

Guidance for Applicants for the Early Access to Medicines Scheme (EAMS) - Step II

The Early Access to Medicines Scheme (EAMS) aims to give patients access to medicines that do not yet have a marketing authorisation but meet a medical need that is currently not being met. Medicinal products expected to be included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions. Under the scheme, the Medicines and Healthcare products Regulatory Agency (MHRA) will provide a scientific opinion on the benefit/risk balance of the medicine, based on the data available at the time of the EAMS submission. The EAMS is primarily aimed at medicines that have completed Phase III trials, but may be applied to completed Phase II trials in exceptional circumstances. The EAMS Criteria that must be met for a positive scientific opinion are:

Criteria	Criteria of an EAMS application
1	(a) Life threatening or seriously debilitating condition and (b) High unmet need, i.e. there is no methods available or existing methods have serious limitations
2	The medicinal product is likely to offer significant advantage over methods currently used in the UK
3	The potential adverse effects of the medicinal product are considered to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance
4	The Applicant is able to supply the product and to manufacture it to a consistent quality standard (GMP)

The scheme is voluntary and the opinion from the MHRA does not replace the normal licensing procedures for medicines. The scheme is not a substitute for appropriate clinical development and inclusion of patients in well-designed clinical studies remains the preferred option, if available in the UK. The scientific opinion will describe the benefits and risks of the medicine and will support the prescriber and patient to make a decision on using the medicine before its licence is approved. As with any unlicensed medicine, General Medical Council guidance states that patients using these medicines should be made aware that they do not have a licence yet and give informed consent to take them. These medicines are prescribed under the responsibility of the prescribing physician to address the medical need of the patient.

How to enter Step II of the Early Access to Medicines Scheme

The Applicant must hold a Promising Innovative Medicine (PIM) designation to enter step II of the early access to medicines scheme – see separate guidance regarding the PIM designation. In addition, the Applicant must request and attend (either in person or via teleconference) a pre-submission meeting.

Pre-submission meeting

The aim of the pre-submission meeting is to ensure that the suitability criteria for the scheme are likely to be met and to discuss the format of the data to be submitted to support the benefit/risk opinion. To apply for a pre-submission meeting, the Applicant should submit a completed request form. Following receipt of the request, the MHRA will arrange a mutually acceptable date for the meeting. The meeting will be carried out at the earliest available opportunity in order to ensure that applications for the EAMS are considered as soon as possible. There is no fee payable for the pre-submission meeting. After the pre-submission meeting, the MHRA will make a recommendation as to whether the product is considered a suitable candidate for step II of the EAMS. However, it is ultimately the decision of the Applicant whether to proceed with an application.

EAMS dossier

The information below should be considered as a guide only and the final content and structure of the dossier will be considered at the pre-submission meeting.

If available, the submitted dossier should follow the Common Technical Document (CTD) format as much as possible. Therefore, the Applicant should complete Modules 1 – 5 of the CTD as far as possible, and include all relevant data that are available. Detailed information on the CTD format can be found in Volume 2B – Presentation and content of the

dossier: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

Non-CTD data can be provided and the format should be discussed and agreed at the pre-submission meeting. For example, if a study is on-going and interim data are submitted, or if a full clinical study report (CSR) is not yet available, a summary of the results obtained after database lock addressing the main sections of a CSR and presenting the data in the form of tables, charts, figures would be acceptable, with the protocol and statistical plan provided in annex. Individual patient listings and SAE narratives should be available on demand.

Specific EAMS aspects of modules 1 and 2 of the CTD are described below.

The use of hyperlinks is strongly encouraged.

Module 1

A completed EAMS application form and appropriate cover letter should be submitted. The cover letter should include the proposed timetable submission slot (slots are found on the EAMS webpage) and the EAMS number. The product information will be described in the 'EAMS Treatment Protocol', which details the conditions for use, ensuring safe and efficacious use of the product. The EAMS Treatment Protocol should be laid out under the following headings:

- Information for the patient
 - It should include patient educational material and a consent form. No user testing is required, however the patient education information should be non-promotional, written in lay language and presented in the format of a Patient Information Leaflet. The lay summary of the RMP will be used to assist with obtaining informed consent from the patient.
- Information for the physician
 - It should be provided in the format of an SmPC, including the conditions of use, direction for administration and posology, warnings and contraindications, use in special populations, information on side effects and their frequencies and comment on clinical uncertainties of importance.
- Pharmacovigilance
 - Case Report Forms and the requirements for clinical monitoring and reporting of Adverse Drug Reactions (ADR) to medicines used under the scheme should be included.

Pharmacovigilance requirements

A Pharmacovigilance system for the fulfilment of pharmacovigilance tasks should be in place and a summary of the pharmacovigilance system master file (PSMF) should be submitted.

A Risk Management Plan (RMP) including a synopsis of a suitable series of pharmacovigilance activities should be submitted in support of the Step II application; this would likely include a drug registry and if required, a full protocol will need to be agreed before a positive Opinion is issued. The RMP should include a summary written for the lay reader which briefly outlines the disease epidemiology, treatment benefits (and uncertainties about benefits), important risks and their preventability, missing information and planned Pharmacovigilance activities (e.g. Registry). Any required additional risk minimisation tools (e.g. DVDs, patient cards, checklists) should also be described.

Registry requirements

The data collected in a Registry must be of relevance to the use of the product whilst the product is prescribed under the scheme. The purpose is to ensure the safe and effective use of the product in line with the EAMS Treatment Protocol.

Given the scheme is designed for products where there are no suitable alternative treatment options, it is highly unlikely that comparative data will add value, and thus a drug, rather than disease registry is likely to be the most appropriate design.

The data that needs to be collected depends on the nature of the known or potential safety concerns identified when a positive opinion is granted.

If there are no specific safety concerns, it is still of utmost importance that the product is being used in line with the EAMS Treatment Protocol, and a full understanding of the real life use is obtained.

Therefore the following information will need to be collected:

- Condition which the product is being used for;
- Patient Age;
- Patient Gender;
- Dose and duration of treatment;
- Other relevant dosing information (e.g. if proposed dosing is weight-based, patients weight would need to be collected);
- Underlying co-morbidities;
- Concomitant medications.

If the EAMS Treatment Protocol specifies measures that are prerequisites for use, for example biomarker status, these should routinely be collected and recorded in the registry.

If other factors are known to be strongly predictive of efficacy or outcome, these should be recorded.

If a specific safety concern has been raised during the review, then factors related to this safety concern should be recorded. For example if there are concerns with respect to cardiovascular toxicity, then collecting baseline data on history of cardiovascular disease and events, or NYHA functional class may be relevant.

The registry should capture all medically-confirmed adverse events, with transmission to the MHRA as appropriate. Reporting of registry data should categorise events by seriousness (serious or non-serious) and include an assessment of causality and relatedness where possible.

When a Marketing Authorisation is granted, the Pharmacovigilance requirements of the authorisation supersede those of the scheme

Module 2

Module 2 should contain the overviews and summaries, prepared by suitably qualified and experienced experts.

Quality

The Quality Expert Report should include a summary of each section listed in the CTD, with sufficient data presented in flow charts/tables/figures to assist rapid review and assessment. In addition, the qualification/ validation status of the assay methods should be listed and provisional specifications provided. Process control criteria should be clearly and concisely presented and justified, with a summary of risk assessments, where relevant. The Quality Expert should also provide a critical review of the data and highlight key information in the report. A list of the Drug Product batches used in non-clinical and clinical trials should be given, so that clear links can be made with these sections. Reference (with hyperlinks) to Module 3 should only be made where further details are provided in support of the expert's discussion and conclusion reached in the Quality Expert Report.

Non-clinical

The non-clinical overview should provide a critical review of the available non-clinical pharmacology, pharmacokinetic and toxicology data, highlighting potential target organs/tissues. Systemic exposures in the non-clinical species at no observed adverse effect levels and at toxic doses, in comparison to those in humans at the maximum recommended human dose, should be discussed; this information may be summarised in tabular form to aid review. Any mechanistic studies that have been conducted to elucidate reported toxicities and/or their relevance to man should also be highlighted.

Clinical

The clinical overview should be a concise summary of the clinical information, with sufficient data presented in flow charts/summary tables/figures to assist rapid review and assessment. Individual study synopses should be appended but Clinical Summaries (section 2.7) are not mandatory. A specific additional section which confirms that the product meets the EAMS criteria should be provided as an annex with the following headings:

- Life-threatening or seriously debilitating condition
- High unmet medical need
- Major clinical advantage over methods currently used in the UK
- Positive benefit/risk balance

In addition, the Applicant should include a section that describes the current and planned clinical programme, and the expected timelines for a marketing authorisation application.

Submission process

The EAMS dossier should be submitted in electronic format by the date specified and agreed after the pre-submission meeting. Late or invalid dossiers will not be able to enter the scheme on the preferred date. For help and advice regarding the submission process, please contact the EAMS co-ordinator (eams@mhra.gsi.gov.uk).

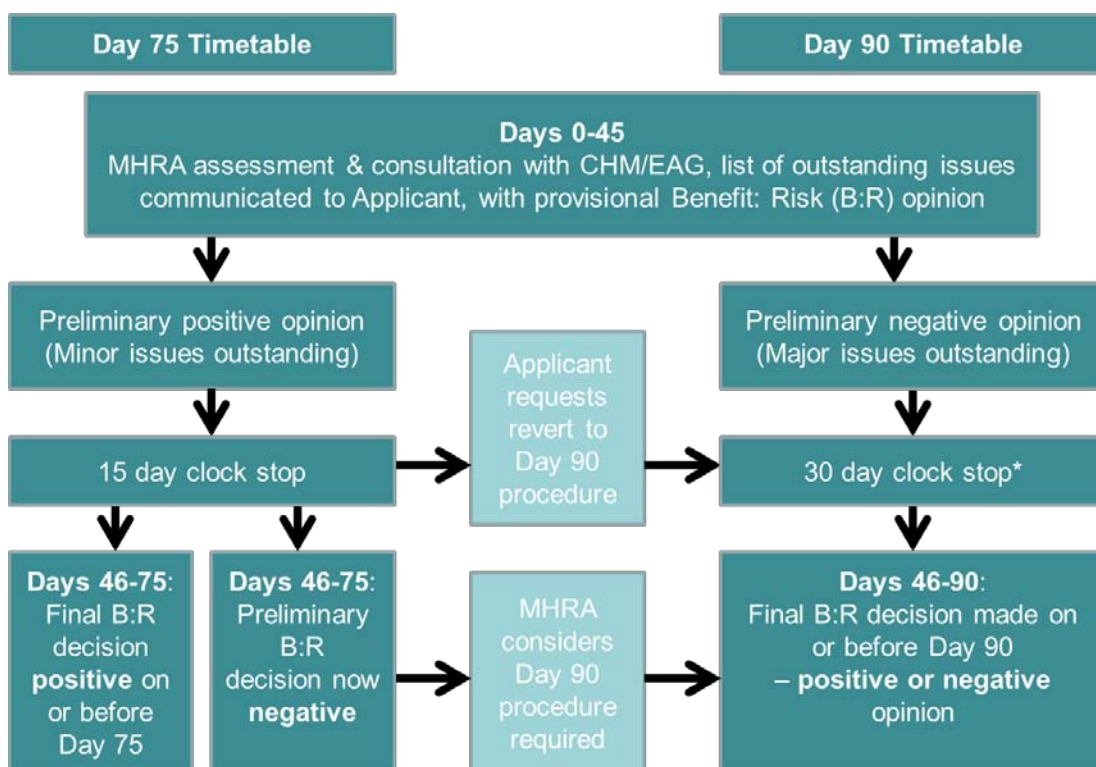
Fees

Fees are set at a cost recovery level. The fee for the assessment of the scientific opinion is £29,000 for new chemical or biological medicinal products and the renewal fee (if applicable) is £14,500. The fee for the assessment of the scientific opinion is £9,232 for new indications and the renewal fee (if applicable) is £4616. There is no separate charge for the pre-submission meeting. There are no other fees in the opinion year.

Assessment timetable and decision

The assessment timetable is illustrated in the figure below. All Applicants will receive an initial benefit/risk opinion by Day 45 of the procedure.

- If a preliminary positive opinion is given, the procedure follows the Day 75 timetable, with a 15-day clock stop period.
- If the preliminary benefit/risk opinion is negative, the procedure follows the Day 90 timetable, with a 30-day clock stop (this may be extended to 60 days in exceptional circumstances).
- The clock stop period allows time for an Applicant to respond to outstanding major (30 days) or minor (15 days) issues. Response to the outstanding issues should be provided within the stated time.



*in exceptional circumstances, the Applicant can request additional 30 days (30+30)

Scientific Opinion

A positive scientific opinion is only issued if the criteria for the EAMS are fulfilled. There is no right of appeal for negative opinions and negative opinions will not be published. The positive scientific opinion will be published on the MHRA webpage alongside a public assessment report and the EAMS Treatment Protocol, within 15 days of the opinion. Any other non-promotional signposting of the opinion

will be considered on a case-by-case basis. The opinion is valid for one year in the first instance and lapses at this time or at the time of the grant of a marketing authorisation. Further information generated during the opinion year should be provided to the MHRA as per the agreed RMP. Any new information that the opinion holder considers may impact the benefit/risk balance must be reported as soon as is reasonably practicable after the opinion holder becomes aware of it. Failure to do so will result in withdrawal of the opinion. If the data submitted change the positive benefit/risk scientific opinion, the MHRA reserves the right to withdraw the opinion. Renewal of an EAMS scientific opinion is possible.

Periodic updates

During the opinion year, it is expected that the scientific opinion holder will provide regular updates. The frequency and scope of these updates will be agreed before the issue of a positive scientific opinion but updates are likely to be expected every 3 months and describe safety and usage of the product under the scheme, along with any safety and efficacy data from newly-completed clinical trials. Please refer to EAMS periodic updates/ renewal template for further information.

Where relevant, quality, safety and efficacy data generated during the EAMS opinion should be submitted at appropriate time points during the marketing authorisation application.

Withdrawal of opinion

The MHRA will withdraw the EAMS positive scientific opinion, if following scientific assessment, the benefit/risk is considered to be no longer favourable or when a marketing authorisation is issued. The scientific opinion public assessment report and EAMS Treatment Protocol will be removed from the MHRA's webpage and the MHRA will communicate the withdrawal of the scientific opinion via the appropriate channels, in order to protect public health or note approval of a marketing authorisation.

Renewal of opinion

The opinion lapses after one year or at the time of the grant of a marketing authorisation. Renewal of an EAMS scientific opinion should be requested at least 2 months before expiry of the opinion by completing the EAMS periodic updates/ renewal template. Please contact the EAMS coordinator for further information (eams@mhra.gsi.gov.uk).