

Summary

Since 2014 there has been a welcome recognition within Europe of the need for improved regulatory mechanisms whereby medicines being developed to target serious or life-threatening diseases that represent an unmet clinical need, can be made available to patients at the earliest opportunity. This has resulted in the introduction of the Early Access to Medicines Scheme (EAMS) in April 2014, to support early patient access to important medicines in the United Kingdom, the first step of which is the Medicines and Healthcare products Regulatory Agency's (MHRA's) Promising Innovative Medicine (PIM) designation. The European Medicines Agency's (EMA's) PRiority MEDicines (PRIME) scheme followed in March 2016, which provides additional regulatory support to the sponsor with the aim of optimising development plans with a view to accelerating the evaluation of important medicines across the EU.

This poster briefly presents the various programmes available to support expedited development of medicines in areas of unmet medical need, with particular focus on Applications seeking PIM and PRIME designation. The main focus of the poster is to provide procedural insight and a critical comparison of the above mentioned UK and EU schemes through the authors recent experience of submitting consecutive PRIME and PIM applications relating to the same medicinal product, which was at the same stage of development and had an identical data package. This included (i) mechanistic studies demonstrating mode of action; (ii) *in vivo* preclinical studies demonstrating efficacy in the target indication (iii) Phase 1 clinical data demonstrating a good safety profile and (iv) Phase 2 data showing promising efficacy in the targeted patient population.

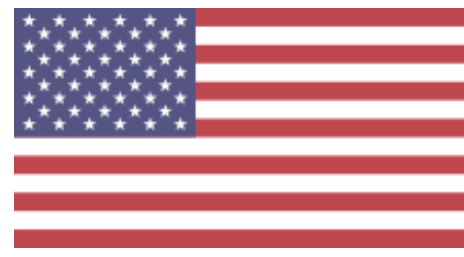
Introduction & Background to PIM and PRIME

- Increasing global recognition of a need to facilitate an expedited pathway for the development of medicines that have the potential to offer major therapeutic advantages over current treatment options to patients suffering from serious or life threatening diseases, which are considered to represent an unmet medical need.
- This has resulted in a number of recently established programmes being rolled out by regulators in both the USA and Europe
- The need for improved regulatory mechanisms in the EU, enabling early patient access to medicines in areas of unmet clinical need has resulted in EAMS in the UK in 2014, the first step of which is the MHRA's PIM designation. PIM designation is a prerequisite to progress to the Scientific Opinion assessment (Step II) where approval can be made for early patient access through EAMS.
- Acknowledged need for an overarching European scheme to promote timely access to important therapies, led to the EMA's PRIME scheme being launched in 2016.

The introduction of these two schemes provides companies with new regulatory tools in addition to those already established in major markets (outlined below), to facilitate expedited patient access to important medicinal products in Europe for conditions with the most urgent need for improved treatment options.

In the US, the FDA has four programmes available to expedite patient access, while a number of established tools have been available in the EU.

Established Regulatory Tools Supporting Accelerated Development for Unmet Medical Need



- Fast-Track Designation
- Accelerated Approval
- Priority Review Designation
- Breakthrough Therapy



- Accelerate Assessment
- Conditional Marketing Authorisation
- Compassionate Use

Eligibility Criteria and What Stage of Development to Apply

The eligibility criteria for PRIME and PIM are described in Figure 1. Guidance documentation is available on the EMA and MHRA websites providing further information relating to what is required by way of justification for meeting the required criteria¹⁻⁴

Figure 1: Eligibility Criteria for PRIME and PIM

PRIME	PIM
<ul style="list-style-type: none"> Products under development where the intention to apply for initial MA through the centralised procedure Targets products of major public health interest (in particular from the viewpoint of therapeutic innovation) Target conditions where there is an unmet medical need, i.e. no satisfactory methods exist or the medicinal product will offer major therapeutic advantage over existing methods Must demonstrate potential to address the unmet medical need The potential to offer major therapeutic advantage to patients, should be demonstrated by clinical data* showing evidence of clinically meaningful improvement in efficacy in patients (i.e. generated in exploratory clinical studies) substantiating the product's potential to significantly address the unmet medical need 	<ul style="list-style-type: none"> Life-threatening or Seriously debilitating condition High unmet need (no method of treatment, diagnosis or prevention available or existing methods have serious limitations). Major advantage over methods currently used in the UK Based on preliminary evidence from non-clinical and clinical data. The potential adverse effects are likely to be outweighed by the benefits providing a reasonable expectation of a positive benefit risk balance

*In exceptional cases applications from academia or SMEs may submit at an earlier stage non-clinical data may be acceptable at an earlier stage based on compelling non-clinical data providing proof of principle or first in man studies indicating positive PK and safety for desired pharmacotherapeutic effect and tolerability.

- A review of both approved and medically accepted unapproved existing methods should be provided.
- Both schemes require preliminary supporting evidence indicating a potential benefit to patients in the target condition, and therefore to address the unmet medical need.
- Preclinical and clinical data (for PIM it is mandatory) providing evidence of an improvement over currently available therapeutic methods. Comprehensive critical review against all available methods in order to clearly justify what benefits it will bring to patients.
- The decision as to when to apply comes down to a sponsor risk decision that should primarily be based on confidence in the conclusions that can be drawn, and the quality of the data available to demonstrate the potential to offer a therapeutic advantage.
- Good quality clinical data demonstrating a clinically meaningful improvement in efficacy to overcome the unmet need will increase the chance of a successful designation.

Key Features and Benefits of PRIME and PIM

The key benefits associated with PRIME and PIM designation are presented in Figure 2.

Figure 2: Key Benefits for Applicants to PRIME and PIM Schemes

PRIME	PIM
<ul style="list-style-type: none"> Provides early regulatory dialogue with the EU regulatory network to aid in optimisation of the clinical development programme to support an expedited review process enabling earlier patient access across the EU Early appointment of CHMP or Committee for Advanced Therapies (CAT) Rapporteur (in line with current process, objective criteria and methodology) to provide continuous support ahead of an MAA Sponsor has a dedicated EMA contact person Initial kick-off meeting with appointed Rapporteur and a multidisciplinary group of experts from relevant EMA committees and working parties (SAWP, CAT, COMP, PDCO), to discuss the proposed development programme, give preliminary guidance on requirements for MAA, and to develop a schedule for giving regulatory and scientific advice and for submissions of applications to fulfil legislative requirements. Scientific advice on key decision points/issues for the preparation of MAA with the possibility to involve multiple stakeholders (e.g. HTA) bodies, patients) Use of early access tools where relevant (e.g. conditional marketing authorisation) or other initiatives (e.g. parallel EMA/HTA advice, adaptive pathways) For SME/Academics: SA fees reduction, SA on the overall development plan and at major development milestone 	<ul style="list-style-type: none"> Provides early regulatory dialogue with the MHRA and NICE (also Scottish Medicines Consortium) to aid in optimisation of the clinical development programme to support an expedited review process enabling earlier patient access in the UK The PIM designation provides a relatively inexpensive method of interacting with regulators and obtaining early validation for a medicinal product in clinical development. A pre-submission meeting to assess suitability of the candidate to progress to step II of the EAMS (primarily aimed at medicines that have completed Phase III trials, but may be applied to completed Phase II trials in exceptional circumstances) The opportunity to meet with the devolved National Health Services and HTAs to discuss how best to support future technology appraisal. For example, through generation of EAMS real world patient data Second EAMS step: scientific opinion on the benefit/risk balance of the medicine Following a positive EAMS scientific opinion, MHRA will publish a public assessment report (PAR) and the EAMS treatment protocol

- Both schemes aim to foster early engagement with relevant agency representatives through meetings and Scientific Advice, which can help optimise development plans.
- Patients benefit from both schemes through earlier availability of promising treatments.
- A key feature of PRIME is a dedicated contact person at the EMA and the appointment of an EMA Rapporteur who will provide continuous regulatory support to build knowledge ahead of an MAA.
- Major focus is to provide support early in development. Majority of applications include phase 1 and/or phase 2 data. More than 50% only have data from a single clinical study.
- PIM designation, (step I of EAMS) provides an opportunity to interact with regulators and receive scientific validation of a product earlier in clinical development.
- PIM designation indicates that the MHRA considers the product to be a promising candidate for entry into step II of the EAMS.
- Sponsor has opportunity to engage with multiple key stakeholders (Regulators, HTA's, NHS) during the EAMS process which can facilitate timely uptake of product within the NHS.

Experience of Successive PRIME & PIM Submissions

- PRIME submitted 4 months prior to PIM for the same medicinal product, which is being developed in cancer patients undergoing chemoradiation therapy.
- The package of data used to support each designation was identical and this included:
 - Mechanistic studies** demonstrating its mode of action.
 - In vivo preclinical studies** demonstrating the ability of the product to **impact the targeted disease indication**.
 - Clinical Phase 1 data** from healthy human volunteers demonstrating the good safety profile of the product and further supporting its anti-inflammatory action; and
 - Clinical Phase 2 data** showing promising results in terms of primary and secondary endpoints in the targeted patient population. Consistent with the preclinical data.
- The key difference between the applications was that following submission of the PRIME Application, the sponsor received EMA Scientific Advice in relation to the design of the pivotal Phase 3 clinical programme **before** meeting with MHRA to discuss the PIM Application. Written feedback was received prior to submitting the PIM meaning that additional information relating to the EMA / CHMP's review of the existing data and the Phase 3 study could be included in this application.

- Application process straightforward for both schemes with relatively quick decision.

PRIME:

- Application consists of 30-page justification document.
- Day 1 Start of procedure (SAWP 1 meeting)
- Day 30 Discussion and **recommendation** during SAWP plenary (SAWP 2 meeting) **by the SAWP** (and after by the Committee for Advanced Therapies (CAT) in case of advanced therapy medicinal products (ATMP))
- Day 40 Final adoption by the CHMP** during the plenary meeting

PIM:

- Application with a 50-page PIM designation template, indicating why and how the product fulfils the criteria.
- Review of PIM application by the assessment team with a designation meeting (1 hour) **within 4 weeks of the receipt of the request (face to face at MHRA is preferred, although can be teleconference)**.
- Recommendation by the assessment team to the internal scientific consistency review group, which will advise the Director of Licensing on whether to grant a designation (**2-4 weeks after meeting**).

Outcome of Applications

- Rejection of the PRIME** and an **approval of the PIM designation**.
- The **outcome of the PRIME** was disappointing as the unmet medical need relating to this application was not disputed and the sponsor had presented positive clinical data demonstrating the potential to address the unmet medical need.
- The rejection was based on a single perceived issue by the EMA/CHMP related to their interpretation of the nonclinical to clinical relationship of a particular parameter not considered to be a primary assessment criterion of the scheme as per the published guidance.
- This was surprising as it seems to go against the focus of PRIME, which is to assist in the development of products in relation to an unmet medical need, especially as there were positive clinical efficacy and safety data in the target population.
- The PRIME procedure does not include a face-to-face meeting following submission, so there is no opportunity to interact with the assessors, where sponsors could respond to and provide clarification on any uncertainties.
- This is probably the most inflexible aspect of the PRIME procedure. It underscores the need to focus clearly and concisely on messaging complex information in the written application, particularly when presenting data that may be potentially difficult to interpret.
- The **outcome of the PIM** application where all the criteria were accepted as being met was aided by the experience of submitting the PRIME and the reasons provided by the assessors for the rejection of the application.
- The opportunity to discuss the application in a face-to-face meeting with the assessors at the MHRA and submit written minutes prior to the decision was a further benefit of the PIM procedure.
- This provided the assessors with the opportunity to request clarification of any perceived issues, and the sponsor with a forum in which to discuss them openly.

Figure 3: Figures on outcome of PRIME requests showing cumulative recommendations made between 7th March 2016 -22nd March 2018 (EMA website)

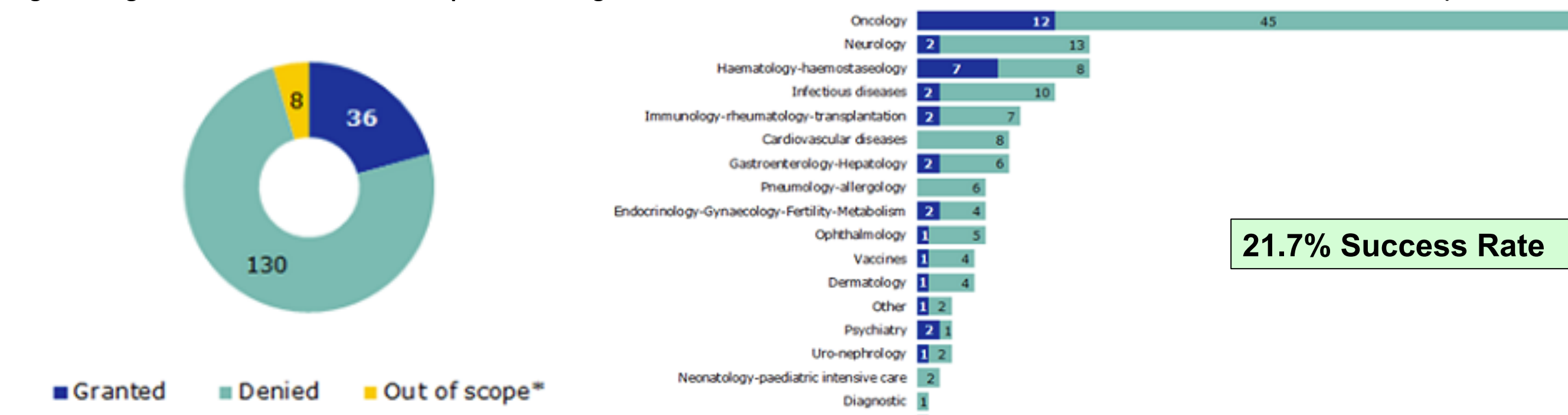


Figure 4: PIM designation statistics from the inception of the EAMS to January 2018

EAMS step I PIM designations - April 2014 to January 2018	
Applications received	66
PIM designations granted	50
PIM designations refused	10
PIM designations withdrawn	2
PIM designations pending	4

Conclusion on PRIME versus PIM and Suggested Improvements

- Both schemes are welcome additions to the EU regulatory framework for expedited development for products in areas of unmet medical need.
- Guidance for both schemes is clear with well-defined pathways relating to how a product will procedurally navigate through the application stage to successful designation and beyond with the key benefits of each scheme being well described.
- Appears that EMA / CHMP go beyond a strict interpretation of the guidance when deciding on approvability. Is the scheme only eligible for game-changing products?
- Coupled with our experience, data available from the EMA website shows a low rate of success (~22%) for requests to the PRIME scheme.
- Low probability of success may put sponsors off applying to PRIME scheme, particularly in therapeutic areas where designations has been particularly low (oncology, cardiovascular).
- Probability of success could be gauged by applicants by introducing a pre-submission stage offering the opportunity to engage with assessors prior to submitting a full application. elimination of unnecessary review of products that are unlikely to meet the designation criteria.
- Very few applications to PRIME have been based on "Proof of Principle" where no clinical efficacy/safety was available.
- It would be useful to attract applicants with more early stage development products to apply for PRIME, in order to maximise the benefit offered by the scheme through scientific advice and strategic regulatory guidance.
- Sponsors should carefully consider potential risks associated with making their product available through EAMS following successful navigation through step II (Scientific Opinion).
- For both the PRIME and PIM schemes, and in the spirit of "regulatory transparency", it would be extremely helpful if EMA and MHRA could publish a rolling list of conditions that they have already concluded do not meet the "unmet medical need" criterion.

References

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- EMA. Enhanced early dialogue to facilitate accelerated assessment of PRiority MEDicines (PRIME). EMA/CHMP/57760/2015.
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- National Institute for Health and Care Excellence, Centre for Health Technology Evaluation. Note to describe procedures at NICE to support the Early Access to Medicines Scheme. Available at: www.nice.org.uk/Media/Default/About/Who-we.../eams-process-jan-16.pdf