMP), a CAT reviewer will also be appointed, and the CAT will provide their recommendation to the CHMP.

These flowcharts outline the criteria examined by the reviewers to determine eligibility to PRIME.

The CHMP will aim to have outcomes adopted **within 40 days from the start of the procedure.** The submission deadlines and procedural timetables are published on the PRIME website.

After adoption by the CHMP, you will receive a letter through IRIS detailing the outcome of the evaluation with a brief outline of the reasons for acceptance or rejection to the scheme. An appeal mechanism in case of rejection is not foreseen. However, there is the possibility to contact the Agency should further clarification on the reasons for rejection be needed. Reports prepared to support the final outcome will not be shared with the applicant.

8. Will the outcome of the review of PRIME eligibility requests be made public?

Yes, the outcome adopted by the CHMP will be made public. After each CHMP meeting, an overview of the recommendations adopted is published in the CHMP meeting highlights, including information on:

- the type of product (chemical, biological or advanced therapy etc.),
- the intended indication,
- the type of data supporting the eligibility request and,
- the type of applicant (SMEs, applicants from the academic sector or others).

For products that are deemed eligible to PRIME, the name of the active substance/international non-proprietary name (INN) is made public, whilst it is not published in case of a negative outcome.

A list of products granted eligibility to PRIME is published and updated on a monthly basis. The document also lists products for which the PRIME designation has ceased (when a marketing authorisation application is submitted, or if a product is withdrawn from the scheme when emerging data show that the eligibility criteria are no longer met, or the development is discontinued).

When a centralised marketing authorisation is granted, eligibility to the PRIME scheme granted by the CHMP is reflected in the European Public Assessment Report (EPAR).

9. What happens once my product is granted entry to PRIME?

Confirmation of eligibility to the centralised procedure

When access to the scheme is recommended by the CHMP, you will also receive in that same month, automatic confirmation of eligibility to the centralised procedure, which will be based on the information submitted for the PRIME eligibility request.

Appointment of the Rapporteur

The appointment of the CHMP Rapporteur will also be initiated (unless you are an SME or applicant from the academic sector and entered the scheme based on data showing proof of principle, therefore resulting in 'Early Entry' eligibility, see below).

For advanced-therapy medicinal products (ATMP), both a CAT Rapporteur and a CHMP Co-ordinator will be appointed.

The appointment procedure will be conducted in line with the Procedural Advice on CHMP/CAT/PRAC

Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology.

The appointment procedure usually takes one month after eligibility. You will be notified of the outcome after the CHMP meeting subsequent to the confirmation of eligibility to the PRIME scheme.

CHMP Co-Rapporteur and PRAC Rapporteur appointment will not occur until you submit a letter of intent to submit an MAA (**approximately 6-7 months prior to submission of the MAA**).

Early Entry PRIME: If you are an SME or an applicant from the academic sector who entered the scheme based on data showing **proof of principle**, the appointment of the Rapporteur will occur once you have generated data confirming eligibility at **proof of concept** stage. You will be required to submit a new application for (full) PRIME designation, including relevant data and a justification as the product development reaches this stage to confirm transition to full PRIME eligibility (see question 4). All other aspects of enhanced support will apply.

EMA dedicated contact point

You will also benefit from a dedicated EMA contact point - the EMA PRIME Scientific Coordinator - during the development, who will coordinate the support offered throughout the scheme. Name and details will be included in the eligibility outcome letter.

EMA will further support the development through guidance on regulatory pathways, and the use of available regulatory/legislative tools (e.g. conditional marketing authorisation, marketing authorisation under exceptional circumstances) or other initiatives designed to facilitate timely access to patients.

For subsequent activities in the PRIME scheme see questions 10 to 14.

10. How is the Kick-off meeting organised?

Once PRIME has been granted, the EMA PRIME team will liaise with you to organise a Kick-off meeting which usually takes place around 3-4 months after PRIME eligibility has been granted.

Participants at the meeting are:

- CHMP/CAT Rapporteur and their assessment team,
- relevant experts from the EU network (e.g. PDCO, COMP, PRAC, SAWP and other experts, as relevant) and,
- relevant EMA product team members.

The Kick-off meeting is an opportunity for the applicant to discuss with a multi-disciplinary assessment team of experts and EMA important development aspects, including potential hurdles and how to address them, as well as important milestones at which additional regulatory support should be sought. ***It is not a substitute of scientific advice,*** *but an opportunity to present the development programme and regulatory strategy for the product.*

In support of the Kick-off meeting, PRIME applicants are required to provide relevant background information and prepare a detailed regulatory roadmap, including information on upcoming and planned regulatory submissions/interactions (for details, see question 13 below). You will receive recommendations on this plan in the course of the Kick-off meeting and during subsequent regulatory interactions (e.g. adequate timepoints to submit request for scientific advice, paediatric investigation plan).

The Kick-off meeting may be an opportunity for early dialogue between applicants and the EMA/PDCO regarding the strategy for the paediatric development programme of the medicine, in advance of a paediatric investigation plan (PIP) application.

Further details on the organisation and conduct of the meeting are provided in the European Medicines Agency guidance to support the preparation of PRIME meetings.

How is scientific advice/protocol assistance provided for PRIME products?

Scientific guidance will mainly be provided in the context of scientific advice, where you will be able to receive overarching advice on your development plan as well as on specific product development topics to support scientific evidence generation for the PRIME eligible indication.

SMEs or applicants from the academic sector located in the EEA, will benefit from a full fee waiver laid down in the fee regulation for requests for scientific advice, and follow-up requests, submitted on PRIME products (restricted to the development in the indication for which eligibility to the PRIME scheme was accepted).

Two coordinators from SAWP will be appointed to each procedure, in line with current practice. Wherever possible, one of these SAWP coordinators will be the same throughout the course of the development of the PRIME product to ensure continuity in the overall regulatory development support. Wherever possible, this SAWP coordinator will be appointed from the same delegation as the CHMP Rapporteur. This is expected to facilitate sharing of knowledge across the product life-cycle and the preparation of SAWP/CHMP advice. A dedicated Scientific Advice scientific officer will be appointed to support continuity and knowledge-building throughout development.

Other committees (e.g. CAT, COMP, PDCO) will be involved in the preparation of the final advice letters, as relevant. Furthermore, applicants are encouraged to request parallel EMA/HTA or EMA/FDA advice.

PRIME product developers are strongly advised to follow the advice provided by the SAWP/CHMP, as this has been shown to increase the success rate of marketing authorisation applications. In case of deviations, in particular if concerning key development aspects, applicants should be prepared to provide a justification and further engage with EMA as needed to explain and agree on the proposed alternative approach. A discussion on the implementation of the advices is expected to take place at the submission readiness meeting (see question 14 below).

11. How do I seek expedited Scientific Advice/Protocol Assistance for PRIME products?

Following the recommendation of the PRIME 5-year analysis to allow for more flexibility in the provision of scientific advice, PRIME-designated products can now also benefit from access to an expedited scientific advice/protocol assistance procedure (hereafter expedited scientific advice). Starting as a 12-month pilot in March 2023, expedited scientific advice is possible in specific circumstances where all the following criteria are met:

- The initial scientific advice procedure has already been sought on the overall development (in the PRIME indication), i.e., the request is a follow-up advice.
- The request for advice concerns issues with a specific, well-defined scope (not limited to a single quality/non-clinical/clinical discipline).

- The advice is justifiably required more urgently than the standard scientific advice timelines allow.

The request for an expedited scientific advice should be first discussed with the PRIME Scientific Coordinator, who will consider with the Rapporteur and the SAWP coordinator(s) how best to address the issue. The PRIME Scientific Coordinator will then confirm the outcome which may be either i) provision of a direct response to the issue, ii) an invitation to submit an expedited scientific advice application via IRIS, or iii) an invitation to submit standard follow-up scientific advice application via IRIS.

Applicants must submit the new question(s) with applicant's position(s) to support the request. Applicants may use the briefing document from the initial scientific advice, updated with the relevant question(s) and applicant's position, as well as relevant background information. The supporting documentation for the expedited scientific advice should be agreed with the PRIME Scientific Coordinator and Scientific Advice scientific officer before submission.

The expedited scientific advice application should be submitted via IRIS as a follow-up advice. The procedure will forego the published submission deadlines; the advice will be validated, assessed by the SAWP coordinator(s) and discussed by the SAWP at the next possible SAWP meeting. The expedited advice will not include the option for a discussion meeting with the applicant; should SAWP decide a discussion meeting is required, the procedure would revert to standard timelines at the time of the initial SAWP discussion. The final written advice will be issued after the same SAWP meeting, following CHMP adoption.

12. How do I keep the EMA/Rapporteur updated on product development? - Regulatory roadmap and development tracker

Following the recommendations of the PRIME 5-year analysis to improve knowledge building to support accelerated assessment, and to support the Rapporteur team in their assessment work, the development progress of products entering the PRIME scheme is monitored through the submission and maintenance of a regulatory roadmap and product development tracker. Starting as a pilot from March 2023, the roadmap and tracker will replace the PRIME annual update.

From the time of the Kick-off meeting, PRIME applicants are required to maintain and update the regulatory roadmap and product development tracker including information on upcoming and planned regulatory submissions/interactions and issues requiring discussion with the regulators.

The **roadmap** aims to increase awareness and preparedness at the level of the PRIME Rapporteur delegation and relevant EMA experts and forms an integral part of the PRIME product development tracker. Both tools will inform on the development progress and help to identify topics warranting further discussion with regulators. The roadmap includes plans for scientific advice/protocol assistance requests and other regulatory interactions and should take into account feedback received from regulators.

While it is appreciated that an accurate estimate of timelines for regulatory submission is not always possible and that timelines are subject to change, it will be of utmost importance for applicants to keep the roadmap as up-to-date as possible at all times to facilitate preparedness at the level of the PRIME Rapporteur delegation and relevant EMA experts. Late changes or regulatory submission not included in the roadmap should be avoided, to better facilitate continued support to scientific advice procedures by the same SAWP Coordinator.

The **development tracker** aims to facilitate effective and efficient tracking of critical development aspects which may be identified during the Kick-off meeting activities or may arise during subsequent development.

Specific issues should be added to the tracker and described with the following fields:

Area	The specific area within quality/non-clinical/clinical development; the template provides a non-exhaustive list, not all examples may be relevant
Summary of topic	**Brief** free text summary of the issue
Milestones	Either a date or milestone (e.g. completion of repeat-dose toxicity studies, end of phase II) relevant to the issue
Impact on evidence generation	The impact on evidence generation is colour-coded by the company **based on their judgement**, and following regulatory touchpoints: ○ ***Low (Green)**: minimal challenges for future evidence generation, regulatory alignment on proposal for evidence generation* ○ ***Medium (Amber):** gaps that might impact evidence generation, possible divergence with advice or need follow-up dialogue* ○ ***High (Red)**: area of divergence/uncertainty expected to substantially impact upcoming evidence generation. This might also be used to highlight the need for expedited advice (see guidance for justification and applicability)*
Company observations	Free text field for any additional comment on impact on evidence generation
Scientific advice planned/advised	If scientific advice is planned, enter expected date (mm-yyyy, or QnYY)
EMA procedure where issue was discussed	When relevant regulatory interaction has been completed, include the relevant procedure number

The colour coding is subject to change as subsequent versions of the tracker are generated. In the first version, the colour is assigned by the company based on their judgement. As this version is submitted to prepare for the Kick-off meeting, it will accompany the agenda of the meeting and highlight the areas where the company has higher priority for discussion. With the finalisation of the Kick-off meeting agenda, and following the discussion at the meeting itself, a new version is drafted by the company, that may include areas arising from the meeting discussion, advice for future regulatory interaction, and a likely revision of the colour codes based on the outcome of the discussion at the Kick-off meeting (agreement, disagreement, urgency).

For topics emerging after the initial discussion at the Kick-off meeting, the tracker should be updated, and the updated tracker should be submitted (via IRIS platform) whenever there are updates **critical** to development or evidence generation challenges (red areas). At this time, a cumulative update of other aspects (amber, green) can be submitted.

The regulatory roadmap and development tracker replaces the previous "PRIME action plan to marketing authorisation", which is no longer required to maintain and submit.

An example of the update is provided below:

New in this update:	Area	Summary of the topic (brief description)	Milestones	Impact on evidence generation Low Med High	Company observations	SA planned/advised (target date if known)	IRIS case number of previous SA/PIP/OD/ ITF on the topic
	II. NON-CLINICAL						
Impact lowered	Carcinogenicity	Requirement to perform rodent carcinogenicity study	Weight of evidence assessment following completion of 6 month repeat dose study	**LOW**	Findings from 6 month study consistent with 13 weeks study	No	EMA/SA/0000 123456

The applicant should contact the EMA PRIME Scientific Coordinator who will advise on the suitable way to address emergent issues. Where appropriate, the PRIME Scientific Coordinator can support interactions with the CHMP/CAT Rapporteur to resolve minor issues or initiate an expedited scientific advice (see question 12). Ad hoc interactions by means of virtual meetings/teleconferences with the CHMP/CAT Rapporteur can be organised if needed, e.g. when major milestones of the development programme are reached.

13. How are MAA pre-submission activities managed within the PRIME scheme?

Submission readiness meeting

Approximately 15 months prior to the intended MAA submission date, applicants should contact the PRIME Scientific Coordinator to organise a submission readiness meeting with the Rapporteur and the assessment team, relevant national experts, as well as the EMA product team.

Meeting format and participation are the same as for the Kick-off meeting. However, the purpose of this meeting is different as it provides an opportunity at a time point closer to the MAA filing date to discuss the status of the development, including the implementation of previous regulatory advice for key development areas and the resulting data package intended to support the MAA. Thus, the meeting should occur 9-12 months prior to the intended MAA submission date; the appropriate timing will depend on the development and should be agreed by the applicant and the Rapporteur. In this context, applicants should consider that, insofar as possible, the package 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 the Pre-authorisation guidance.

Appointment of Co-Rapporteurs

Once the applicant sends a 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 pre-submission meetings, respectively with the EMA, Rapporteur and Co-Rapporteur can be organised.

Accelerated assessment

As the entry criteria for PRIME are based on those for accelerated assessment, medicinal products that have been granted PRIME support are also eligible for accelerated assessment. However, the appropriateness of this needs to be formally confirmed 2-3 months before submission of the application for marketing authorisation (see guidance on accelerated assessment). The submission readiness meeting is part of the preparedness to a smooth accelerated assessment procedure.

14. Will support from PRIME be withdrawn if the data emerging during development no longer support the criteria?

The development progress of designated PRIME products is monitored on a regular basis as part of the scientific advice procedures, and updates of the product development tracker.

Based on the data presented in the scientific advice requests, the SAWP and CHMP will, in the scientific advice letter:

- Advise the applicants on the next milestone/key points for which scientific advice should be requested.
- For products that entered the scheme in early development stages, advise whether the data support proof of concept and enable access to incentives provided by the scheme in later phases of development (i.e. CHMP Rapporteur appointment).

Over the course of medicine development, it is possible that new data emerge showing that a product granted PRIME support no longer meets the eligibility criteria as defined in question 3 of this guidance. Similarly, the therapeutic landscape may have changed over time affecting the progression of the development programme of some PRIME products. In these situations, the applicant/sponsor should contact EMA and discuss the issue(s), including next steps. Furthermore, the applicant/sponsor should inform the dedicated EMA contact point if they no longer intend to pursue the development.

EMA may also proactively reach out to applicants to request additional information on the status of the development programme, following new information presented in the development tracker, or to provide a justification whether the criteria for eligibility to PRIME are still met. This information will be discussed and reviewed, if appropriate, by the SAWP/CHMP and CAT. PRIME support may be withdrawn if the SAWP/CHMP determines that the PRIME eligibility criteria are no longer met. This may also be the case when applicants fail to adequately engage with EMA, to respond to requests or withhold relevant information on the development.

Withdrawal of PRIME support does not impact on the eligibility of the product to the centralised procedure.

15. Submitting an application for Withdrawal or Transfer of granted PRIME eligibility status (Regulatory Entitlements)

Companies with products that have been granted PRIME regulatory entitlement are now able to withdraw and transfer regulatory entitlements through the IRIS platform, by choosing the correct process type (Withdrawal of PRIME regulatory entitlement and Transfer of PRIME regulatory entitlement) when submitting a new application.

Further details on these two procedures can be found in the IRIS User guide for applicants.

16. What happens if my product is not granted eligibility to PRIME?

While many new medicinal products add value to the therapeutic armamentarium by providing alternatives and incremental benefits over established products, they may not necessarily qualify for eligibility to PRIME in accordance to the eligibility criteria. For example, the development plans could be already advanced, or the pivotal trials started, therefore there would be no benefit from the provision of enhanced development support. This should not be seen as a negative view on the merit of the product and the planned development, nor does it affect the possibility for granting accelerated assessment.

Applicants may submit a new request if new clinical evidence is obtained that demonstrates the product's potential to be of major public health interest. A preparatory discussion with the PRIME Scientific Coordinator is advisable in these cases. A different SAWP reviewer and EMA scientific officer will be appointed to review such new request.

17. Can I still request accelerated assessment if my product is not part of PRIME?

Yes, applicants not applying for, or not qualifying for PRIME support, will still be able to request accelerated assessment prior to filing, provided that the criteria are met.

18. What other regulatory tools and scientific support are available to developers?

Other tools supporting early patient access to medicines include conditional marketing authorisation, accelerated assessment and compassionate use. These are available to applicants, irrespective of their eligibility to PRIME scheme. Further information, including a comparative overview of these tools is included here.

EMA also offers a range of medicine development support tools, including scientific advice and protocol assistance, parallel consultation with regulators and health technology assessment bodies, the small and medium-sized enterprise office, the Innovation Task Force (ITF) and early paediatric interaction meetings.

19. What information is exchanged between the EMA and the US Food and Drug Administration (FDA) on the EU PRIME scheme and US Breakthrough Therapy designation programme?

The PRIME scheme and the US Breakthrough Therapy designation share the same objective of timely patient access to innovative medicines but have a different legal basis and different eligibility criteria.

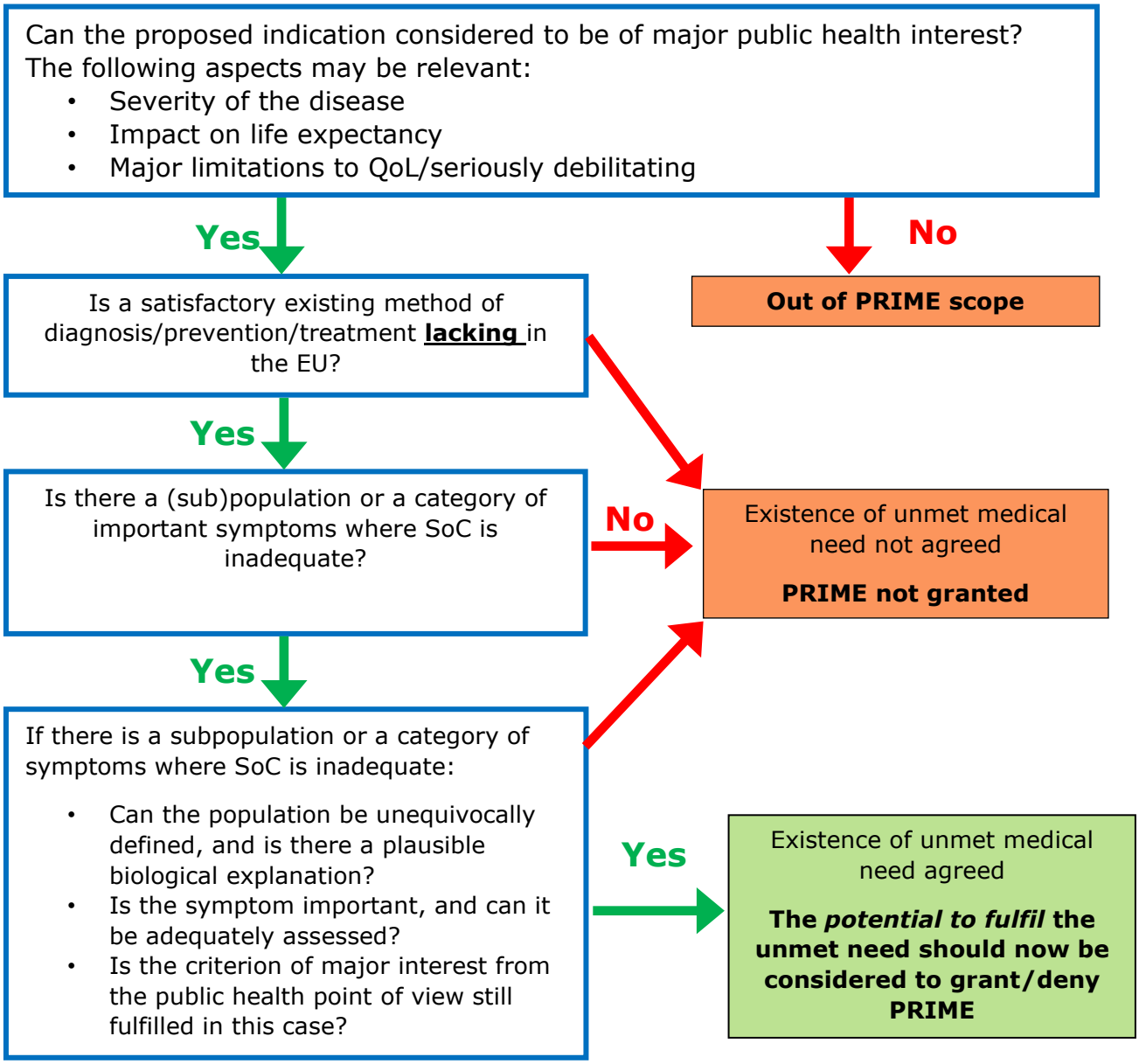
EMA and FDA share on a regular basis information on outcomes of requests received for PRIME and Breakthrough/RMAT designation. The main goal is to facilitate identification of FDA/EMA dually designated products and thus support global evidence generation for such products through early dialogue by therapeutic area experts in both regions, either on an ad hoc basis within the existing clusters, or in the context of Parallel Scientific Advice (PSA) programme.

When requesting Breakthrough Therapy designation or eligibility to PRIME, sponsors are encouraged to inform the Agency whether they have submitted a request for designation or eligibility to the other agency and the outcome of this request.

For successful planning of global development and clinical studies, both agencies encourage sponsors to contact FDA and EMA on a dually designated product's development programme and seek joint advice under the PSA programme. Information can be found here. Applicants are also invited to consider whether they would welcome participation of FDA as observers to the PRIME Kick-off or PRIME submission readiness meetings, subject to FDA consent. In such case, the applicant should directly liaise with FDA on this regard.

Annex I. PRIME Eligibility requests Flowcharts

1. Assessing the existence of unmet medical need



2. Assessing the potential to fulfil the unmet medical need

Note: for SMEs seeking **Early Entry** to PRIME the review focuses on the highlighted aspects. These, together with the rest, are also relevant to support the general entry route into the scheme.

Are the following **non-clinical aspects** convincing?

- Relevance of chosen model and setting
- Plausibility/specificity of effect based on mechanism of action
- Magnitude/consistency/duration/relevance of observed PD effects
- Early safety signals and exposure indicators (non-clinical +/- FTIH data)
- Clear presentation of analyses

Clinical data

Discuss:

- For Early Entry applications: human PK, tolerability at clinically relevant exposure
- Magnitude and duration of observed effect(s)
- If intermediate endpoints or surrogate markers are used: relevance of these to the clinical outcomes
- Relevance to longer term clinical outcomes (e.g. morbidity; mortality; progression)
- Expected major **therapeutic advantage** over existing methods, including limitations, risks and benefits of existing treatments?
- If the **development is at an advanced stage** (i.e. advice on pivotal study already given, pivotal study ongoing), the applicant should justify in the application the benefit expected by the PRIME development support (e.g. post-authorisation study design; registries, study relevance for access and reimbursement) and provide a plan of the sought regulatory interactions in the application.
- If the **development is at an early stage** and the submission is based on non-clinical and very preliminary, limited clinical data: the applicant should discuss how relevant these data are to support the promise to fulfil the unmet need, and justify the need at this early stage of PRIME development support (e.g. global definition of CMC specifications; specific early clinical issues, limited experience in product development for SME and Academic applicants). A plan of the regulatory interactions sought in the early stages of development should be outlined.

Have the above been discussed and assessed as relevant?