EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRIME: a two-year overview

Highlights

- 177 requests for eligibility to PRIME received and assessed since launch in March 2016.
- Number of requests has been fairly constant and have matched forecasts, with an average of eight requests received per month.
- Quality of applications received is good; guidance can be considered sufficiently clear for applicants to understand the scope and requirements of PRIME.
- Requests have been received in a wide range of therapeutic areas, being the majority for oncology or haematology products.
- 21% of requests have been accepted in the scheme, totalling 36 medicines accepted into PRIME scheme. The rate eligible/granted indicator has remained stable since launch.
- Of the total 36 medicines included 30 are for rare diseases.
- High number of requests for advanced therapy medicines, representing 40% of products granted eligibility.
- Three applications had been granted the so-called early entry into PRIME. While two are still early in the development, one of these medicines has since then progressed progress to proof of concept.
- PRIME products have received enhanced support from the Agency, with so far:
  - 31 kick-off meetings organised;
  - followed by 37 scientific advices (on 22 different products) many including input from multiple committees as well as other stakeholders (Health Technology Assessment (HTA) bodies, patients).

Background

The European Medicines Agency (EMA) launched the PRIority MEdicines (PRIME) scheme in March 2016. The scheme provides early and enhanced scientific and regulatory support to medicines that have the potential to significantly address patients' unmet medical needs.

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 in patients indicating the promising activity of the medicinal product and its potential to significantly address an unmet medical need (proof of concept).

Applicants from the academic sector and micro-, small-and medium-sized enterprises (SMEs) may submit an eligibility request at an earlier stage of development if compelling nonclinical data in a relevant model provide early evidence of potentially promising activity (proof of principle) and first-in-man studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.

In the present document, EMA continues to report on the scheme after two years of experience, in particular on how the criteria for eligibility have been applied and the types of support that applicants have received so far. The report reviews practical examples that illustrate some of the benefits of PRIME and how the scheme makes optimal use of existing tools supporting regulatory and scientific advice.

Overview of two-year experience of PRIME eligibility assessment

PRIME focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. The scheme is voluntary and subject to application justifying that the eligibility criteria are met.

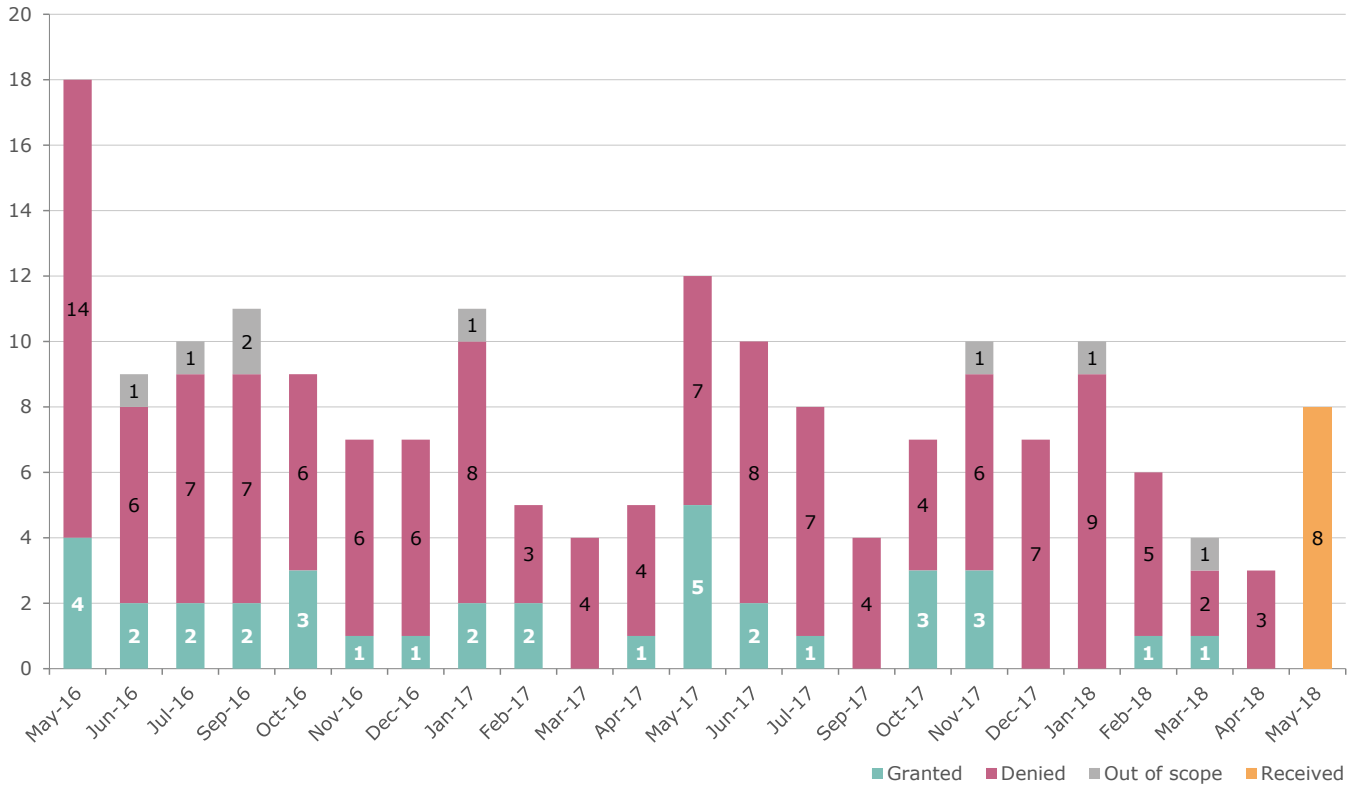
Medicines eligible for PRIME support shall target diseases where there is an unmet medical need, i.e. for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

A product eligible for PRIME support should demonstrate the potential to address to a significant extent the unmet medical need for maintaining and improving the health of the Community, for example, by introducing new methods of therapy or improving existing ones. A request for eligibility in a given indication should be supported by data demonstrating that the product has the potential to bring a major therapeutic advantage to patients, through a clinically meaningful improvement of efficacy, such as having an impact on the prevention, onset or duration of the condition, or on the morbidity or mortality of the disease.

Since the launch of PRIME in March 2016, the Agency has received and assessed a total of 177 requests for eligibility to PRIME.

Notwithstanding the expected monthly fluctuation, the number of requests has been fairly constant and in line with the Agency's forecast over the two years since launch, with an average of 8 requests received per month (Figure 1).

Figure 1. Overview of PRIME eligibility requests received



Note: Requests received between 7 March 2016 and 28 February 2018 and assessed with recommendations adopted by Committee for Medicinal Products for Human Use (CHMP) by 26 April 2018. Eight additional requests have been received and are under review for adoption of recommendations in May 2018.

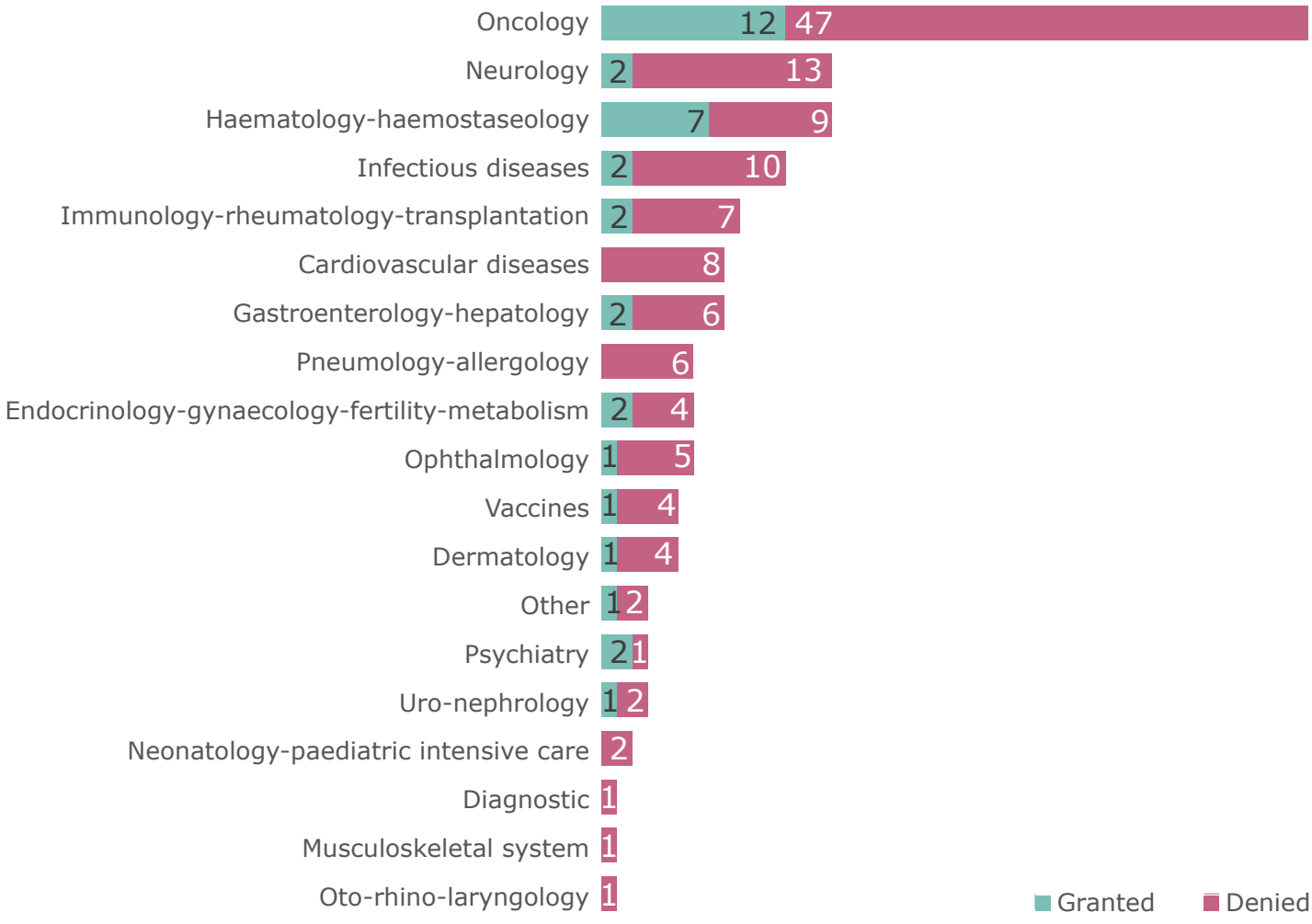
Overall, the quality of applications received is good. Only a few requests (8) were out of scope and not deemed suitable for review. The main reasons were that either the product was too early in its development (e.g. too early for proof of principle for SME or for proof of concept for non-SME) or that it was unclear whether the product could fall under the definition of a medicinal product and thus be within the remit of EMA. In view of the limited number of requests found to be out of scope, the guidance can be considered sufficiently clear for applicants to understand the scope and eligibility criteria for PRIME.

Out of 169 requests received and assessed, 36 were granted eligibility to PRIME. Twenty-one percent of requests have therefore been accepted in the scheme. This indicator has remained stable since launch.

Since its launch, PRIME has generated a high interest from SMEs which have constantly represented more than half of the requests received. On the other hand, only three requests have been received from applicants in the academic sector. As set out in the framework for collaboration between EMA and academia and supporting action plan published in April 2017, EMA will raise awareness on the support the Agency can offer with the aim to promote and further develop regulatory support to translate academic research into novel methodologies and medicines.

While the majority of requests and products granted still pertain to oncology or haematology products, the Agency continues to receive requests in a wide range of therapeutic areas (Figure 2).

Figure 2. Overview of PRIME eligibility requests granted and denied by therapeutic area

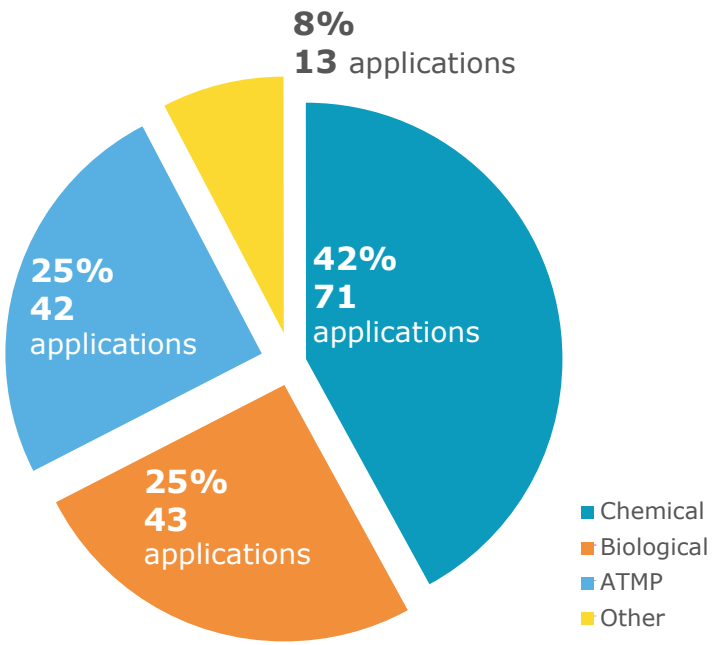


Note: Requests (n=169) received between 7 March 2016 and 28 February 2018 and assessed with recommendations adopted by CHMP by 26 April 2018.

Notably during this second year, six additional requests were received for indications in infectious diseases areas/ vaccines. Out of these, two products were granted eligibility in the treatment of septic shock and the treatment of chronic hepatitis D infection, respectively. In addition other applications have succeeded in rare diseases that are in clear need for development of therapies such as achromatopsia associated with defects in CNGB3, X-linked hypohidrotic ectodermal dysplasia, Primary Hyperoxaluria Type 1 and osteogenesis imperfecta types I, III and IV, to mention some examples.

The Agency continues to receive a high number of requests for advanced therapy medicinal products (ATMPs) (see Figure 3).

Figure 3. PRIME eligibility requests by type of product



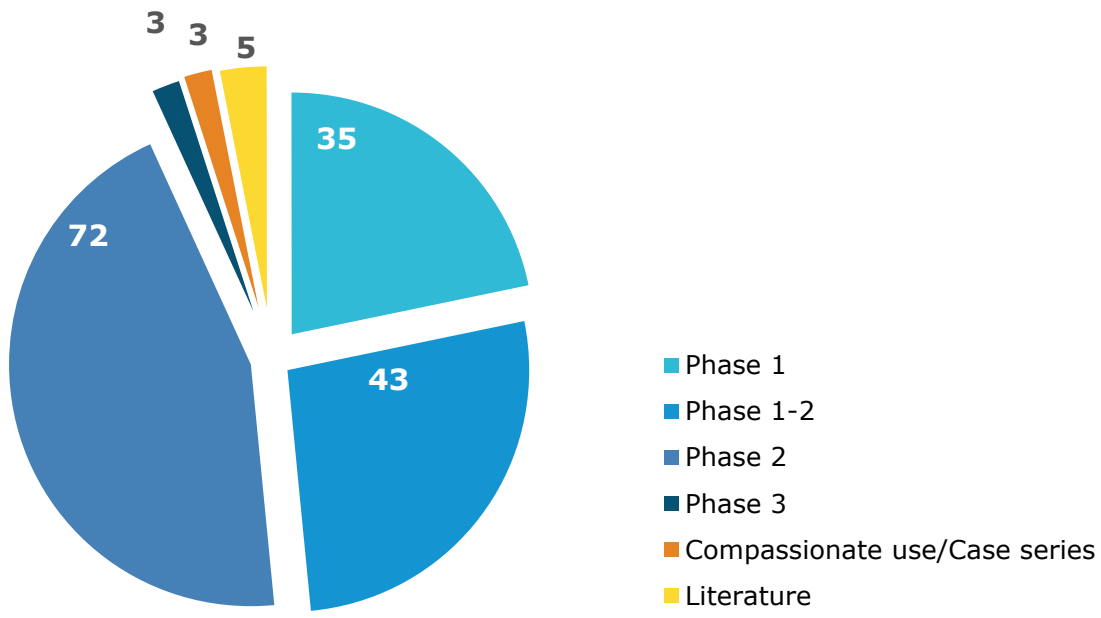
Note: Requests (n=169) received between 7 March 2016 and 28 February 2018 and assessed with recommendations adopted by CHMP by 26 April 2018.

While PRIME is open to all companies on the basis of preliminary clinical evidence (proof of concept), applicants from the academic sector and SMEs can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials (proof of principle).

Over this two year period, only eight requests were submitted by SMEs at the proof of principle stage. Out of these, three had been granted eligibility to PRIME at this early stage of development. Notably, the sponsor for one of these products has subsequently provided the Agency with exploratory data on its progress to proof of concept, enabling confirmation of PRIME eligibility.

Most eligibility requests received (161 out of 169) are at the proof of concept stage supported by exploratory data. The source or phase of clinical trial of the supportive data is illustrated in the Figure 4 below. Overall, the majority of applications base their request on phase 1 or a combination of phase 1 and phase 2 data.

Figure 4. Source of exploratory clinical data of eligibility requests at the proof of concept stage



Note: Requests at the proof of concept stage (n=161) received between 7 March 2016 and 28 February 2018 and assessed with recommendations adopted by CHMP by 26 April 2018.

The Agency has analysed the main reasons for not granting eligibility to 128 out of 161 requests received at the proof of concept stage. During the first year of PRIME, 14 requests were denied eligibility, because the products were too advanced in their development for advice to be taken into account . As expected, over the second year, only three requests were denied eligibility for this reason.

Grounds for denial of all other requests (87%) were:

- issues with robustness of presented data that did not sufficiently support the assumption of a major therapeutic advantage (e.g. trial design issues, failed study, inconsistency of results, inappropriate claim in subgroup, lack of comparator, inadequate comparison to historical data);

- inconclusive or insufficient effect (magnitude, duration, relevance of endpoints).

While this was not the only reason for denial, there were a small number of cases (11) where the committee also considered that the unmet medical need was not acceptable as proposed or not sufficiently justified by the applicant. In many of these cases, while the committee would have agreed that an unmet medical need may still exist in the concerned condition (e.g. in a subgroup of patients or in view of limitations of existing therapies), the applicant's arguments did not appear to be targeting the remaining unmet medical need.

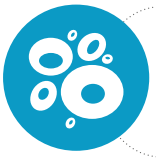
Based on its experience, the Agency has updated its guidance and applicant's template to further clarify expectations with respect to robustness of data and applications.

36 products eligible to PRIME since launch

30 in rare diseases | **16** for paediatric patients | **15** advanced therapy medicinal products

Areas of unmet medical need and therapeutic indications covered

Cancer

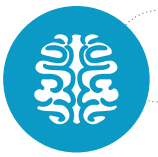


- Acute lymphoblastic leukaemia
- Diffuse large B-cell lymphoma
- Glioma
- Sarcoma
- Multiple myeloma
- NTRK fusion-positive solid tumours

Haematology/Haemostaseology

- Beta-thalassaemia
- Haemophilia
- Post-Transplant Lymphoproliferative Disorder
- Primary haemophagocytic lymphohistiocytosis
- Sickle Cell Disease

Neurology



- Alzheimer's disease
- Major depressive disorder
- Post-partum depression
- Spinal muscular atrophy Type 1

Infections

- Hepatitis D
- Septic shock
- Ebola Virus Disease

Immunology/Rheumatology/Transplantation

- ANCA-associated vasculitis
- Prevention of graft rejection

Metabolism

- Acid sphingomyelinase deficiency
- Hepatic porphyria

Uro-nephrology

- Primary Hyperoxaluria Type 1

Hepatology/Gastroenterology

- Primary Biliary Cholangitis
- Progressive Familial Intrahepatic

Dermatology

- X-linked hypohidrotic ectodermal dysplasia

Ophtalmology

- Achromatopsia associated with defects in CNGB3

Other

- Osteogenesis imperfecta types I, III and IV

3 marketing authorisation submitted and under evaluation

Overview of support to products eligible to PRIME

Support provided through the scheme is tailored to meet the needs of development at different stages. Key benefits for applicants are:

- Early appointment of a rapporteur from EMA's Committee for Medicinal Products for Human Use (CHMP) or the Committee for Advanced Therapies (CAT), to provide continued support and guidance that would allow the developer to prepare a robust data package in view of the data requirements for a marketing authorisation application (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 advice and (3) open the discussion on the recommended regulatory strategy;

- Dedicated single contact point at EMA who will coordinate the regulatory support offered throughout the scheme;

- Scientific advice on the overall development plans, at major development milestones and on key issues, with possibility to involve additional stakeholders (i.e. HTA bodies, patients);

- Confirmation of the potential for accelerated assessment at the time of an application for marketing authorisation.

Eligible products have entered the scheme on average three years before the planned marketing authorisation application. This can however vary from product to product, in view of very different type of diseases and development programmes required to support a marketing authorisation.

Kick-off meetings

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 EMA. This unique type of meeting for PRIME eligible products is one of the key features of the scheme.

It usually takes place within two to three months following entry into the scheme after the CHMP/CAT Rapporteur has been appointed. This meeting aims at initiating the interaction between the applicant, experts from the EU regulatory network and the Agency. It establishes a discussion platform for 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.

During the meeting, participants do not engage into detailed scientific and technical discussions around the identified topics, but the aim is to agree on the next steps to address any identified issues or to identify potential additional issues to be discussed in the context of scientific advice. The kick off meeting is also a great opportunity to enhance inter-committee coordination.

The first kick-off meetings were organised in July 2016 and to date, 31 kick-off meetings have taken place. In these meetings, EMA, Rapporteur and relevant assessors are participating, as well as the chairs of CHMP, CAT or the Scientific Advice Working Party (SAWP), as appropriate.

In order to guide applicants for future interactions with other committees, this meeting often includes participants from the Paediatric Committee (PDCO) to discuss the paediatric investigation plan, Committee for Orphan Medicinal Products (COMP) to discuss matters related to orphan designation and its maintenance or the Pharmacovigilance Risk Assessment Committee (PRAC) to plan for post-authorisation activities.

In April 2018, the Agency conducted a short anonymous survey to gather feedback from applicants for which a kick-off meeting was held in the past 12 months. Responses were received from 15 out of 20 applicants contacted. As summarised in the Table 1 below, very positive feedback was received on the preparation, conduct and usefulness of the kick-off meeting. Need for improvements on the understanding of how to interact with different committees and the post-meeting follow-up were noted.

Results of survey on kick-off meeting conducted in April 2018 (15 responders)
87% agree the written guidance provided was helpful to prepare the briefing document
100% agree the support provided by EMA was helpful to prepare for the meeting
93% agree the meeting objectives were clear to the applicant
73% agree the meeting met their objectives and expectations
60% agree the meeting helped them to understand how to interact with different committees
80% agree the meeting had an impact on the next development steps or planned interactions with regulators
93% agree the recommendations were realistic
93% agree the meeting was useful
While **40%** agreed the follow-up after the kick-off meeting was adequate, 40% neither agreed or disagreed

Based on its experience with this new type of meeting and feedback received, the Agency has now published guidance for applicants on interactions in the context of PRIME which covers the preparation and conduct of the kick-off meeting. The coordination of support across committees and expectations for follow-up interactions have also been included in this guidance, which the survey highlighted as an area that the Agency will aim to improve.

Overall, the Agency and applicants consider that the kick-off meeting to be a useful tool and valuable feature of the PRIME scheme.

Scientific advice

After the kick-off meeting, the enhanced scientific support to optimise the development programme is channelled through scientific advice by the SAWP. This procedure allows the applicant to discuss the details of the development plan, the design of pivotal studies and post-authorisation activities.

Since launch of the scheme, a total of 37 scientific advice requests have been received concerning 22 products accepted into PRIME and for which a kick-off meeting has taken place.

Scientific Advice have been requested not only on clinical but on all aspects of the development, i.e. quality, nonclinical and clinical, as well as questions related to the post-authorisation follow-up studies and registries.

As illustrated in the Table 2 below, Scientific Advice procedures for PRIME products often included input from multiple committees of the Agency (in addition to SAWP and CHMP) but also from other stakeholders such as HTAs and patients.

37 scientific advices for 22 PRIME products		
Topics covered	Quality Nonclinical Clinical, including post-authorisation activities	
EMA committees involvement	CAT: 18 PDCO: 10	COMP: 6 PRAC: 3
Multi-stakeholder involvement	Patients: 6	HTA: 7

At the request of the applicant, the Agency was also able to prioritise Scientific Advice of PRIME products. 12 procedures (32%) were finalised within the shorter 40-day timeframe (compared to the standard 70 days).

Two SMEs benefited from 100% fee reduction in view of their eligibility to PRIME.

Based on its experience, the Agency has also included in the above mentioned guidance for applicants its expectations in terms of interactions during the development up to the submission of the marketing authorisation application. This is to ensure that applicants keep EMA and Rapporteur informed on the implementation of the scientific advices received and on the progress made or hurdles encountered on the development programme.

Additional initiatives

As indicated in the document 'Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME)' setting the objectives and format of PRIME, it has been expected that engagement within the scheme would provide the possibility for greater regulatory preparedness to support scientific opinions of the Committees. It was also foreseen that EMA would facilitate collaboration and coordination of support across Committees.

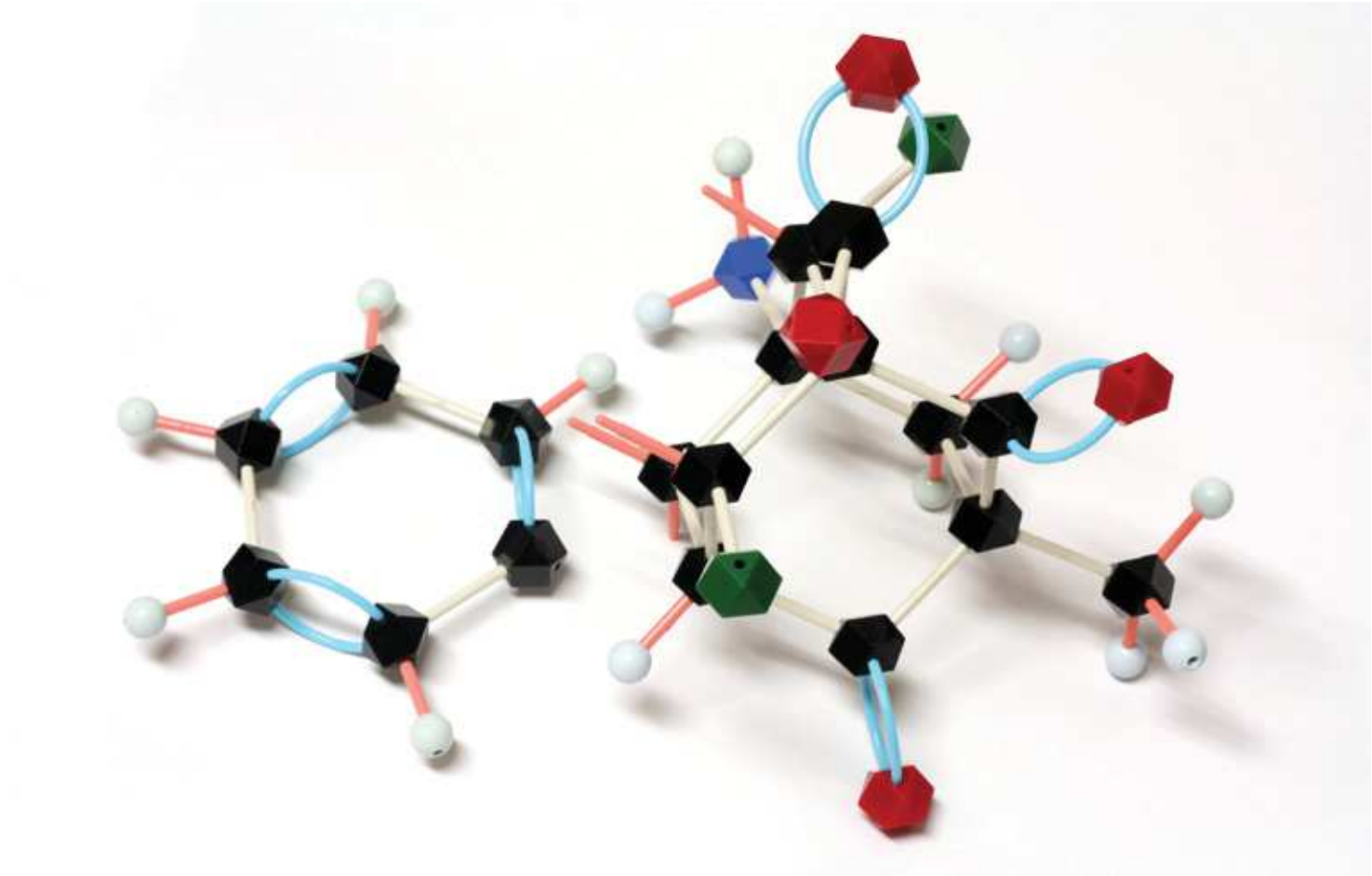
The recent Workshop on CAR T-cell therapy Registries held at the Agency on 9 February 2018 is an example where early engagement enabled to explore in detail the opportunities and challenges of using existing registries to support CAR T-cell therapy benefit-risk evaluations and post-authorisation follow up. The expected outcome of the workshop was agreement by all stakeholders on implementable recommendations.

Furthermore, as part of the confidentiality arrangements, EMA has regular exchange of information with the FDA regarding breakthrough therapy designation programme and PRIME, focusing on high level topics and comparing general experience and program implementation challenges. The objective is also to facilitate increased awareness of FDA/EMA dually designated products, stimulate early dialogue and support global development.

Conclusion

Overall, after a successful launch in 2016, the PRIME scheme continues to meet expectations in terms of performance. Experience and feedback from stakeholders has been implemented in the key supporting documents and guidance. Kick-off meetings and scientific advice procedures are considered key features of the scheme, enabling support that is not only provided by EMA and Rapporteurs but is coordinated across all of the Agency's Committees.

So far the Agency has received three marketing authorisation applications for products eligible to PRIME and these are still under evaluation. It is too early to draw conclusions on whether PRIME is meeting its objectives and thus facilitating accelerated assessment and, ultimately, timely access to patients. This will be the subject of future analyses and reporting once more applications have been received and assessed.



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