



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# PRIME: Analysis of the first 5 years' experience

---

Findings, learnings and  
recommendations



The European Medicines Agency would like to dedicate this report to the memory of Jordi Llinares Garcia who was the driving force behind the creation of PRIME and always had patients' needs at heart. The Agency is immensely grateful for his hard work, dedication and commitment to enabling patients' access to the medicines they need all along his time at EMA.

# Table of contents

<b>1. Executive summary</b>	<b>4</b>
<b>2. Introduction</b>	<b>5</b>
<b>3. Methods</b>	<b>7</b>
3.1. Surveys to obtain feedback from developers and regulators	7
<b>4. Areas of analysis and recommendations</b>	<b>9</b>
4.1. Overview of PRIME eligibility requests	9
4.2. PRIME eligibility: addressing unmet medical need	13
4.3. PRIME eligibility: stage of development at time of submission	20
4.4. Impact of PRIME on marketing authorisation applications	21
4.5. Use of regulatory interaction opportunities	32
4.6. Improving the process	40
<b>5. Overall recommendations</b>	<b>41</b>
<b>6. Conclusion and next steps</b>	<b>44</b>
<b>7. Annexes</b>	<b>46</b>

## Abbreviations used in this report

<b>AA:</b> Accelerated Assessment	<b>PA:</b> Protocol Assistance
<b>ATMP:</b> Advanced Therapy Medicinal Product	<b>PAES:</b> Post-authorisation efficacy study
<b>BT:</b> Breakthrough Therapy designation	<b>PASS:</b> Post-authorisation safety study
<b>CAT:</b> Committee for Advanced Therapies	<b>PDCO:</b> Paediatric Committee
<b>CMA:</b> Conditional Marketing Authorisation	<b>PIP:</b> Paediatric investigation plan
<b>CHMP:</b> Committee for medicinal products for human use	<b>PRAC:</b> Pharmacovigilance Risk Assessment Committee
<b>COMP:</b> Committee for Orphan Medicinal Products	<b>PRIME:</b> Priority Medicines
<b>EC:</b> European Commission	<b>PSA:</b> Parallel Scientific Advice
<b>EMA:</b> European Medicines Agency	<b>QoL:</b> Quality of life
<b>EUnetHTA:</b> European Network for Health technology Assessment	<b>RMAT:</b> Regenerative Medicine Advanced Therapy Designation
<b>FDA:</b> Food and Drug Administration	<b>RPI:</b> Research Product Identifiers
<b>HTA:</b> Health Technology Assessment	<b>RSS:</b> Regulatory Science Strategy to 2025
<b>HTABs:</b> Health Technology Assessment Bodies	<b>SA:</b> Scientific Advice
<b>ITF:</b> Innovation Task Force	<b>SAWP:</b> Scientific Advice Working Party
<b>MA:</b> Marketing authorisation	<b>SoC:</b> Standard of care
<b>MAA:</b> Marketing authorisation application	<b>SME:</b> Small and Medium Enterprise
<b>MO:</b> Major objection	<b>TC:</b> Teleconference
<b>MS:</b> Member State	<b>TT:</b> Timetable
<b>NCA:</b> National Competent Authority	<b>UMN:</b> Unmet medical Need
<b>ODD:</b> Orphan drug designation	

# 1. Executive summary

This document summarises the experience acquired during the first 5 years of operation of the EMA's PRiority MEDicines (PRIME) scheme.

**PRIME was set up in March 2016 to provide early and enhanced scientific and regulatory support to medicines that have the potential to significantly address patients' unmet medical needs.**

The scheme provides a dedicated support hub to promising medicines under development, so that developers can access the array of scientific input and regulatory support avenues available at the Agency in the most effective way. This support will ultimately help patients benefit from therapies that may significantly improve their quality of life as early as possible.

PRIME medicines represent significant progress in their therapeutic areas. They include innovative technologies such as the first CAR T-cell therapies to be authorised, one-time potentially curative gene therapies, rare cancer treatments and a vaccine for the Ebola virus.

This report follows the initial 2-year [overview](#), and analyses the PRIME eligibility requests and marketing authorisations for PRIME products in the period March 2016- June 2021, comparing them to equivalent non-PRIME submissions over the same period.

Whilst acknowledging the relatively small size of the dataset, the results of the analysis suggest that PRIME has had a positive impact in supporting marketing authorisation evaluation review, reducing overall time to marketing authorisation.

The benefits of PRIME appear more pronounced for more complex products and/or applications that rest on smaller datasets (ATMPs, orphan diseases).

In particular the analysis showed that:

- Medicines that benefitted from PRIME support and were granted marketing authorisation had a consistent reduction of the clock-stop duration (the time required by the applicant to answer

questions from EMA during the evaluation) compared to equivalent non-PRIME submissions; the reduction of the clock-stop was more pronounced for SMEs;

- Despite their complexity, the 7 advanced therapies (ATMPs) that benefitted from PRIME support and were granted marketing authorisation had on average shorter active assessment time and clock-stop duration than the average assessment time for all types of new active substances in 2020;
- PRIME products were more likely to be granted accelerated assessment and maintain it during evaluation, compared with equivalent non-PRIME submissions;
- There is a correlation between compliance with scientific advice, maintenance of accelerated assessment and a positive marketing authorisation procedure outcome, confirming the findings of previous studies.

The analysis identified areas for improvement or enhancement of the scheme, particularly the elimination of low impact activities, and the recognition that adjustment to the entry criteria and timing can be useful to optimise support to development of promising products, when accompanied by good regulatory oversight.

The recommendations made in this report centre around three main themes:

- Scope and timing of the PRIME eligibility requests;
- Considerations around the flexibility of scientific advice provision for PRIME;
- Knowledge building to support accelerated assessment.

## 2. Introduction

PRIME is a scheme launched by the European Medicines Agency (EMA) in March 2016 to enhance support for the development of promising medicines that target an unmet medical need, i.e. medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no current treatment options for their disease.

**The scheme provides early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications, so patients can benefit as early as possible from therapies that may significantly improve their quality of life.**

The scheme builds on the existing regulatory framework, which includes various tools to provide guidance on the overall development plan and regulatory strategy and to help building knowledge ahead of a marketing-authorisation application.

Once a candidate medicine has been selected for PRIME, the Agency:

- appoints a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy, to provide continuous support and help to build knowledge ahead of a marketing-authorisation application;
- organises a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts, so that they provide guidance on the overall development plan and regulatory strategy;
- assigns a dedicated contact point;
- provides scientific advice at key development milestones, to facilitate quicker access for patients to the new medicine.

Medicines eligible for PRIME are also potentially eligible for accelerated assessment at the time of application for a marketing authorisation.

To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Applicants from the academic sector and micro-, small- and medium-sized enterprises (SMEs) can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

After 5 years of operation of the PRIME scheme, an in-depth review of experience of scientific and procedural aspects was conducted as follow-up to the previous 2-year report, considering that several PRIME-designated medicinal products have reached marketing authorisation stage.

Such review was suggested in the EMA's [Regulatory Science to 2025](#) strategy in the context of the strategic goal to promote and invest in the PRIME scheme, to catalyse the integration of science and technology in medicines' development. The actions envisaged in this strategy are:

- Review the performance of the scheme after 5 years, to ensure that it delivers the expected impact on public health (i.e. faster access to patients of priority medicines), and adapt its scope and features, if applicable;
- Improve external communication to better explain and promote PRIME;
- Review the scientific advice provided in PRIME with a view to allow more flexibility in the

procedure and identify opportunities for more agile discussions;

- Optimise the current regulatory system that supports PRIME in order to enable a shortened time frame for development and MA review while ensuring high quality evidence generation plans to improve access for patients;
- Explore opportunities for further engagement and collaboration with patients, healthcare professionals, academia and international partners;
- Explore possible impact and benefits of expanding the earliest possible entry to the PRIME scheme to a wider range of applicants, including for new indications of existing products.

The [Pharmaceutical Strategy for Europe](#) advocates incorporating PRIME in the regulatory framework to provide enhanced support so as to accelerate product development and authorisation in areas of unmet needs.

The [European Parliament report](#) on the strategy *“encourages the Commission, in cooperation with the EMA, to consider how established tools such as accelerated authorisation, early dialogue, the PRIME scheme and expanded guidance can be used to make medicine available to patients at a faster pace, especially medicine that has the potential to address an urgent public health threat or an unmet medical need; calls on the Commission to further the application of the EMA’s PRIME scheme for life-saving medicines and to include a PRIME designation in the legislative framework, without affecting the safety of patients; recalls that accelerated schemes should not be misused where sufficient evidence on regular marketing authorisation is lacking.”*

The findings and recommendations of the present review together with the principles stated in the Regulatory Science Strategy and the Pharmaceutical Strategy should allow to maximise the effectiveness of the scheme and curtail activities of limited value, in order to achieve a

benefit/effort proportionate process that truly supports the development of deserving products in areas of high unmet medical need. This report draws **actionable conclusions** (either in terms of **process or scientific content improvement**) towards the design of an agile process that allows the EU medicines regulatory network to effectively support the development of promising medicines in areas of unmet medical need, by optimising development plans and facilitating evaluation so these medicines can reach patients earlier.

## 3. Methods

This report is based on data available at EMA, covering the PRIME eligibility process, pre-authorisation interactions and data provided at the time of marketing authorisation application. Additionally, developers' and regulators' views on PRIME were collected in four separate surveys.

### All data refer to the PRIME eligibility submissions in the period March 2016 - June 2021, unless stated differently.

The parameters for the analysis were pre-specified to ensure they covered key indicators of effectiveness of the scheme:

- PRIME eligibility submission metrics, including subcategories of products (ATMP, Orphan), therapeutic areas and type of applicant;
- Unmet medical need (existence and potential to be addressed by the product)
- Most frequently encountered development issues (in SA and MAA)
- Global development interactions
- Impact of the scheme on MAA assessment time and outcomes
- Interaction with downstream decision makers (HTA bodies)

Data sources included:

- Information included in the PRIME eligibility reports (positive and negative);
- Information published in the European Public assessment reports (EPAR), in CHMP monthly reports on PRIME eligibility and EMA databases;
- Information included in Scientific Advices;
- Developers' and Regulators feedback (gathered via surveys and from experience in the assessment of eligibility requests);
- Comments received during the public consultation on the [Toolbox](#) guidance on scientific elements and regulatory tools to support quality data

packages for PRIME marketing authorisation applications.

For certain areas, since the overall number of products subject to the analysis was limited, the report contains descriptive summaries of experience without analysis of statistical significance. Additional information on the medicines included in this analysis can be found in the Annexes to this report, as well as published references (e.g. EPARs).

Of note, in the design phase of the analysis, it was determined that it was not possible to reliably analyse the impact of PRIME on development times: these depend on variables such as the clinical endpoints for a given indication, the structural characteristics of the medicine, and the applicant's capability to recruit and run a trial in relation to patient numbers and treatment centers.

To afford a meaningful comparison on development duration, a larger sample of PRIME and non-PRIME products approved in the same therapeutic indication would be needed.

### 3.1. Surveys to obtain feedback from developers and regulators

In addition to the data analysis, four complementary surveys were considered collecting developers' and regulators views on the PRIME scheme<sup>1</sup>.

---

<sup>1</sup> The questions of the surveys can be found in Annex 7.2

### **EMA surveys to companies that applied to the scheme**

EMA conducted two separate surveys to companies that applied to the PRIME scheme and had eligibility confirmed and whose product was either still under development or submitted for marketing authorisation (completed or ongoing). The scope of these two surveys was to gather feedback on the support received via the PRIME scheme during development and MAA assessment. If a company had more than one eligible product, a questionnaire was sent per product.

Seven of the pre-submission responders were SMEs (19%), while none of the 15 responders to the survey on submitted MAA were SMEs.

### **EMA survey to regulators involved in PRIME products**

The scope of this survey was to gather feedback on the regulators experience on the scientific and procedural aspects relating to eligibility, development support and MAA evaluation of PRIME products.

A questionnaire was sent to 52 regulators who played a part in either assessing PRIME eligibility requests or MAAs for PRIME products. Eighteen responses were received (35% response rate). Of the 18 responders, 72% had experience as Rapporteurs of MAAs (in pre-submission phase or for products which had submitted a marketing authorisation application) and the rest had experience as reviewers of PRIME eligibility requests and development support.

### **Industry-led survey to companies on the PRIME scheme**

The scope of this survey was to capture developers' general feedback on the PRIME scheme and it was conducted via an inter-association effort, to which the following EMA-eligible industry stakeholder organisations contributed: Alliance of Regenerative Medicine (ARM), the European Federation of Pharmaceutical Industries and Associations (EFPIA), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) and European Association for Bioindustries (EuropaBio).

This industry-led survey was designed and methodologically defined to complement the EMA survey to companies, particularly to gather feedback from developers who did not have experience with the PRIME scheme, either because they never applied for it or because their applications were rejected. The survey ran between 7-30 June 2021, in parallel to the surveys launched by EMA, and a single response per company was collected via different trade associations.

The survey received 45 responses from different companies. Of the 45 responders, 10 out of 45 (22%) were SMEs and amongst the respondents, a wide variety of product development experience was represented, from small molecules, to biologics, to advanced therapeutic medical products (ATMPs). Twenty out of the 45 respondents (44%) had PRIME-designated products at the time of the survey and 25 out of 45 respondents (56%) had no products accepted in the scheme. The survey was analysed by the contributing trade associations and results were provided to EMA, for consideration.

**Table 1. EMA Surveys to companies with PRIME products**

	<b>Invited</b>	<b>Responded</b>	<b>% Responded</b>
1) pre-submission	63	37	58.7%
2) MAA submitted (completed or on-going)	24	15	62.5%
<b>Total for both questionnaires</b>	<b>87</b>	<b>52</b>	<b>59.8%</b>

## 4. Areas of analysis and recommendations

### 4.1. Overview of PRIME eligibility requests

#### Submission of requests

In the period 7 March 2016 to 30 June 2021, a total of 384 requests for PRIME eligibility were received, 372 were validated and 95 granted, corresponding to an overall acceptance rate of 25%.

The monthly average of requests was 6.1, with on average 1-2 eligibilities granted every month. While the yearly number of requests decreased after the initial influx, the acceptance rate increased.

#### Therapeutic areas

There are substantial differences in the number of products applying to PRIME across the therapeutic areas, and in their acceptance rate. Oncology

Figure 1. PRIME eligibility requests received

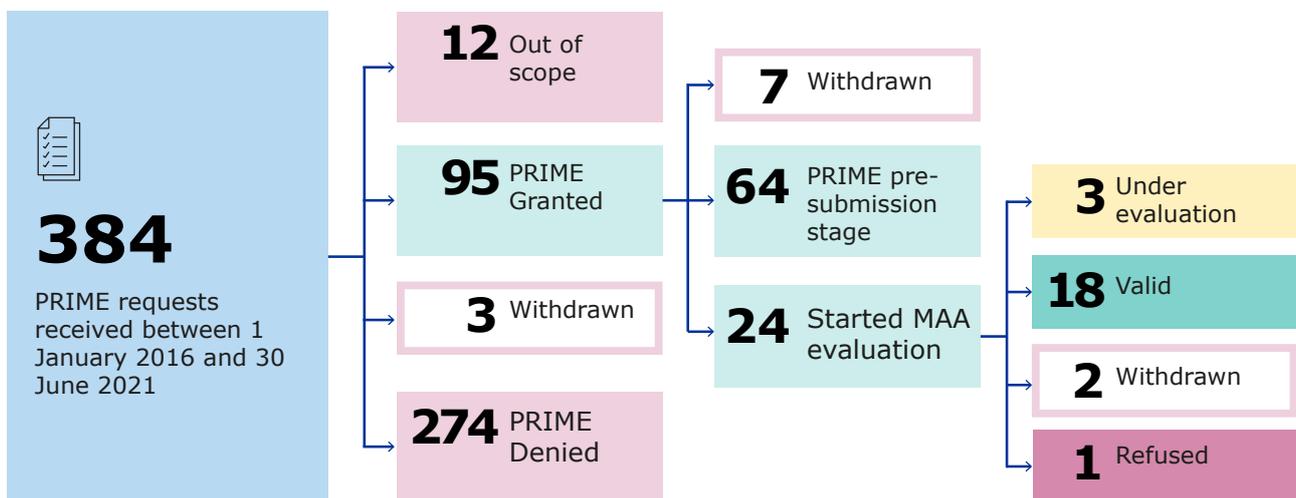
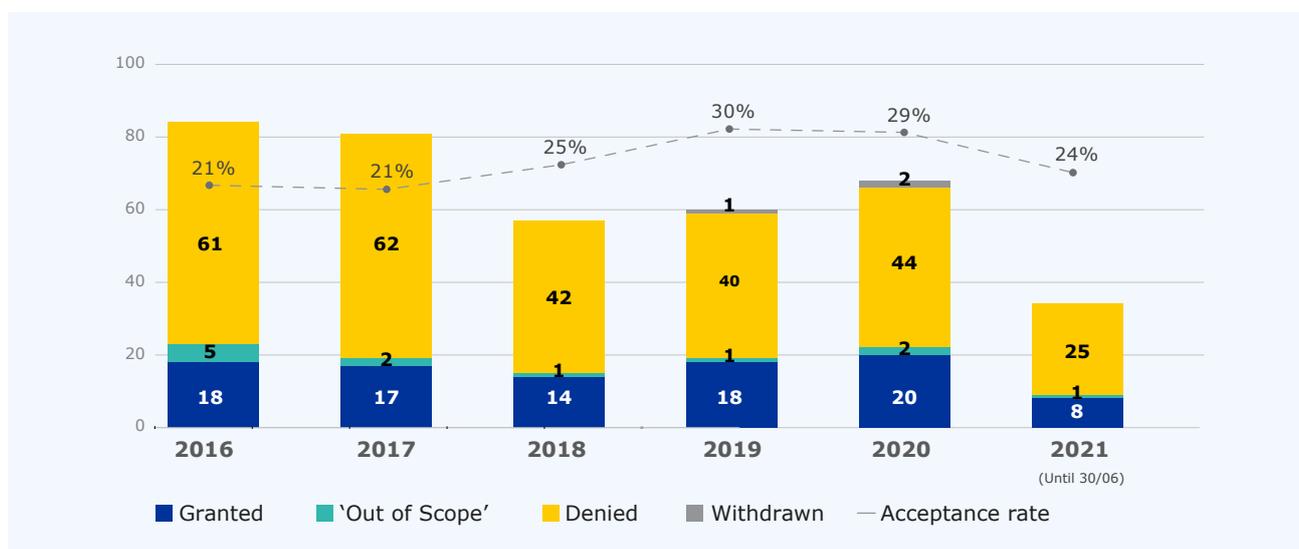


Figure 2. Outcome of PRIME eligibility request

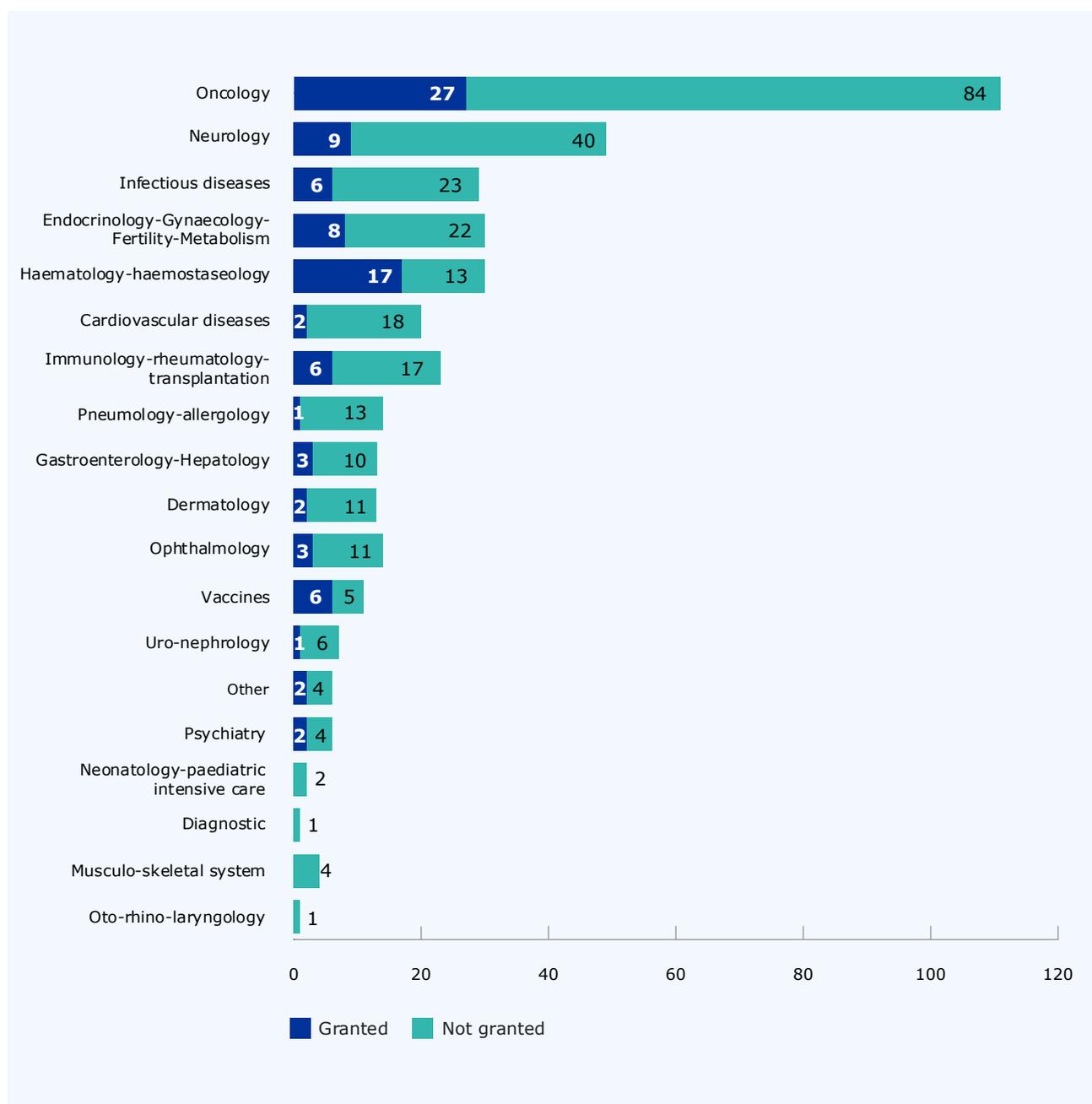


products constituted the vast majority of applications (29%).

The overall success rate of applications for PRIME eligibility is 25%. The success rate across the therapeutic areas mostly ranges between 20 and 30%, with the exception of vaccines (55% success

rate over 11 submissions). Haematology is also an outlier as 57% of the 30 applications were successful. For these two areas, a combination of factors might account for the difference, such as presenting a very strong mechanism of action; showing decidedly high response rates in the initial clinical tests, in some cases supporting a potential

**Figure 3. Outcome of PRIME eligibility requests per therapeutic area**



curative effect, and the feasibility to identify clinical laboratory test to support early stage proof of concept.

### ATMPs

Although ATMPs account for approximately 27% of the requests received for PRIME eligibility, they present the highest success rate (corresponding to 46% of all PRIME products). This is because the submitted requests generally combined a high potential to address an unmet medical need with a usually very specific mechanism of action and strong demonstration of proof of concept.

### Orphan designated medicines

Although orphan designated products account for ~42% of PRIME eligibility requests, the majority

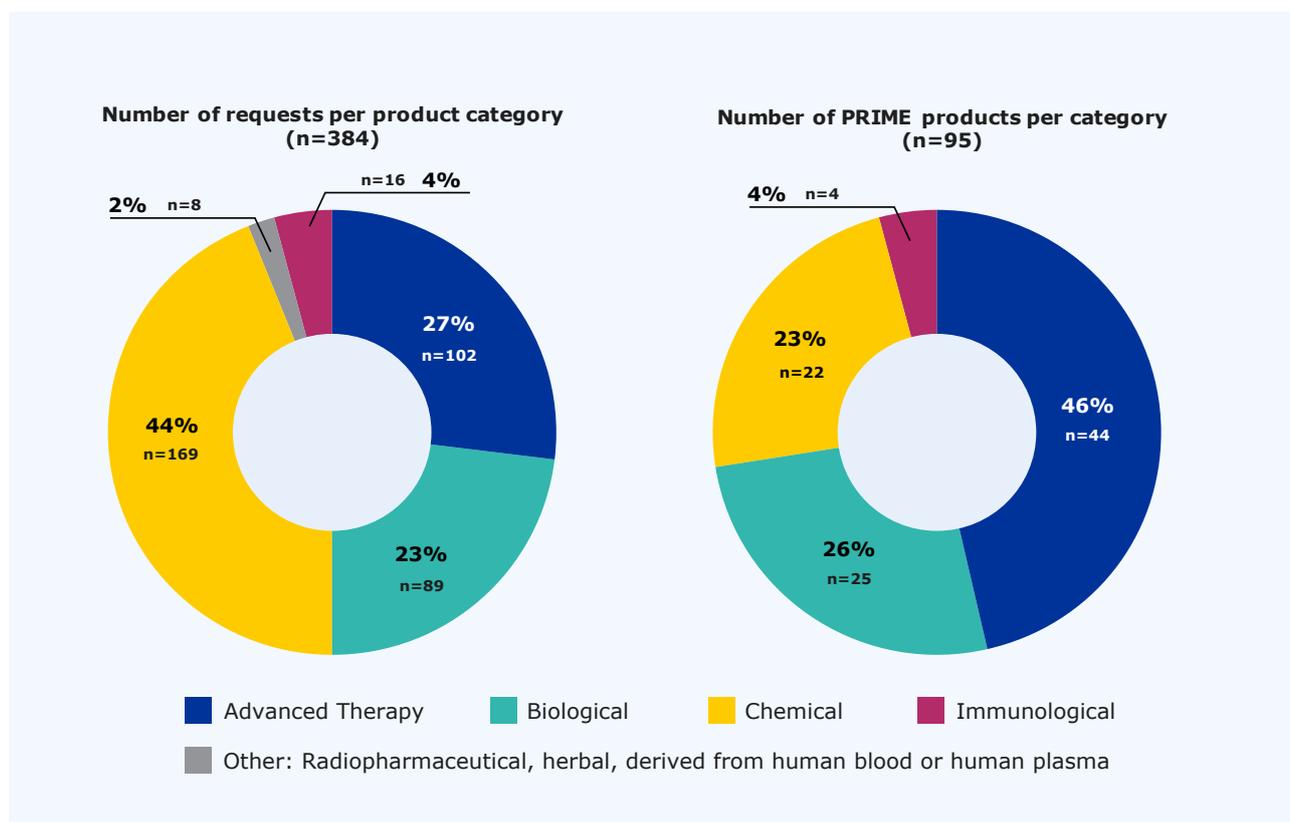
(56%) of PRIME products granted eligibility had an orphan designation. The fact that orphan designation appears to increase the probability to be granted PRIME is likely to reflect the fact that addressing unmet medical needs is one of the criteria for PRIME eligibility.

### Type of applicant

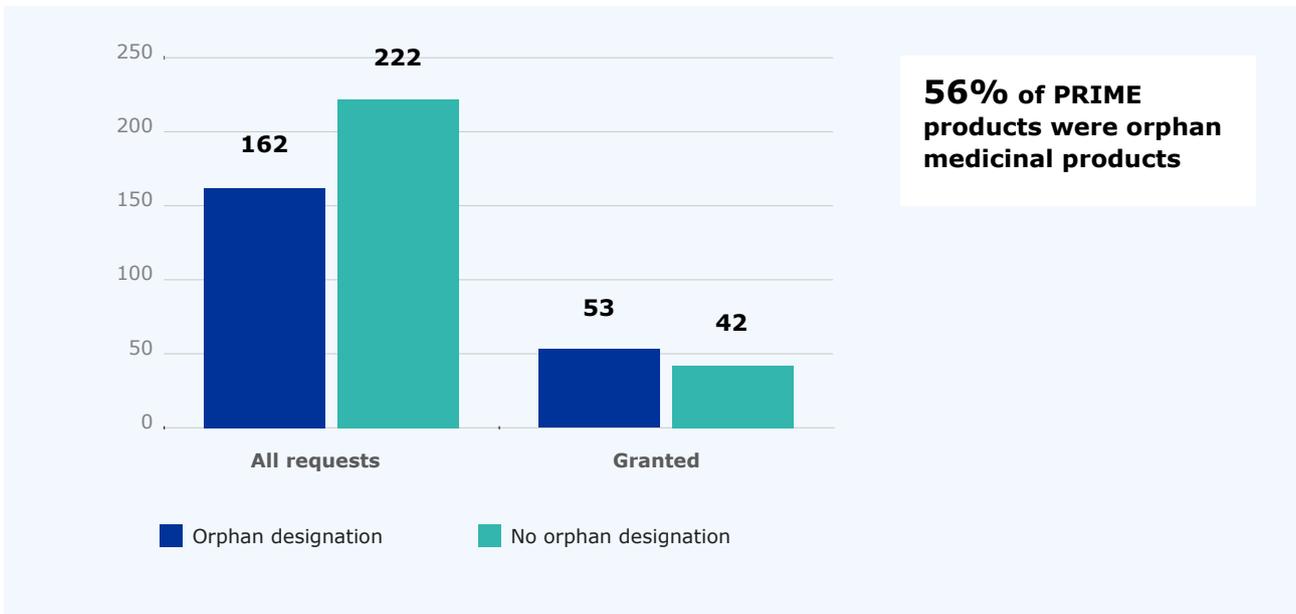
The majority of the eligibility requests were from SMEs (207/384; 54%), and only five academic applicants approached EMA for eligibility to PRIME scheme (1% of requests).

The success rate of PRIME eligibility applications by SMEs is 19%, versus 33% for non-SMEs. Only a limited number (18 out of 384) of these applications concerned a PRIME early entry (i.e. earlier in the medicine development, based on

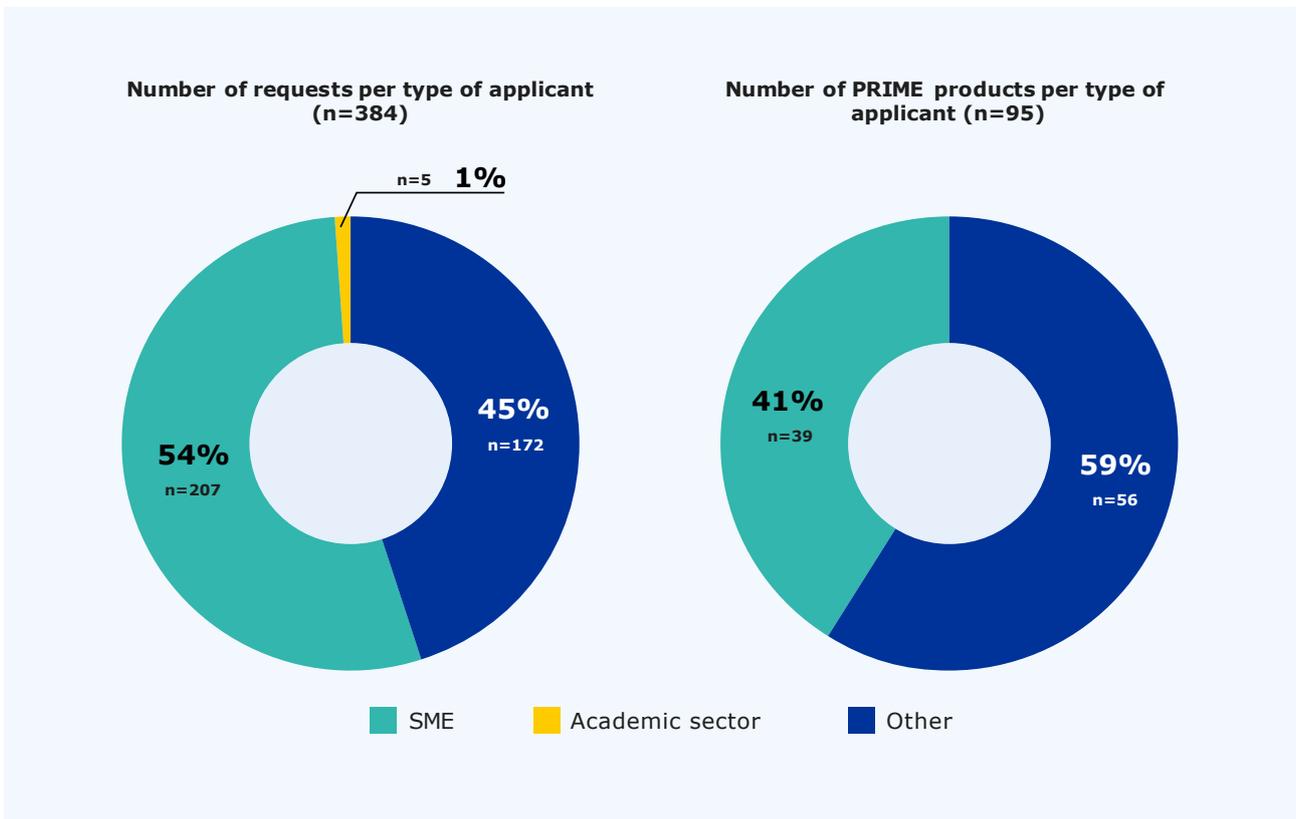
Figure 4. Product category



**Figure 5. Orphan designation: outcome of PRIME eligibility requests for orphan and non-orphan medical products**



**Figure 6. Outcome of designation requests per type of applicant**



non-clinical data and tolerability data from initial clinical), which is a route available only to SMEs and Academia and which was successful in 4 cases, highlighting the difficulty to provide a convincing proof of principle at this development stage.

The availability of a larger product portfolio for the selection of possible successful candidates, and capacity and preparedness for the application process may potentially be contributing factors for the higher success rate of non-SME companies in receiving PRIME eligibility.

None of the five Academic applicants eventually obtained a PRIME eligibility: one was out of scope and in the other cases the potential to significantly address an unmet medical need was not considered sufficiently demonstrated. They all had limited clinical data and two of them also had non-compelling nonclinical data. The low number of applications may reflect a lack of knowledge of the scheme and the regulatory/scientific challenge faced by smaller applicants in developing medicinal products.

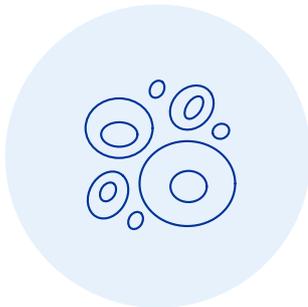
## 4.2. PRIME eligibility: addressing unmet medical need

Supporting the development of medicines that show a promise to address an unmet medical need (UMN) is the core reason of existence of the PRIME scheme.

### **Findings**

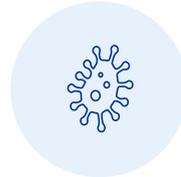
PRIME is granted if the applicant provides convincing arguments in their submission with regards to the existence of UMN in the condition under consideration, and of the potential of the medicine to address it. A wide array of unmet medical need areas is covered by the 95 eligible PRIME products, as illustrated in the figure below, including the stage of the PRIME products (in development/pre-submission or MA granted).

**Figure 7. PRIME: area of unmet medical need**



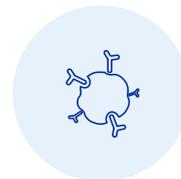
### Oncology

- Multiple myeloma
- Diffuse large B-cell lymphoma
- B-cell acute lymphoblastic leukaemia
- Mantel cell lymphoma
- Locally advanced or metastatic solid tumour
- Primary mediastinal large B-cell lymphoma
- Metastatic synovial sarcoma
- Glioblastoma
- Rituximab refractory post-transplant lymphoproliferative disorder
- Hodgkin lymphoma
- Myelodysplastic syndromes
- Sezary syndrome
- Urgent allogeneic haematopoietic stem cell transplantations



### Infectious diseases

- Hepatitis D virus infection
- Septic shock
- Respiratory syncytial virus
- BK virus, cytomegalovirus, human herpes virus-6, Epstein Barr virus, and/or adenovirus in allogeneic HSCT recipients



### Immunology/Rheumatology/Transplantation

- Prevention of graft rejection following solid organ transplantation
- X-linked severe combined immunodeficiency
- Dermatomyositis
- Leukocyte Adhesion Deficiency-I



### Endocrinology/Gynaecology/Fertility/Metabolism

- Acute hepatic porphyria
- Obesity and control hunger caused by genetics
- Primary hyperoxaluria type 1
- Mucopolysaccharidosis
- Acid sphingomyelinase deficiency
- X-linked myotubular myopathy
- Thymidine kinase 2 deficiency
- Type 1 diabetes
- C3 glomerulopathy



### Ophthalmology

- X-linked Retinitis Pigmentosa owing to defects in Retinitis Pigmentosa GTPase Regulator
- Achromatopsia associated with defects in CNGB3
- Leber's congenital amaurosis due to the p.Cys998X mutation in the CEP290 Gene



### Haematology/Hemostaseology

- Transfusion-dependant B-thalassemia
- Haemophilia B
- Sickle cell disease
- Epstein-Bar Virus-associated Post Transplant Lymphoproliferative Disorder
- Haemophilia A
- Paroxysmal nocturnal haemoglobinuria
- Fanconi anaemia Type A
- Myelofibrosis



### Gastroenterology/Hepatology

- Progressive familial intrahepatic cholestasis
- Non-alcoholic steatohepatitis
- Primary biliary cholangitis



### Cardiovascular Diseases

- Reversal of antiplatelet effects of ticagrelor in patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure
- Pulmonary arterial hypertension



### Neurology

- Spinal muscular atrophy
- Early cerebral adrenoleukodystrophy
- Huntington's disease
- Variant late infantile neuronal ceroid lipofuscinosis 6
- Friedreich's ataxia



### Dermatology

- Dystrophic Epidermolysis Bullosa
- X-linked hypohidrotic ectodermal dysplasia



### Vaccines

- Ebola
- Chikungunya
- Tuberculosis
- Zika virus
- Lower respiratory tract disease (LRTD) caused by RSV



### Pneumology/Allergology

- Non-cystic fibrosis bronchiectasis



### Psychiatry

- Postpartum depression



### Other

- Osteogenesis imperfecta types I, III and IV

The **existence of unmet medical need** relates to the **condition** under consideration. The assessment is made based on the applicant's justification that there exists no satisfactory method of diagnosis or prevention, or existing treatments present limitations.

Generally, the existence of UMN was found to be well substantiated in the PRIME applications received, and only exceptionally it has been the reason for denying PRIME eligibility.

The analysis has nevertheless evidenced, from feedback from applicants and eligibility reviewers, that a description of the criteria considered for the assessment, and on the process followed, would be desirable. Such overview is presented in the discussion section of this chapter.

The **potential to significantly address the unmet medical need** relates to the **medicine** submitted for PRIME eligibility. The assessment considers the information presented in the context of available authorised treatments (including whether the medicine could be of major public health interest), taking also into account the type of applicant (in case of early PRIME application). Furthermore, the stage of development is considered versus the expected benefits of PRIME: if PRIME eligibility is granted once the pivotal trials design has been finalised, there is less potential for regulators to facilitate development and access, unless specific development support needs exist.

A decision on granting or denying PRIME eligibility is taken on this basis.

Given that the existence of unmet medical need was found to be questioned only rarely in the submitted PRIME proposals, a PRIME eligibility outcome rests mostly on the potential of the medicine to address the unmet medical need.

For the products that were granted PRIME eligibility, the survey to regulators indicated a high level of consensus that the right products have

been selected in the scheme, in terms of the potential to address unmet medical need.

For the products that were rejected, the analysis showed that there are several possible reasons:

- the data available to support the medicine's effect (plausibility, robustness, magnitude);
- the amount and relevance of data presented;
- the timing of the submission (too early, and therefore with insufficient data; or too late for regulatory support to make a difference to the design of the clinical development).

The industry-led survey noted that the clarity of the grounds for refusal of eligibility to PRIME could be improved. Of the 12 companies that responded to this question, five (41%) rated the grounds for refusal 1 or 2 on a 5-point scale, while five (41%) found them sufficiently clear (with a score of 4 or 5). A suggestion made in this survey was to organise a post-refusal meeting to clarify the grounds for the outcome, if required.

The survey with regulators also noted that in the current framework the determination of what constitutes an unmet medical need is solely based in the context of a specific product for which eligibility is requested. Applications to PRIME are encouraged in underserved therapeutic areas where an unmet medical need exists.

### ***Existence of unmet medical need: discussion and recommendations***

The first step of a PRIME application is the justification of existence of unmet medical need in the condition.

The survey conducted by industry organisations indicated the desirability of clarification on the approach taken by EMA when considering the arguments presented by an applicant in support of the existence of unmet medical need. A decision tree can be found below and should be considered by applicants when presenting their arguments.

It will inform a revised consolidated PRIME application guidance to be developed after publication of this report.

### **Potential to significantly address the unmet medical need – discussion and recommendations**

An analysis of the PRIME eligibility requests was carried out to identify deficiencies in the substance or presentation of the applicant's arguments to support the claim that their medicine address an unmet medical need.

There seems to be a need to support applicants towards an effective presentation of their findings to facilitate review of the appropriateness of a PRIME application, and the best way to present their available scientific arguments in a clear and convincing way. In the next section of this report, we summarise the thinking process behind the assessment of an eligibility request by EMA concerning the promise to address the unmet medical need, so that applicants can present their data more effectively.

As the aim of PRIME is to offer support to the development of promising products that address UMN to a relevant extent, it is also important to explain and justify in which way additional scientific and regulatory support will help to shape future development plans.

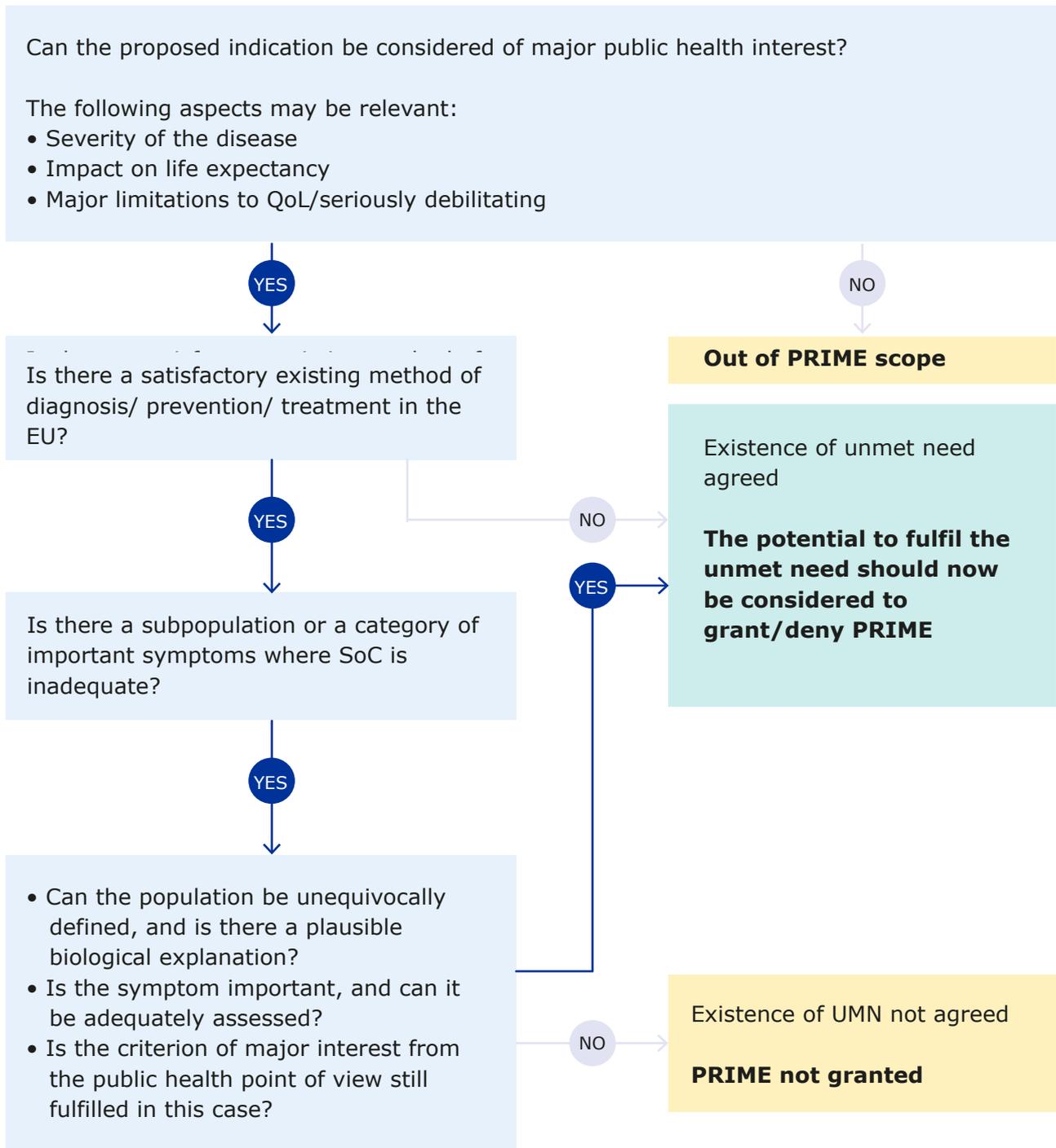
Clearly presented scientific and regulatory support arguments will help regulators in reaching a conclusion on whether the product shows a promise to address an unmet medical need, and whether regulatory network resources should be invested in supporting its development

This below also intends to assist applicants in interpreting at a deeper level the comments they receive in the case of refusal of PRIME eligibility, by putting the EMA feedback in the context of the approach taken for the assessment of PRIME eligibility requests.

The steps below outline the approach to be taken for the submission of a PRIME eligibility application. This description no longer includes an early entry route (the reasons for proposing a more flexible timepoint of access to PRIME are discussed in section 5.6).

These concepts will also inform a revised consolidated PRIME application guidance to be developed after publication of this report.

**Figure 8. Decision tree**



## **Considerations to applicants for the preparation of an application**

### *First step: consideration of available nonclinical data*

The strength of arguments and data from nonclinical studies could in theory, if sufficiently convincing, be acceptable to grant PRIME. In practice, this is generally difficult, as few animal models with good predictability of efficacy in humans exist.

The submission of clinical evidence, even early and preliminary in nature, is desirable and welcome to strengthen the nonclinical arguments. It is preferable to submit in the PRIME application any clinical data that could support the preclinical conclusions, even if they lack statistical conclusiveness and are of a preliminary nature.

The first aspects EMA will consider are whether the following **nonclinical aspects** are convincing:

- Relevance of the chosen model and setting
- Plausibility/specificity of effect based on the mechanism of action
- Magnitude/consistency/duration/relevance of observed pharmacodynamic effects
- Early safety signals and exposure indicators (nonclinical, and first-in-human data, if available)
- Clear presentation of analyses

If the answer to the above is no, i.e. a convincing nonclinical argument is unfeasible or limited (as it may, for example, be the case for some ATMPs), then the presence of **clinical data** will be considered:

- Are there clinical data that **override** the lack/ limitations of nonclinical arguments?
- Are the additional presented clinical data sufficiently relevant and informative?

A positive answer to the above points is expected before granting PRIME.

For medicines granted PRIME eligibility, a kick-off meeting could then take place once the applicant signals that they are ready to present and receive input on the full development package. This is likely to be around the time of the end of phase 2 clinical studies.

### *Second step: consideration of available clinical data*

If at the time of PRIME eligibility submission, the applicant possesses compelling clinical data, the totality of the presented nonclinical and clinical arguments will be considered to assess the potential to address the unmet medical need. The following scientific and clinical arguments would be considered:

- Magnitude and duration of observed clinical effect(s)
- If intermediate endpoints or surrogate markers are used: relevance to clinical outcomes
- Relevance of the preliminary clinical findings to further clinical outcomes (e.g.

morbidity; mortality; progression; major safety advance; major posology or administration advantage)

- Expected major **therapeutic advantage** over existing methods, including limitations, risks and benefits of existing treatments

The industry survey finding that the time window to apply for PRIME is limited, and impacts global development plans, is also recognised. This might result in diminishing the impact of PRIME support in shaping the development both in terms of study design and acceleration. There are temporal considerations in evaluating the effectiveness of the additional support that the CHMP/EMA could provide at this stage:

- Is the **development at an advanced stage?** (i.e. advice on phase 3 study already given, phase 3 study ongoing)
- Would there be **benefit** in providing development support at this **late stage?** (e.g. post authorisation study design; registries, study relevance for access and reimbursement)? The **applicant should justify** whether the CHMP input would result in a meaningful assistance to the design of these studies.

As PRIME is a development support tool, and not a mere recognition of the potential therapeutic importance of a product, the above considerations are paramount to devote the available resources into shaping the development of products which would benefit from EMA input. It does not seem effective to invest resources on products whose development program is already designed and finalised.

EMA wants to proactively support development of products in underserved indications, as shown by agency-led or EU research support initiatives in the areas of antimicrobial resistance and neurodegenerative disorders. While for specific PRIME applications the area of UMN and its justification remain in the hands of companies that decide to apply, regulators can play a proactive role, by designing initiatives in specific therapeutic areas and encouraging to apply for PRIME when promising products submit a SA or PIP request. PRIME eligibility could also be useful for SMEs and academic applicants in furthering the clinical development, facilitating clinical trial approval and forging partnerships.

### 4.3. PRIME eligibility: stage of development at time of submission

The two currently possible routes for a PRIME eligibility depend on applicant type and application content. SMEs and academic applicants can receive an “early entry” PRIME on the basis of compelling nonclinical data and tolerability data (proof of principle), while access to PRIME based on preliminary clinical evidence (proof of concept) is possible for all developers.

#### **PRIME early entry**

The analysis found that very few applications for early entry were made (18, ~ 5% of all requests) in the first 5 years of the operation of the PRIME support scheme. Of these 18, four were granted PRIME early entry status. All these requests originated from SMEs, none from academic applicants.

Feedback in the EMA survey to applicants indicates that considerable work is required to prepare an application of sufficient quality for a successful eligibility outcome. Additionally, analyses of the early entry requests showed that it is often hard to gather evidence of sufficient quality to support ‘early entry’ access to PRIME (i.e., no suitable animal models, insufficient predictability of NC data for clinical efficacy). In several instances, the provided literature references were considered generic and not relevant to support the potential of the specific medicine to address an unmet medical need.

#### **PRIME standard entry**

This route constitutes the vast majority of PRIME applications (95%) and is based on a promising clinical proof of concept, based also on (early) clinical data.

Consequently, the focus on the development support is primarily on clinical aspects and potentially quality elements. The non-clinical

development is generally well-advanced by the time of full PRIME eligibility application.

Considering feedback from the industry-led survey the window of opportunity to apply for PRIME eligibility is narrow, estimated to be between 6 and 9 months in the drug development lifecycle. This is due to the need to have sufficient supportive clinical data for the PRIME applications available and that the pivotal clinical plans are at sufficiently early stages to benefit from additional regulatory support. In the industry survey, the highest scoring reason (40% of responses) for not applying to PRIME was that the product was too late in the development process.

Global development plans were often found to be already outlined by the time Phase 2 data were available for PRIME application. In about half of the cases the requests for eligibility are made to EMA and FDA around the same time, and this reduces the scope for global alignment. ATMPs face additional challenges in terms of definition of clinical trial material, specifications and inspection readiness.

The feedback from the survey conducted by industry organisations advocated the possibility for earlier PRIME eligibility for all companies (not only SMEs), and extending granting PRIME to important post-authorisation additional indications (extension of indication).

#### **Late applications**

When the development plans were already finalised, or with the Phase 3 studies already ongoing, the application was likely to result in denial of PRIME eligibility, unless there was a clear justification of benefit from the provision of additional support. The reason for the denials at a late stage of application was that EMA concluded that its input on the development plan would have no or limited impact in these cases. PRIME was granted to late applications in the cases where the

applicant presented convincing arguments on the fact that enhanced regulatory support would be needed for effective development progression.

The responses from the EMA regulators' survey also underlined that PRIME products at late stage of development have been accepted when a convincing justification of the expected support was presented, including detailing on which type of planned studies the support could have an impact.

### **Discussion and recommendations**

The early entry route is minimally used. The difficulty to provide a convincing proof of concept at this stage is recognised, as, for example, for many indications only few animal models with good predictability exist. On the other hand, potentially valuable products for which early support could be important are excluded from this route by the nature of the eligible applicants (non-SME companies). This should be recognised, and flexibility on the best timepoint for access should be considered if the product is promising and the need for support justified, independently from the category of company. The opportunity to achieve convergence in multistakeholder interaction and parallel advices (FDA, HTA) will also be enhanced by this increased flexibility.

Concerning late applications, the limited conditions under which late applications could be considered should also be clarified.

Taken together, these considerations form the basis of proposed adjustments procedure which are discussed further in the document (section 5.6, improving the process).

## **4.4. Impact of PRIME on MAA**

### **Overview**

The first Marketing authorisation applications for PRIME products were submitted to EMA in 2017, a year after the start of the scheme, when the development of the first eligible products was completed. Therefore the analysis of marketing authorisations for PRIME products encompasses the

applications that received a CHMP opinion or were withdrawn in the period between 1 January 2018 and 30 June 2021.

In the study period, 24 PRIME products were submitted for marketing authorisation<sup>1</sup>, of which 21 concluded the MAA procedure (18 positive opinions, 1 negative opinion and 2 withdrawn). Three applications<sup>2</sup> were still undergoing assessment at the data closure point.

Patients were involved in the MAA evaluations through 12 consultations organised during SAGs or Scientific Committees and 31 reviews of the draft medicine overview, package leaflet or safety communications concerning the marketing authorisation.

To investigate the effect of PRIME support on MAA conduct and outcomes, non-PRIME products granted accelerated assessment were used as the most relevant comparator group, as they are likely to present similar characteristics in terms of bringing a major public health impact.

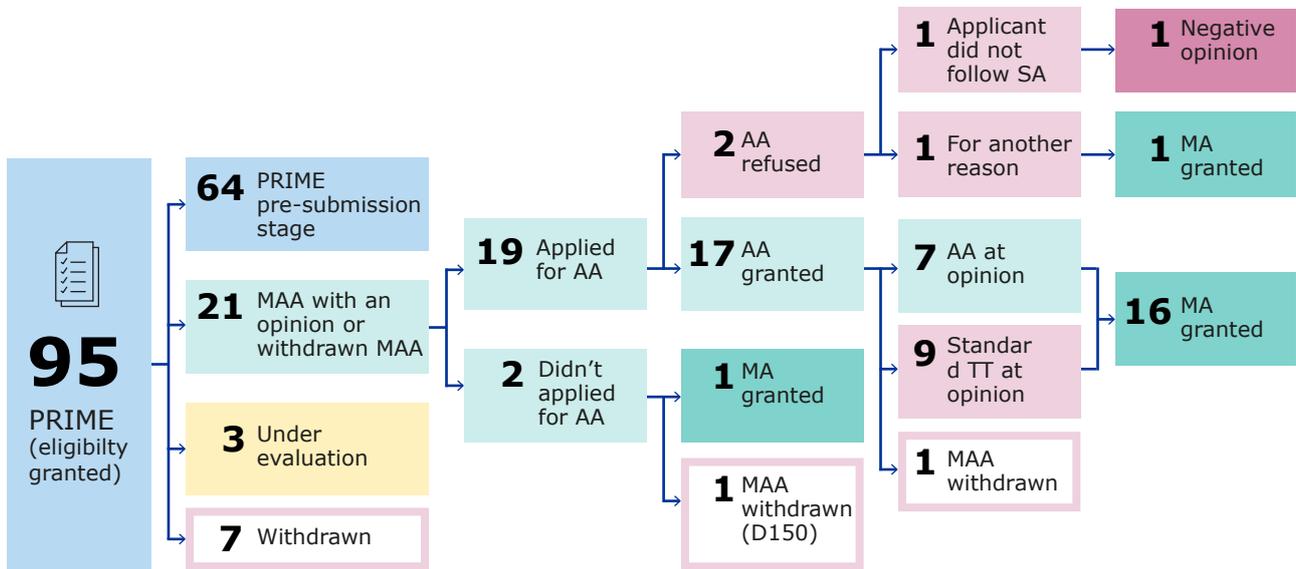
Of the 21 PRIME products that concluded an MAA procedure, 17 started under accelerated assessment (AA) and 16 of these received a positive opinion from the CHMP. The other four PRIME products were evaluated under a regular timetable; two of these had not applied for accelerated assessment.

Over the same period, 23 non-PRIME products<sup>3</sup> started evaluation under Accelerated assessment and received a CHMP opinion; 22 products received a positive CHMP opinion and one received a negative CHMP opinion.

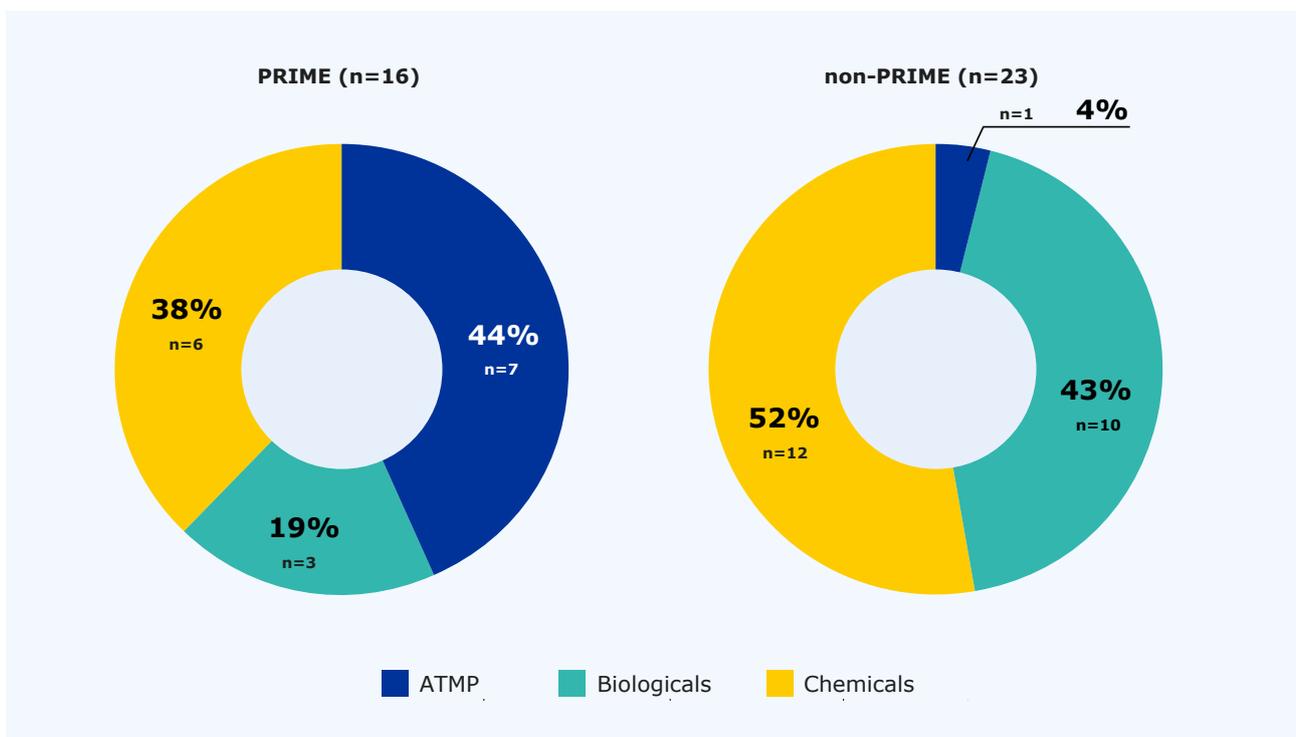
---

1 Abecma, Blenrep, Breyanzi, Bylvay, Carvykti, Ervebo, Evryssi, Gamifant, Givlaari, Hepcludex, Idefirix, Imcivree, Kymriah, Oxbryta, Oxlumo, Polivy, Roctavian, Rozlytrek, Skysona, Tecartus, Vynpenta, Yescarta, Zolgensma, Zynteglo  
2 Breyanzi, Carvykti, Oxbryta  
3 Amglicia, Elzonris, Enhertu, Enspryng, Evkeeza, Fetcroja, Fexinidazole Winthrop, Hemlibra, Jemperli, Kaftrio, Libmeldy, Mvabea, Nexpovio, Onpattro, Rukobia, Takhzyro, Tegsedi, Trogarzo, Vanflyta, Vitrakvi, Vyxeos, Xospata, Zabdeno

**Figure 9. Overview of eligible PRIME products and MAA status**



**Figure 10. Category of products which started MAA under AA with a CHMP opinion - PRIME vs non-PRIME**



As these numbers are relatively small, the considerations on the MAA conduct and outcome are mostly of a qualitative nature.

The PRIME products under Accelerated assessment had a higher degree of structural complexity than the non-PRIME.

Seven out of 16 PRIME products (44%) were ATMPs while only 1 non-PRIME ATMP (4%) started evaluation under accelerated assessment. Fifteen out of the 16 PRIME products (94%) were orphans vs 11 out of 23 non-PRIME products (48%).

The impact of PRIME on two specific MAA aspects, accelerated assessment and major objections raised during the MAA assessment is discussed below.

#### 4.4.1. Accelerated assessment

##### Findings

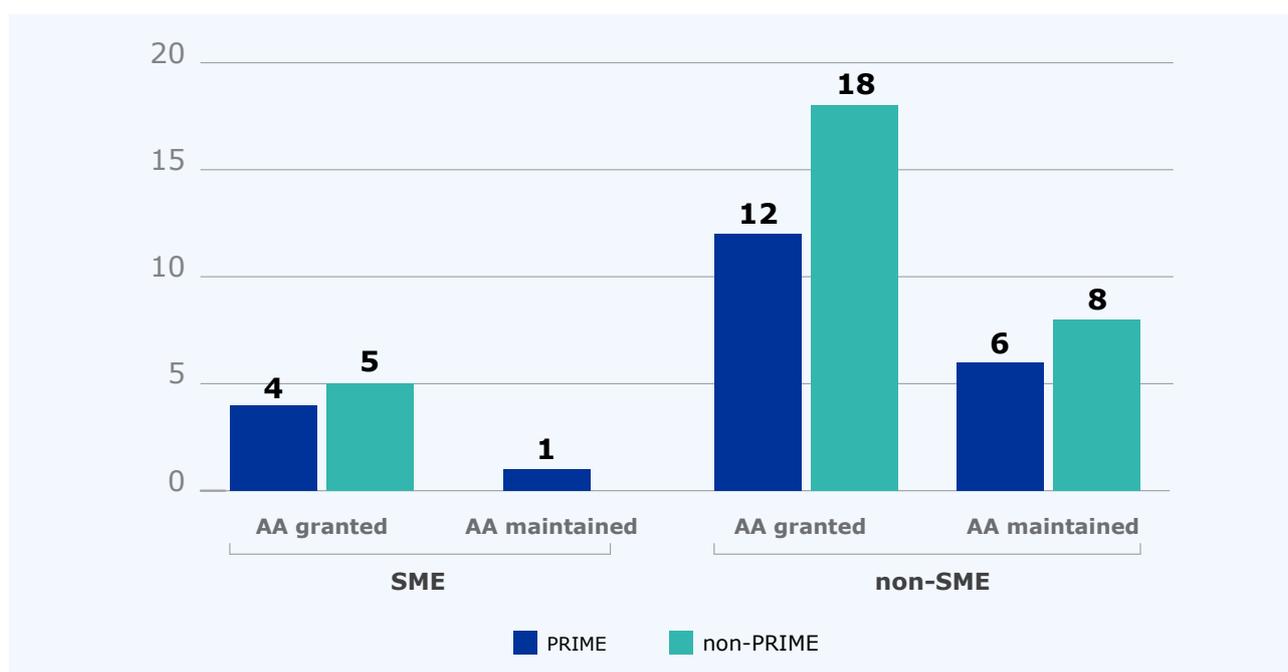
To investigate the effect of PRIME support on MAA conduct and outcomes, the 23 non-PRIME products granted accelerated assessment, which received an opinion between 1 January 2018 and 30 June

2021, were compared with the 16 PRIME products that started their evaluation under accelerated assessment and received a CHMP opinion in this time period.

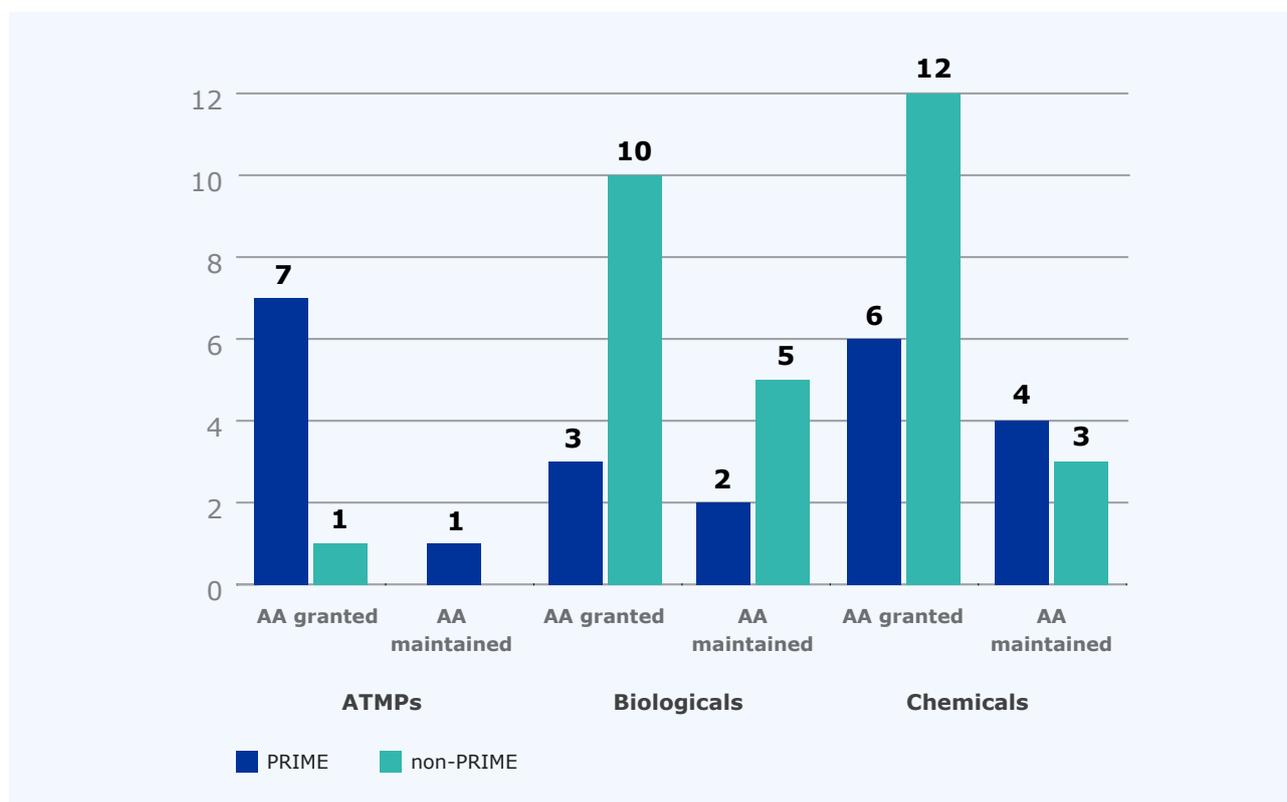
Over the study period, 24 MAAs were submitted for PRIME products, of which 19 received a CHMP opinion (18 positive and one negative) and two applications were withdrawn. Three PRIME applications were still undergoing evaluation at the cut-off date of 30 June 2021. Nineteen of the finalised 21 applications had initially requested an accelerated assessment timetable, which was granted in 17 cases. The reasons for not granting accelerated assessment to the two products were in one case the company not following the Scientific Advice, and in the other the inclusion of an additional non-PRIME therapeutic indication, which impacted acceptance for accelerated assessment.

Of the 17 PRIME applications granted accelerated assessment, 16 received a CHMP opinion (one application was withdrawn) compared to the 23 non-PRIME products which started also under AA in this time period and received a CHMP opinion in this time period.

**Figure 11. Accelerated assessment per type of applicant for PRIME and non-PRIME products**



**Figure 12. Accelerated assessment per category of products for PRIME and non-PRIME products**



For the MAAs applied for over the study period that started under accelerated assessment, the proportion of SME applicants was similar between the PRIME and non-PRIME products (25% vs 22%). Seven PRIME products and eight non-PRIME products maintained the AA timetable throughout the assessment.

The majority of products starting under an accelerated assessment timetable, reverted to a normal timetable, which can be seen as a general area for future improvement of this process. However, whilst acknowledging the overall small sample size, it was found that PRIME products were slightly more likely (7/16) to maintain accelerated assessment than non-PRIME products (8/23). Furthermore, the only SME and ATMP products that maintained accelerated assessment until opinion were both PRIME.

Given the complexity of ATMPs, the overall duration of the evaluation is considered a more relevant

indicator of effectiveness of PRIME support than simply considering maintenance of accelerated assessment until opinion. The 7 PRIME ATMP products had an average active evaluation time of 185 days and 125 days of clock-stop. Both the active time and the clock-stop duration are lower than the average assessment duration for all types of new active substances in 2020 (193 days of active time and 140 days of clock-stop).

A reduction of clock-stop and overall assessment time was observed across all subgroups, with an average (across all product/company types) of 49-day (35%) reduction of the clock-stop duration for PRIME products compared to non-PRIME products. The reduction of the clock-stop was more significant for SMEs with a 201-day (67%) decrease of the clock stop for PRIME products when compared to non-PRIME products (97 days vs 298 days) while for non-SME a reduction of clock stop of 10 % (89 vs 99 days) was observed between PRIME and non-PRIME.

Overall, there was no difference in the duration of the active assessment time for PRIME and non-PRIME products which started their evaluation under accelerated assessment (166 days), however these timelines are procedurally guided, and were, as expected, shorter than the average duration of the active time for new active substances in 2020 (193 days active time).

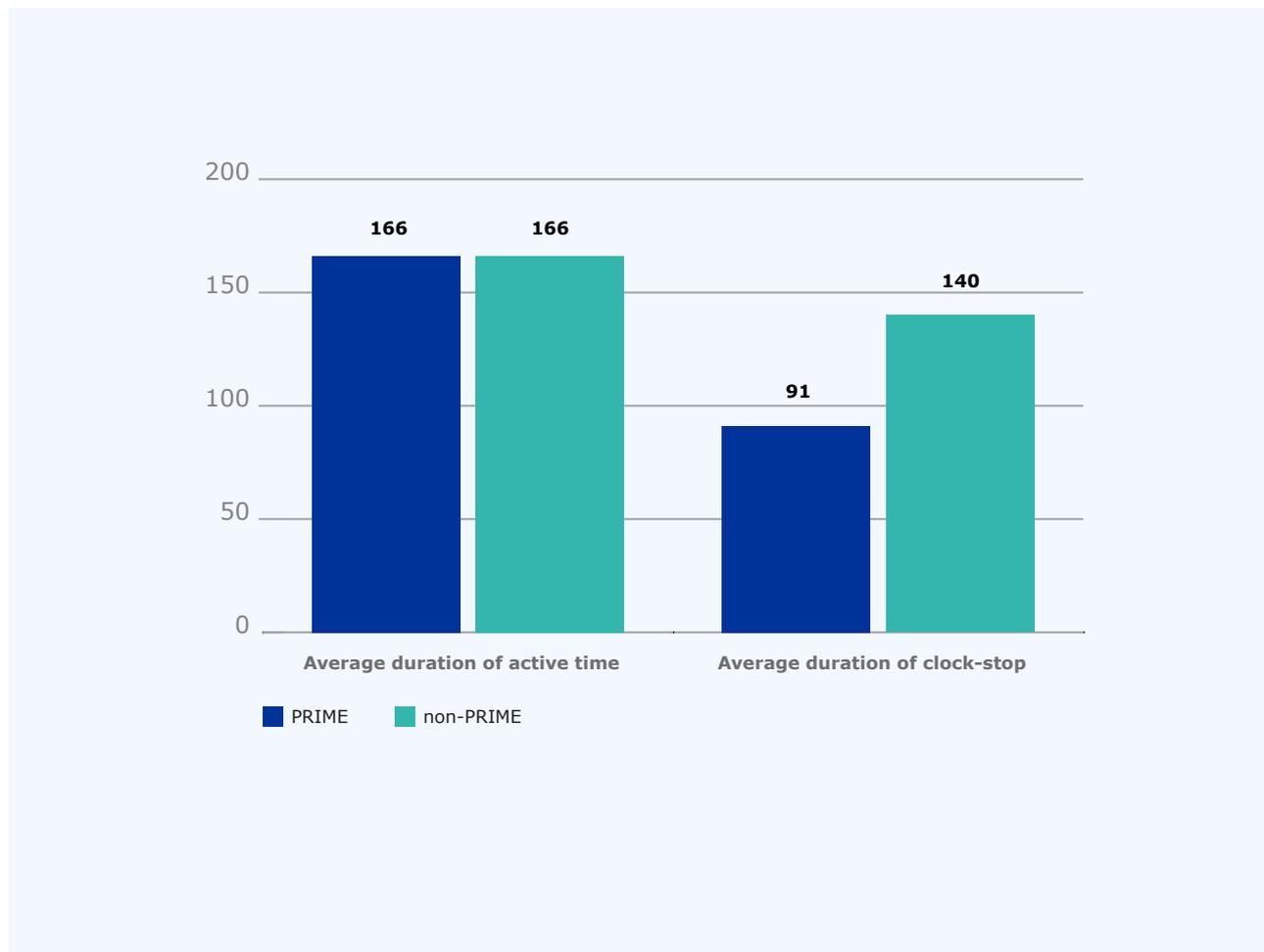
In terms of type of products, for biological medicinal products, a 61-day decrease of the clock stop and a 9-day reduction of the active time was observed for PRIME products compared to non-PRIME products and for chemical medicinal products a 90-day decrease of the clock stop and a

21-day reduction of the active time was observed. No comparison of evaluation times was performed for ATMPs, as only one non-PRIME ATMP started its evaluation under accelerated assessment.

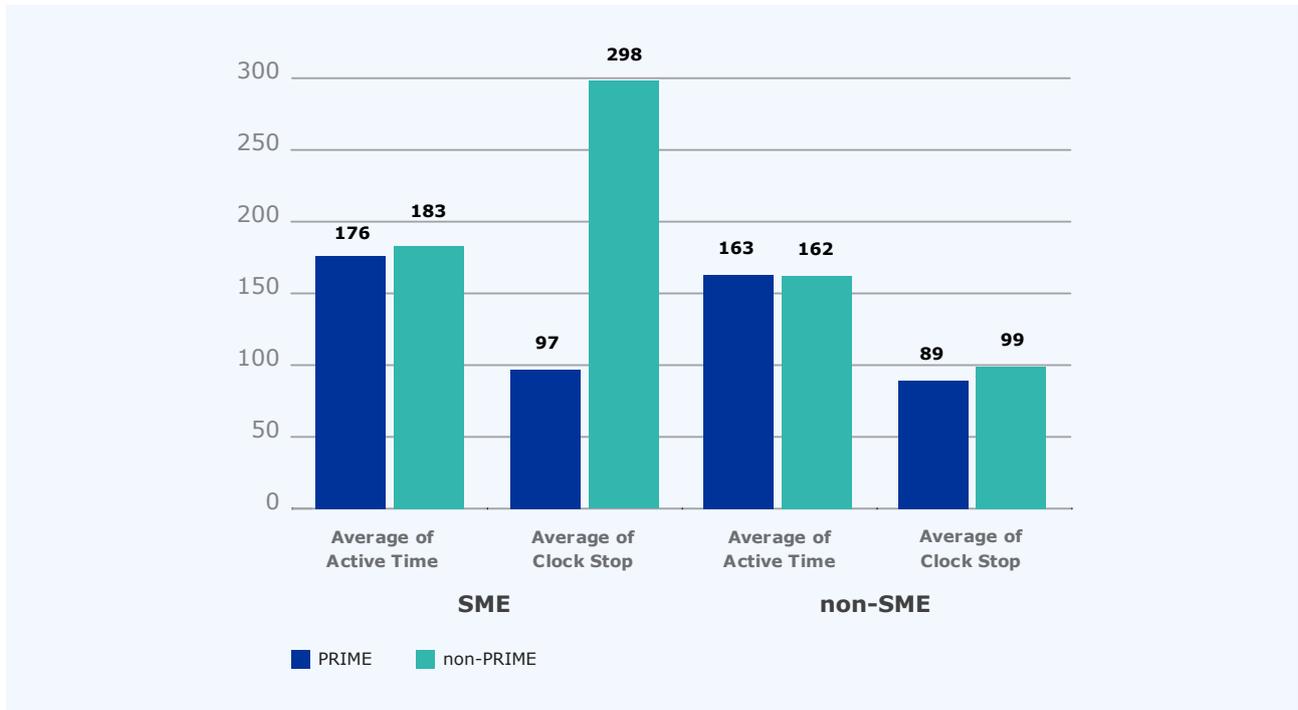
For orphan medicinal products, a 61-day decrease of the clock stop for PRIME products was observed compared to non-PRIME products.

As expected, there was a relevant difference in the number of major objections for PRIME products that maintained accelerated assessment until CHMP opinion vs those that reverted to standard timetable during the procedure (average of 2.9 vs 4.1 major objections).

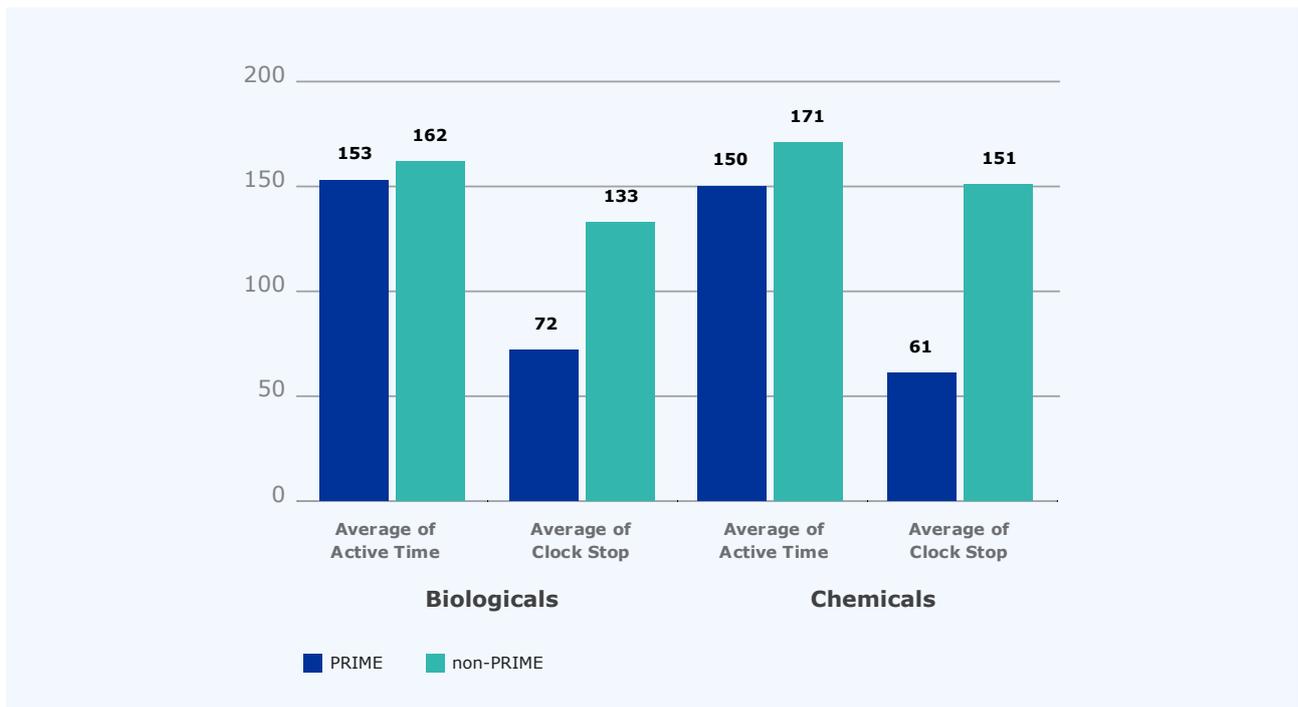
**Figure 13. Evaluation times for products started under accelerated assessment: duration of active time and clock stop for PRIME and non-PRIME products (in days)**



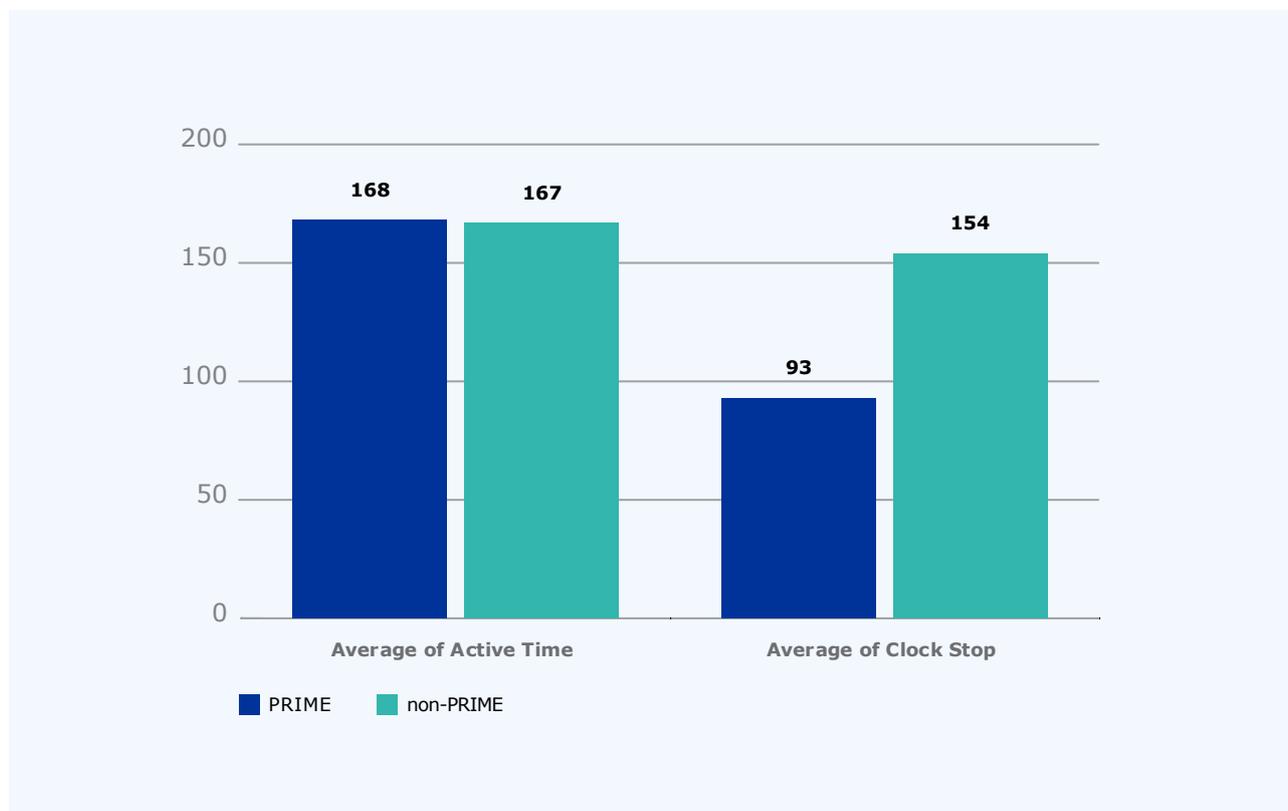
**Figure 14. Evaluation times for products started under accelerated assessment: duration of active time and clock stop per type of applicant for PRIME and non-PRIME products (in days)**



**Figures 15. Evaluation times for products started under accelerated assessment: duration of active time and clock stop for PRIME and non-PRIME non-ATMPs (in days)**



**Figures 16. Evaluation times for products started under accelerated assessment: duration of active time and clock stop per PRIME status for orphan medicinal products (in days)**



In terms of the **reasons for the switch to normal timetable** for the PRIME products, these were mainly clinical, however 22% had GXP major objections, and a significant amount of quality questions for ATMPs.

The main reason to switch to standard timetable were clinical major objections, particularly the fact that the initially proposed indication did not represent, in the opinion of the CHMP, the population included in the pivotal clinical trial or the population that would demonstrably benefit from treatment. Refinement of the indication population is a frequent objection encountered in the assessment of marketing authorisation applications, examples include line of treatment or age range. Other clinical major objections were linked to safety issues and insufficiency of the data set. Some of these discussions require convening an expert group (SAG), which also prolongs assessment times.

For ATMP products, as mentioned, quality-related major objections were often one of the reasons to switch to standard timetable.

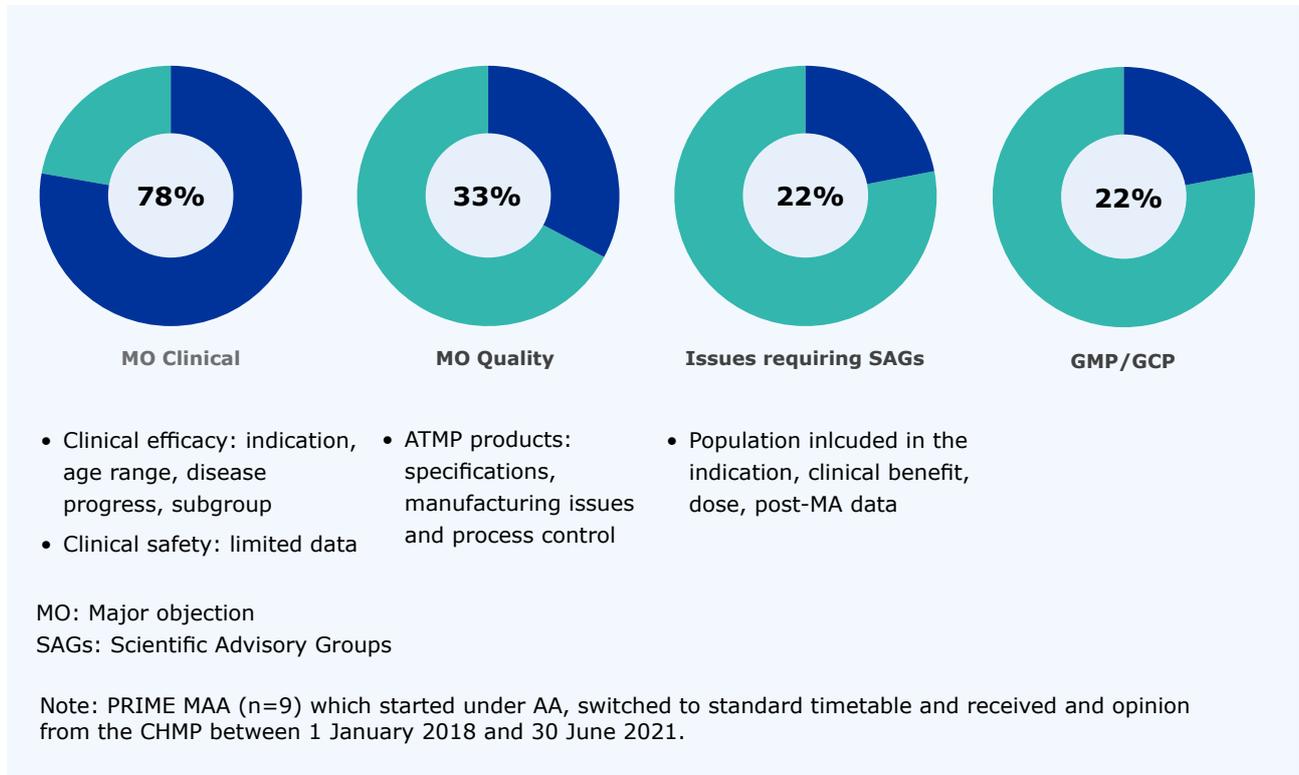
These findings are in line with the conclusions of a recently conducted analysis of accelerated assessments covering the period 2016 -2020.<sup>4</sup>

Accelerated assessment is a key aspect of PRIME, however, in the PRIME analysis both data and feedback show that reversion to normal timetable was frequent (56%) and potentially avoidable, if effective pre-discussion of the stumbling blocks takes place.

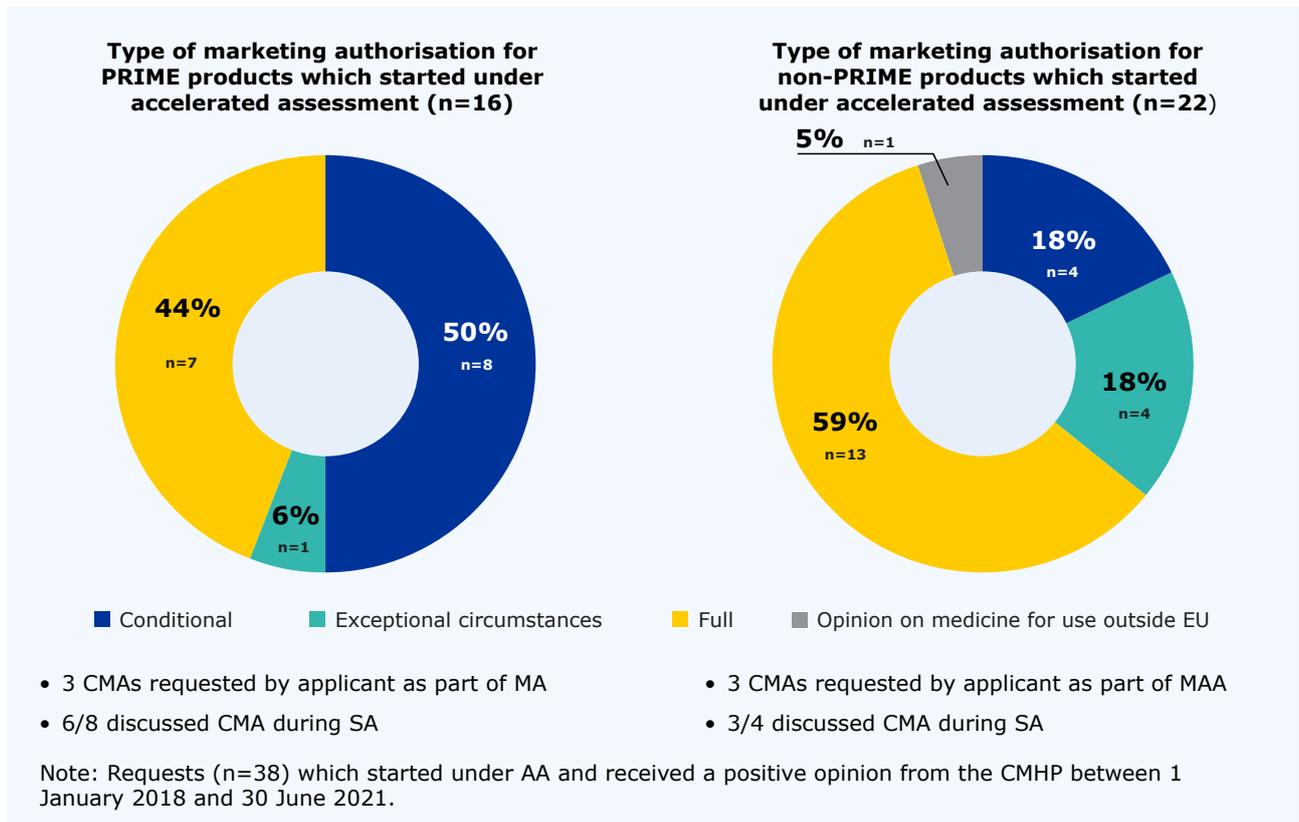
Nevertheless, the data suggest a positive impact of PRIME support on evaluation times: more PRIME MAAs were granted AA and slightly more

<sup>4</sup> [Microsoft PowerPoint - 05a. V. Palmi & C. Pothelet Analysis on Accelerated Assessment 2020 \(europa.eu\)](#)

**Figure 17. Reason to switch to standard timetable for PRIME products**



**Figure 18. Type of marketing authorisation per PRIME status**



maintained it. There was also a shorter clock-stop duration observed across all analysed categories. The clock-stop reduction was particularly significant for SMEs.

Regarding the type of marketing authorisation granted in the study period, PRIME products had a higher proportion of CMAs as compared to non-PRIME (8/16), and in 6 out of 8 cases this was discussed during the Scientific Advice (either at the initiative of the company or at the prompting of SAWP).

### ***Discussion and outcomes***

The findings on evaluation times suggest a likely positive effect of PRIME both in terms of starting their review under accelerated assessment (17 out of 19 requests for accelerated assessment for PRIME products were granted) and in terms of maintaining it during evaluation (7 out of 16 PRIME products maintained accelerated assessment until opinion), despite the increased complexity of the products (7 out of the 16 PRIME were ATMPs and 15 out of 16 were orphan designated products). There is however room to optimise current interactions to support the necessary knowledge acquisition throughout development and thus facilitate maintenance of accelerated assessment, as shown by the fact that some of the reasons for switching to a normal timetable could be proactively addressed in the pre-submission phase (see section 5.6).

Increased predictability of the chance of maintaining an accelerated assessment timetable could also support better workload planning for the regulatory network and for applicants.

The fact that half of the PRIME products received a conditional marketing authorisation confirms the selection of these products at PRIME eligibility stage, since they were subsequently deemed to significantly address an unmet medical need at the MAA stage.

Granting of a conditional marketing authorisation to 8 PRIME products affords the potential to enable them to reach patients approximately 3.75 years earlier on average than if a comprehensive data package had been required prior to regulatory approval. This is estimated based on the time gap between the initial authorisation and the expected date for completion of the last specific obligation at time of marketing authorisation for these products. There were two additional PRIME products, which did not start evaluation under accelerated assessment and which received also a conditional marketing authorisation.

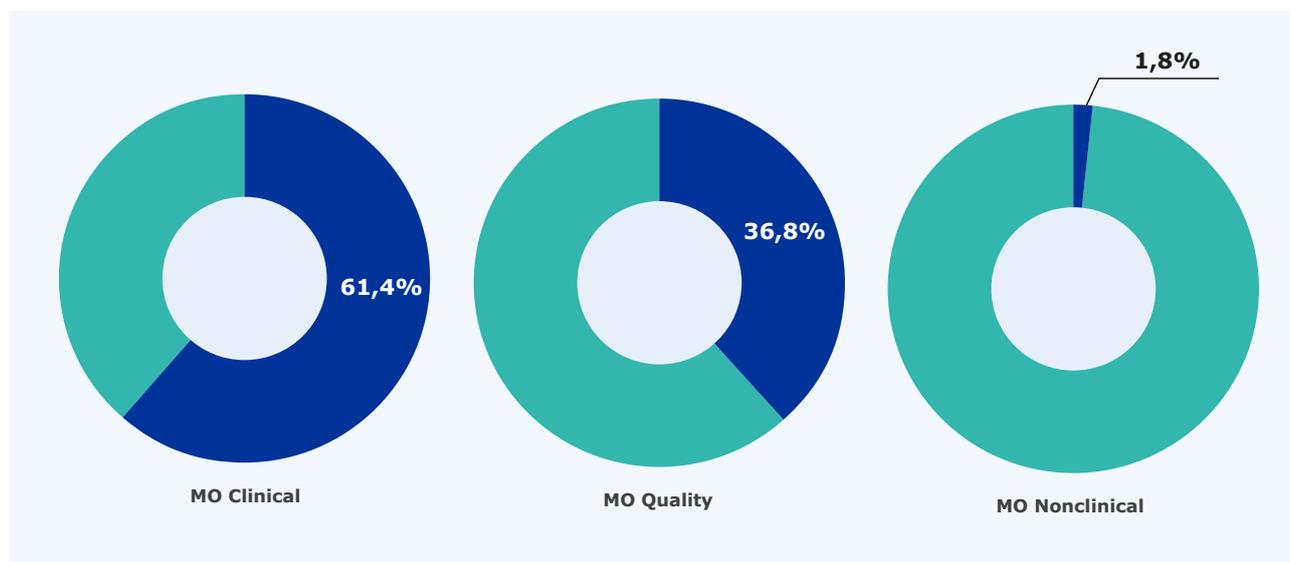
Based on the information submitted in PSURs regarding marketing status at the time of writing this report, which was available for 8 of the 10 PRIME products which received a CMA, 3 had been placed on the market in more than 10 EU MSs, 2 in 5-10 EU MSs and 2 in 1 to 5 EU MSs. One product had not been marketed in any EU MS.

#### **4.4.2. Major objections in the Marketing Authorisation**

As mentioned in section 5.5.1 (Scientific Advice), the analysis of the PRIME MAA applications included the areas of development that were raised as Scientific Advice questions and those that appeared in the Major Objections in the MAA evaluation. The scope of this review was:

- to identify what were the most frequent development hurdles, as highlighted by the scientific advice topics,
- whether these were (or were not) resolved by the time of MAA (as indicated by major objections in the same area of advice),
- whether any important aspects, as indicated by the major objections, were missed during development (no prior advice given in the area),
- and, if possible, whether the provision of advice, and compliance with it, helps facilitating the MAA assessment.

**Figure 19. Major objections of all PRIME products with a MA which started evaluation under accelerated assessment**



The majority (61.4%) of Major objections raised for PRIME products were of a clinical nature. These included the adequacy of the data to support the populations covered by the proposed therapeutic indication, the type of marketing authorisation (conditional vs full), the duration of study or population size, etc.

The most frequently areas encountered in advices and major objections were the following, with those in purple occurring most frequently:

#### **QUALITY**

- (Q1) Stability
- (Q2) Specifications
- (Q3) Manufacturing issues and process controls
- (Q4) Comparability (changes to manufacturing process / site)
- (Q5) GMP Issues /inspections readiness

#### **NONCLINICAL**

- (NC1) Oncogenesis potential (ATMP)

- (NC2) Germ line integration
- (NC3) Adequacy of animal model chosen
- (NC4) Chronic toxicity
- (NC5) Immunotoxicity
- (NC6) Juvenile animal studies
- (NC7) Reproductive toxicity

#### **CLINICAL DEVELOPMENT**

- (CD1) Inclusion & Exclusion criteria
- (CD2) Adequacy of dose and/or regimen proposed
- (CD3) Choice of comparator
- (CD4) Trial duration
- (CD5) Endpoint choice
- (CD6) Interim analysis
- (CD7) PIP
- (CD8) Strength of evidence to address unmet need (including significant benefit if orphan)

(CD9) Post Authorization Study Plan

(CD10) GCP issues/inspections

(CD11) Type of MA (CMA vs full)

## **SAFETY**

(S1) Safety dataset for MAA, including follow up duration

(S2) Risk management

## **METHODOLOGY – Statistical analysis**

(M1) Adequacy of sample size

(M2) Population used for analysis - Intent to treat population (ITT)/Intercurrent events

(M3) Confounders

(M4) Non-inferiority / superiority

(M5) Extrapolation

(M6) Method used for data analysis  
– Uncommon Stat Strategy

(M7) Post-hoc data analysis

GCP and GMP issues have resulted in Major Objections and switches to standard evaluation timetable. As inspection planning normally starts at the time of AA request: the survey conducted by industry organisations noted that this can make inspection timelines (including closure) very tight under AA timelines, particularly for complex inspection cases for ATMPs.

For PRIME products a reduction in the number of Major Objections during the MAA assessment was observed. The average reduction across all products and question areas was modest (3.6 major objections given in all areas for PRIME products versus 3.9 major objections given in all areas for non-PRIME products), but it was consistently positive and more pronounced in certain categories: Conditional MA (38% fewer MOs with PRIME products than with non-PRIME), Orphans (20% reduction), and SME (19% reduction).

The survey with regulators noted that effective development support is not a unilateral regulators' exercise: responsiveness of the applicant to the scientific input is equally important for maximising the chance of a positive MAA outcome. This was also noted in a recent survey of global facilitated regulatory pathways.<sup>5</sup>

## **Discussion and recommendations**

The relevance of the observed reduction in the number of MOs for PRIME products versus non-PRIME is unclear, as in practice it does not translate, on average, in the reduction of a full major objection, and the sample of applications (39 overall) is relatively small. However, as all findings on the number of major objections go in the same direction, it could indicate a positive effect of the additional scientific and regulatory support provided by PRIME, as it is coupled with the observed shorter MAA clock-stop times.

The analysis of the major objections raised during the PRIME MAAs versus the SA provided during the development has confirmed the importance to seek concurrence on the previously identified pivotal variables in the design of pivotal clinical studies: choice of primary endpoint, selection of control and statistical methods. It also highlighted the importance of GXP issues for PRIME products as an important area to follow prior to submission of an MAA: this is an important prompt to increase proactive EMA support to the topic and add GXP preparedness as a routine item for discussion at KOM.

The identified list of key areas could be also considered to design a blueprint for a comprehensive, structured and proactive discussion of frequently encountered development issues with PRIME products, and of the relevant regulatory interactions (so called 'development tracker'). This tracker (further discussed in Section 5.5) would be updated as development progresses so that regulators could easily access an up-to-date snapshot of the development status, facilitating the provision of future advices and knowledge building

---

5 [The Qualitative Value of Facilitated Regulatory Pathways in Europe, USA, and Japan: Benefits, Barriers to Utilization, and Suggested Solutions \(cirsci.org\)](#)

throughout development. This is seen as crucial to follow the implementation of the scientific advice given, to understand whether it was adhered to, or what the rationale for deviation is.

#### 4.5. Use of regulatory interaction opportunities

Feedback from regulators clearly highlighted that the core scope of PRIME should be to **provide effective support to the development of products in areas of unmet medical need**. The focus should be on granting PRIME to products for which the strengthened scientific and regulatory support provided to a responsive company would be useful and effective to optimise the evidence generation as basis for the later MAA.

Expectations on the PRIME scheme were explored in the EMA survey to companies. The highest scoring aspect was "facilitation of the regulatory review process" (4.4 out of 5), followed by "facilitating maintenance of accelerated assessment" (4.1/5), "facilitation of post authorisation follow up" (3.8/5), and "acceleration of development timelines" (3.7/5).

Supplementary data came from the survey conducted by the industry associations, where the

main advantage of PRIME was seen as the early rapporteur appointment and the provision of a dedicated EMA contact point, to assist navigating the vast array of scientific and regulatory support avenues available at EMA<sup>6</sup>. The lowest scoring aspects in that survey were regarding the HTA evidence package generation and the facilitation of global development, highlighting the need to strengthen the PRIME scheme to better support these areas.

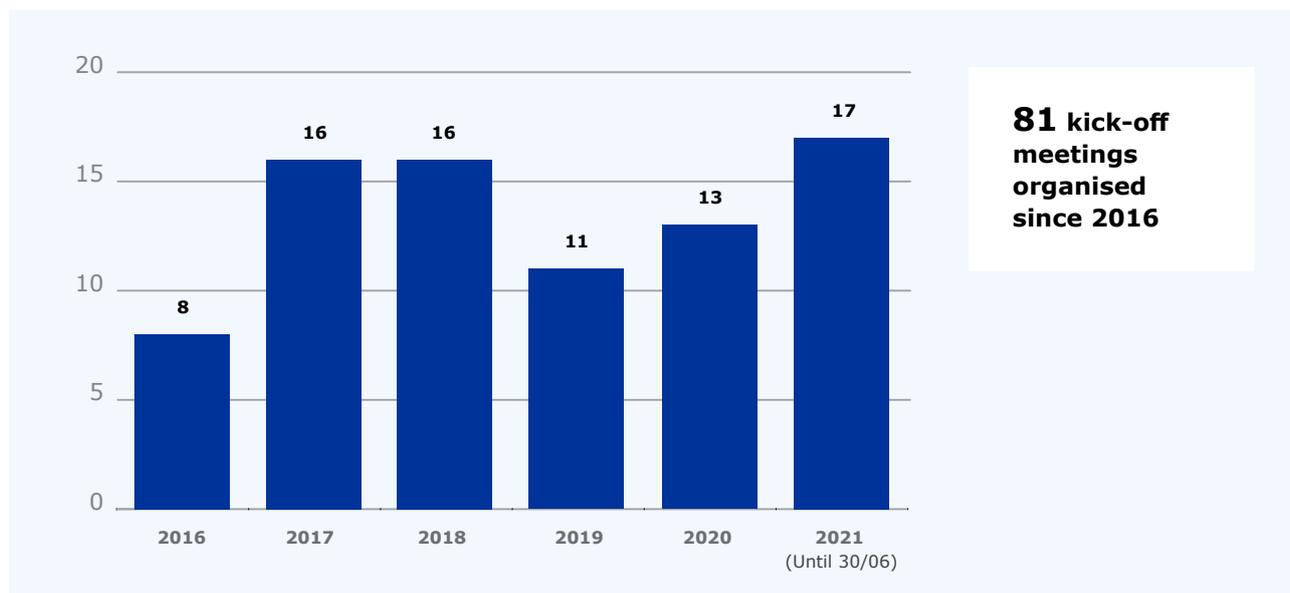
The below reviews pre-MAA development interactions (Scientific advices, PIPs, global agency interactions, parallel HTA advices) and process improvement areas.

##### 4.5.1. Kick-off meetings

Once a medicine has been accepted in the PRIME scheme, EMA organises a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts from relevant EMA scientific committees and working parties; 81 kick-off meetings were organised in the study period, reflecting the continued effort provided by the regulatory network in supporting PRIME products.

<sup>6</sup> [Research and development | European Medicines Agency \(europa.eu\)](https://www.europa.eu)

Figure 20. Kick-off meetings per year



The feedback received through the surveys conducted from developers and regulators on kick off meetings identifies them as one of the most relevant features of PRIME: they give companies the opportunity to present an overview of their development and discuss planned regulatory interactions, and to the Rapporteur team to provide feedback and suggest further aspects for consideration during development.

Kick off meetings are, at the time of writing this report, structured around an agenda template that is sent to applicants at the time of granting eligibility. The surveys conducted by EMA and the industry associations highlighted how the meetings are considered useful, however they could benefit from having an expanded scope. Various elements were suggested:

- a more in-depth discussion of scientific issues, to support the preparation of more relevant scientific advice briefing books;
- expanding the scope of the agenda templates to a more structured and granular format, to allow subsequent tracking of development issues;
- organising a follow-on meeting later in the development.

The proposals made in section 5.6 of this report aim to improve the usefulness and impact of kick-off meetings in accordance with these suggestions.

Additionally, the current guidance on PRIME will be revised to provide further clarity for all prospective applicants on the format and content of the discussions at the kick-off meeting. This should support prospective applicants in the decision to apply for PRIME, and in the preparation of the relevant documentation should the eligibility request be granted.

#### **4.5.2. Scientific Advice and Protocol Assistance**

A total of 156 advices (initial and follow-ups) with a start date in 2016-2020 were given to PRIME products, while over the same period 3,602 advices (initial and follow-ups) were given to non-PRIME products.

To consider the impact of the advice provision on

the development and MAA outcomes of the product, the subset of advices provided to the 21 PRIME products with an MAA outcome (opinion or withdrawal) was reviewed, as products still under development would not provide useful information in this respect. For the 21 MAA PRIME products, 87 Scientific advices were issued, with the involvement of multiple committees in addition to CHMP (32 PDCO; 32 CAT; 7 PRAC; 7 SA with patient representative involvement, 6 COMP; 6 HTA). For these 21 products, this corresponds to an average 4.1 scientific advices per PRIME product which has reached MAA stage. As a comparison, the average number of advices per product provided by EMA is below 1.5, however this covers all types of products, including very early stage and discontinued developments. The areas of advice were distributed as follows (average number of advices per PRIME product):

- 3.0 SA with clinical questions
- 2.1 SA with quality questions
- 1.9 SA with nonclinical questions

When comparing the 16 PRIME and the 23 non-PRIME products which started regulatory evaluation under accelerated assessment and received a CHMP opinion between 1 January 2018 and 30 June 2021, PRIME products had on average 1.5 additional scientific advices compared to non-PRIME products (4.6 vs 3.1) indicating more close regulatory support provided to PRIME products through scientific advice.

As a starting point the positive correlation between an MAA successful outcome and three important variables in the design of pivotal clinical studies (choice of primary endpoint, selection of control and statistical methods) was analysed. Such a correlation was demonstrated in an earlier study<sup>7</sup> when MAAs were analysed for compliance with SA. The study concluded that compliance with these clinical study design elements was an independent predictor of success together with company size.

Compliance with the three clinical development parameters identified by the previous study (primary endpoints, comparators and statistical

<sup>7</sup> Nature Reviews Drug Discovery | AOP, published online 17 April 2015; doi:10.1038/nrd4621

methods) was analysed. In addition, for ATMPs, compliance with quality parameters (comparability and potency assay) was reviewed.

Compliance was categorised as adherent, non-adherent, not assessable (meaning that the SA/PA request did not concern the aspects of development used for estimation of adherence).

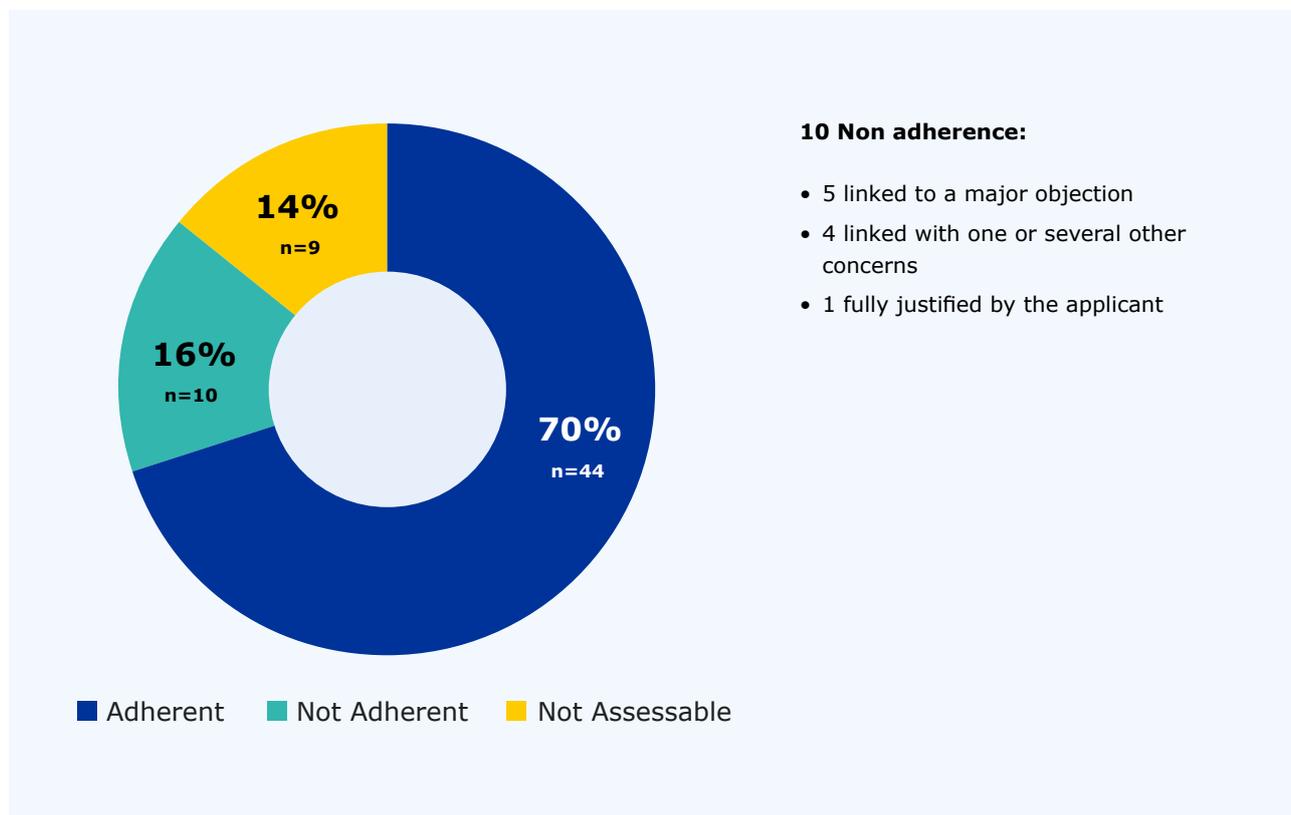
For the 21 products, the three clinical parameters give a total of 63 (21x3) observations: of these, ten were instances of non-adherence to the advice. These resulted in major objections in five cases and in other concerns in four cases; in one case, the applicant satisfactorily justified the deviation. This highlights the importance to follow SA or to clearly justify the deviations.

There is an overall good compliance with SA for the clinical parameters analysed with only 16% not adhering to scientific advice.

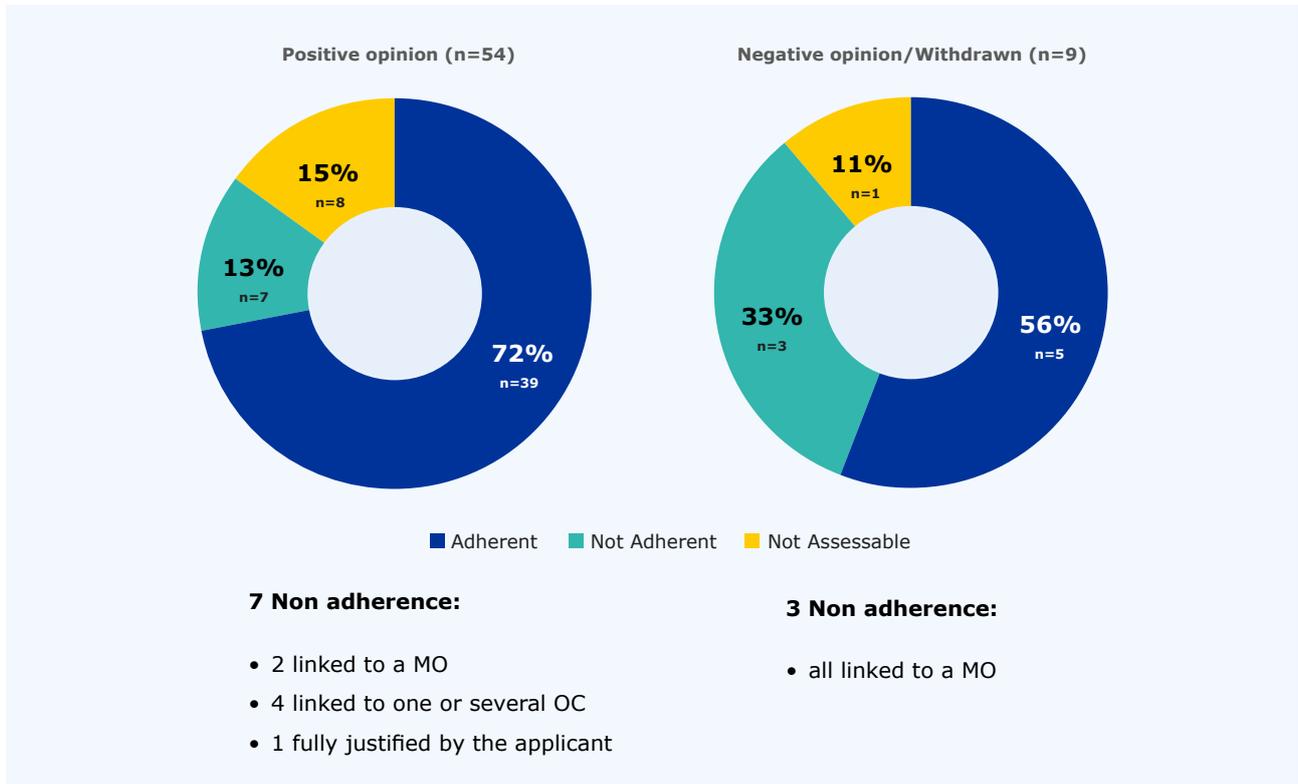
Greater compliance with scientific advice was found to be linked to MAA positive outcomes.

- There is a relevant difference in terms of adherence to SA between the PRIME applications that resulted in a positive CHMP opinion and those that were negative or withdrawn: 13% non-adherence for positive opinions vs 33% non-adherence for applications that resulted in a withdrawal or refusal of MAA; in this later group, all non-adherence to SA resulted in major objections raised during the procedure;
- There is a difference in terms of adherence to SA between the applications that maintained accelerated assessment and those that switched to standard TT: 5% non-adherence for those that maintained AA vs 19% non-adherence for those with positive opinions that reverted to standard timetable.

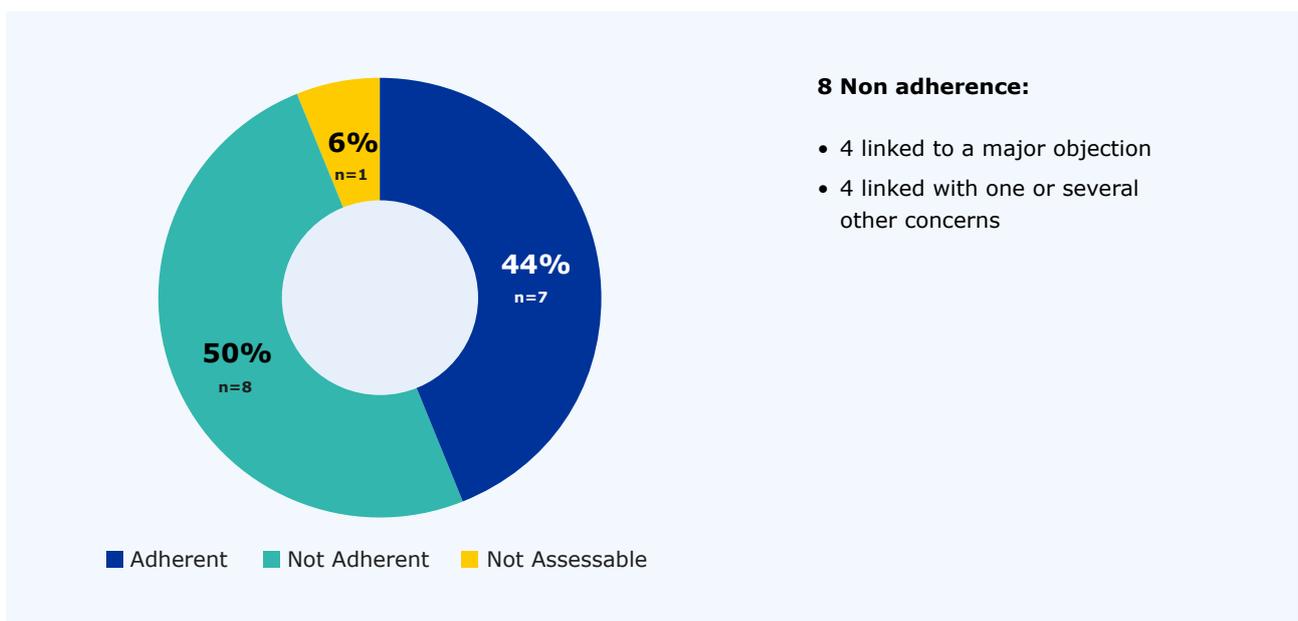
**Figure 21. Compliance to clinical SA**



**Figure 22. Compliance to clinical SA - MAA outcome**



**Figure 23. Compliance to Quality SA (n=16)**



### **ATMPs and quality parameters**

Of the eight ATMPs products, seven had positive opinions and one MAA was withdrawn; seven ATMPs started under AA and one maintained it until the opinion; three applicants were SMEs.

The two additional quality parameters analysed specifically for ATMPs were comparability and potency assay, which gave a total of 16 (8x2) observations.

The dataset of 16 observations is small; also in this context adherence to the scientific advice appears to be important: of the 8 parameters not compliant with SA, half resulted in major objections.

Amongst the sample of 21 PRIME products analysed there was no relevant difference observed in terms of non-adherence to scientific advice between SMEs (24%) and non-SMEs (22%). Overall, SMEs requested an average of 3.1 scientific advices while non-SMEs requested on average 4.9 scientific advices.

### **Discussion and recommendations**

In line with these results, the feedback received from the EMA industry survey highlighted that a more in-depth discussion of scientific issues at kick-off meeting would be welcome to support proactive and precise identification of important development stumbling blocks, so that well-targeted advice requests can be submitted. A holistic approach and tracking of these development issues was also indicated as important (Regulators and Industry EMA surveys), starting from the Kick-off meeting and supplemented by the recording of earlier interactions prior to PRIME eligibility.

Targeted support to Scientific Advice requests might be considered for PRIME products. Under this scenario, an SA request on specific topics could be enhanced via comments on the draft package and, if necessary, a pre-submission meeting (with the input of the EMA scientific Officer, and extended PRIME support team), supporting a refined SA package to enable a streamlined SA assessment.

### **4.5.3. Paediatric development plans**

#### **Findings**

Of the 95 PRIME eligible products, 54% (51/95) include a paediatric indication while 14% (13/95) include a paediatric-only therapeutic indication.

Of the 21 PRIME products with an MAA outcome, 11<sup>8</sup> (52%) included a paediatric indication, of which 2<sup>9</sup> (10%) had a paediatric-only indication. Of the Scientific Advices provided to these 21 PRIME products, 54% (54/95) include a paediatric indication. A PDCO representative is also involved in the Kick-off meeting as needed.

At time of request for PRIME eligibility, 10 out of the 21 products had an agreed PIP, and when looking at the subset of 11 (52%) included a paediatric indication in the MAA, the vast majority (8 out of 11) had an agreed PIP.

#### **Discussion and recommendations**

PRIME aims to provide holistic support to prospective development plans, including Paediatric Investigation Plans, and this is confirmed by the significant proportion of advices discussing specific paediatric issues.

The PDCO provides input within the established framework of Scientific Advice, as the paediatric committee contributes to the provision of scientific advice when paediatric issues are discussed.

The timing foreseen in the Paediatric Regulation for the submission of a PIP broadly corresponds to the PRIME submission time window, which could afford the opportunity for strengthened support to PIP design.

Planning a PRIME eligibility application before a PIP application could be of interest for companies desiring continuity in the follow-on of paediatric development issues by the Rapporteur team. A

<sup>8</sup> Bylvay, Evrysdi, Gamifant, Givlaari, Imcivree, Kymriah, Oxlumio, Rozlytrek, Skysona, Zolgensma, Zynteglo

<sup>9</sup> Gamifant, Skysona

more proactive approach by PDCO and SAWP could also be envisaged, by inviting companies to consider applying for PRIME if a promising product is submitted for review.

#### 4.5.4. Designing global development plans

##### **Findings**

Since the launch of the PRIME scheme in 2016, EMA and US FDA have established regular exchanges of information and discussions around their respective scheme to support promising medicines: PRIME, FDA Breakthrough Therapy (BT) designation and Regenerative Medicine Advanced Therapy Designation (RMAT).

Over the years, the agencies have conducted comparative reviews of requests received for PRIME eligibility and BT designations. Since the establishment of PRIME in 2016 up to 31 December 2020, 151 requests were made to both Agencies's respective BT and PRIME programmes. The agencies reached concordant outcomes for 93 out of 151 requests (61.5%) submitted for both PRIME eligibility and BT designation: 42 were designated as both Breakthrough and PRIME, 51 were denied both eligibility or were withdrawn by the applicant. The agencies reached different decisions on eligibility in 58 cases.

Exchanges of information for dually designated products consisted in regular updates on designation status, ad-hoc discussion on advices, orphan designations and PIPs via the respective [clusters](#). In the study period, there were 22 formal parallel EMA/FDA scientific advices, none of those on dually designated products.

The survey conducted by the industry associations collected information on companies' experience with other global expedited pathways. The most frequent interactions were with FDA, but 33% of respondents referred to the Japanese Sakigake scheme. The timing of application to other authorities with respect to the PRIME application was the same for half of the responders.

The Industry survey collected opinions on

Companies' experience with other global expedited pathways: while most companies were supportive of strengthened global dialogue (rated 4.4 out of 5), this aspect did not rate highly as a perceived advantage of the PRIME scheme (facilitating global development scored 2.7 out of 5), also because the parallel interaction with FDA has been found logistically challenging.

The EMA survey to Industry showed that there was also moderate expectation on the part of companies on facilitation and convergence of development plans (3.3 out of 5 for products on pre-submission, and 2.5 out of 5 for submitted MAA).

Finally, the survey by the industry associations commented on the desirability of prioritisation of PRIME products for FDA scientific advice interactions, and the pursuit of the alignment on the quality toolbox flexibilities with other global regulators.

14 out of the 21 PRIME products that received a CHMP opinion or were withdrawn were dually designated PRIME and Breakthrough Therapies by EMA and FDA, respectively.

At the time of writing this report, of the dually designated products, 10 were authorised in both regions, 2 were authorised only in the EU, 1 was authorised only by FDA and 1 was withdrawn in the EU and rejected by FDA.

Of the 7 PRIME products that did not receive breakthrough designation 4 were authorised in both regions, 2 were authorised in the EU only and 1 was authorised by FDA only.

#### **Discussion and Recommendations**

Given the different entry criteria, it is often possible to start the FDA designation process at an earlier timepoint in the pharmaceutical development. As a consequence, pivotal clinical plans can be already at an advanced stage of design by the time the Phase 2 data are available for the current PRIME application process.

FDA also allows designation of subsequent indications for authorised products, which broadens the pool of eligibility.

The EMA survey findings were very supportive of strengthened support to global development, but this was not perceived as a major draw in the decision to apply for PRIME. This probably indicates that the full potential of PRIME to support global development is still untapped and reduces the opportunity for global alignment.

When FDA designation as Breakthrough or RMAT happens at an earlier timepoint, the potential for early interaction between agencies is reduced, particularly for products like ATMPs where specifications, clinical trial material definition, and inspection planning would benefit from early input. This would support consideration on increased flexibility on the timepoint for PRIME application (see Section 6, improving the process).

Developing procedural flexibility would also be important as logistic hurdles were identified both in the survey and previously conducted studies. Guidance should be developed for applicants explaining the various formal and informal possible routes of interaction (parallel advice, parallel consultation, clusters discussion), and a framework of specific support to dually designated EMA/FDA products could be developed.

Consideration could be also given to expand the collaboration on global development with other Agencies with whom confidentiality arrangements are in place or are being introduced.

Proactive collaborative action could also be explored to support the development of specific classes of products which have global health significance.

#### **4.5.5. Interaction with downstream decision makers**

A total of 101 parallel EMA/HTA advices were given in the study period (April 2016-June 2021) of which 6 were given to the 21 PRIME products with an

MAA outcome over a total of 87 advices (of any type) for this group of products (7% of advices to PRIME products were HTA advice, as compared to approximately 2.7% of advices to non-PRIME products).

A sizeable number of PRIME products are ATMPs and are approved with a Conditional Marketing Authorisation. Both these factors are recognized as challenges for HTA and Payer decision making<sup>10</sup>.

The survey conducted by the Agency highlighted a marked difference between expectations of the benefits of the PRIME scheme in the pre-authorisation phase as compared to the expectations post MAA: while PRIME was considered important to indicate the potential of the product to address an unmet medical need, its perceived usefulness to support multi-stakeholder study design input and reimbursement was much lower for the companies that had received a marketing authorisation. The same survey indicated desirability to prioritise PRIME products in the EMA/HTA interaction framework under development.

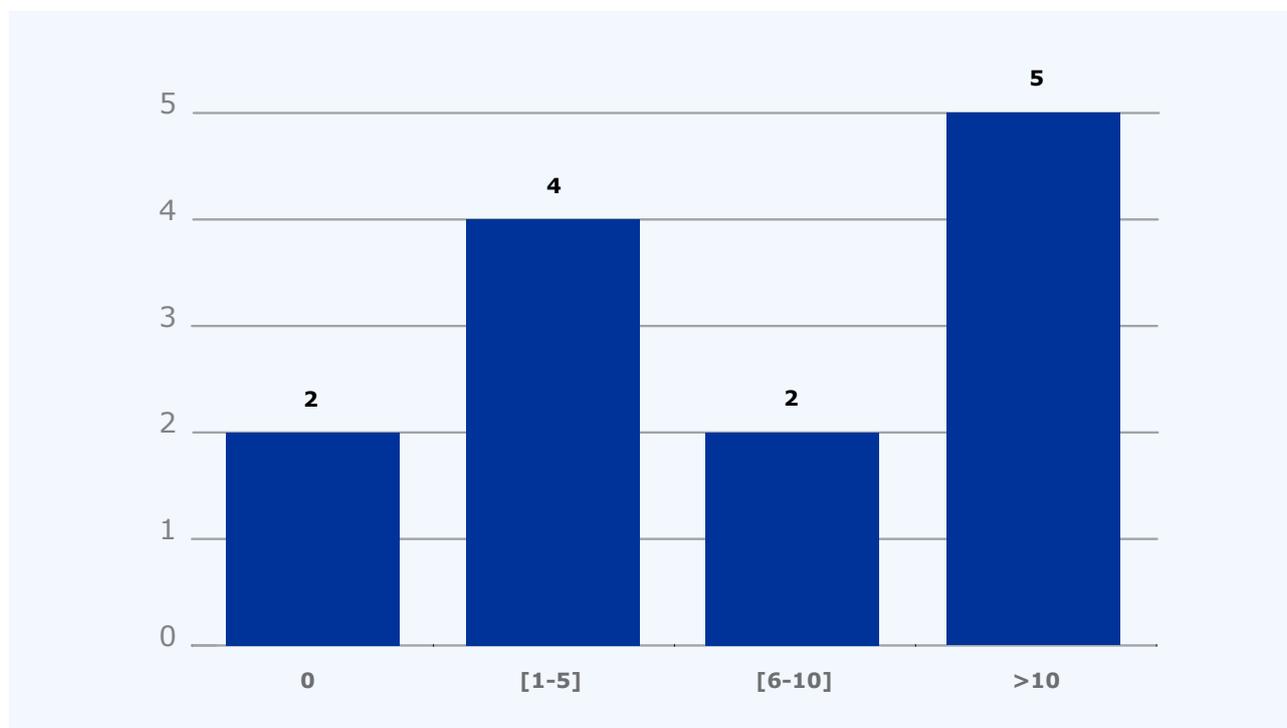
In the survey conducted by EMA for PRIME products that received an MA, 6 companies responded to the questions on HTA post-authorisation decisions. The sample is very small both in terms of products and of HTA bodies represented (mostly one per product). Time for HTA decision outcome varied from 11 to 6 months. This is in line to the findings from another study. One company noted the limited time to amend the HTA submission package if the indication wording is changed in the late stages of the MAA review.

Of the 18 PRIME products authorised in the EU, the Agency received, through the PSURs, information on the marketing status for 13 of them.

Of these, 5 have been placed on the market in at

<sup>10</sup> Cai, J., Wang, T., McAuslane, N., & Liberti, L. (2019). PP30 Do Conditional Regulatory Pathways Affect Health Technology Assessment Recommendations? *International Journal of Technology Assessment in Health Care*, 35(S1), 42-42. doi:10.1017/S0266462319001946

**Figure 24. Marketing status of PRIME products in the EU (n=13)**



least 11 EU MSs, 2 in 6-10 EU MSs, 4 in 1-5 EU MSs and two products had not been marketed in any EU MS at the time of this report. Of the 5 remaining products for which no information was yet available, 4 were authorized in 2021.

**Discussion and recommendations**

Engagement with downstream decision makers on the evidence generation plan is fundamental for seamless and effective patient access, as noted in the findings of the industry survey, which proposed prioritisation of PRIME products for EMA/HTA interactions.

In the new HTA Regulation, the selection criteria for Joint Scientific Consultations have been defined as follows: (a) unmet medical needs; (b) first in class; or (c) potential impact on patients, public health, or healthcare systems; (d) significant cross-border

dimension; (e) major Union-wide added value; (f) Union clinical research priorities. This approach would encompass in principle PRIME products as eligible for consideration for such prospective advice on evidence planning.

PRIME could also be envisaged as a contributor to horizon scanning activities foreseen in the new HTA regulation. In coordination with other initiatives, arrangements could be developed for EMA to share information on PRIME products with the HTA network to support selection of products for scientific consultations and preparedness for effectiveness assessment.

## 4.6. Improving the process

### Findings

The industry-led survey indicated high interest in the PRIME scheme, and of the 25 companies without PRIME products that responded, none indicated lack of interest as a reason for not planning an application/not having applied. PRIME is routinely considered by companies in 53% of cases to support an expedited development strategy, and 69% of companies have it under active consideration for a product.

In the survey conducted by Industry, enhanced **regulatory and scientific support** is seen as a pillar of PRIME, with early appointment of Rapporteur (4.2 out of 5) and a dedicated EMA contact point (4.1 out of 5) highlighted as the main strengths of the scheme, followed by development support (3.8 out of 5).

This feedback is reflected also in the results of the EMA survey to Companies in PRIME, which showed a high degree of satisfaction with the EMA and regulators' support (4.1 and 4.3 out of 5, respectively), and a stated high likelihood to use PRIME again in the future (4.5 out of 5): early rapporteur appointment and an element of continuity of assessment teams are seen as an additional value of PRIME as compared to the provision of Scientific Advice via the regular route.

The clarity of **guidance documents** available on the EMA website was considered good (3.8 out of 5), as well as the usefulness of the pre-submission discussion interactions (3.7 out of 5).

Different **avenues for interaction** with the EMA and the Rapporteur are currently used by companies, ranging from questions on regulatory submission aspects, to contacts with the various EMA offices (SA, Paediatric, Orphan), to direct contact with Rapporteur teams, to formal procedures. When feedback was requested in the regulator's survey on the interactions:

- There was almost unanimous preference for the EMA to act as initial contact point for company queries; in this context, guidance can be developed covering rules for engagement with the Agency, Rapporteur or via scientific advice procedure.
- The importance of maintaining traceability of interactions, the collegial nature of assessment, and transparency of input to company, with the main route of choice being SA, was outlined.

The Industry survey also explored what would make companies more likely to apply for PRIME. Broadening access criteria and timing, flexibility in advice provision, and procedural improvements were the highest scoring areas.

A common element acknowledged by both Regulators and the industry is the considerable resource investment required for PRIME products, covering in one hand, preparation of a PRIME submission by applicants and the review of requests by Regulators as well as preparation from both parties for the kick-off meeting and subsequent interactions. It is therefore critical that support is given to those products the most likely to benefit from it and with the potential to bring major benefits in terms of public health.

## 5. Overall recommendations

This analysis covers the scientific and procedural learnings emerging from the first 5 years of experience with the EMA's PRIME Scheme. On this basis three areas for enhancement of the scheme were identified:

- PRIME eligibility: scope and timing
- Flexibility of SA provision for PRIME
- Knowledge building to support AA

Recommendations on these areas will translate into actions aiming to achieve a benefit/effort proportionate process, focused on effective support and oversight, and delivery of the overall aim of the scheme.

### 1. PRIME eligibility: scope and timing

PRIME exists to **support the development** of promising products that would benefit patients in areas of unmet medical need. PRIME should only be granted to products that have the potential to address an unmet medical need *AND* that would benefit from the additional input in the design of the development plans.

Very few early entries in the scheme (i.e. at time or preclinical/early clinical studies) were granted in the first 5 years of the operation of PRIME, as it can be difficult at this stage to substantiate the promising nature of the medicine, partly due to the fact that few animal models with good predictability of efficacy in the human body exist. Nevertheless, later entry in the scheme limits the possibility of input (particularly in the CMC, dose finding and nonclinical areas), and the opportunity for global alignment. If a medicine shows promise, and the need for early input is justified, the product deserves to be supported earlier, regardless of the type of developer.

Therefore, consideration will be given to the **best time point for access** to the scheme, as it might afford the greater impact on shaping development plans. EMA will explore the following aspects:

- Strengthen the need for applicants to outline the

expected benefit from PRIME when seeking entry to the scheme, and the interactions they intend to avail themselves of.

- Consider learnings from the experience in orphan designation to inform on the suitability of nonclinical data to support earlier applications on this basis.
- Proportionate resource investment geared towards the most effective support at a given point in time to deserving products.

To make sure that the **right expertise is involved at the right time** EMA will:

- **Strengthen EMA support** to be the first point of contact for applicants. A cross-functional EMA support team could be strengthened, and leveraging current forums such as ITF, business pipeline meetings, interconnecting regulatory tools (e.g. ITF/NCA innovation offices & PRIME) will help supporting early assets;
- Clarify the situations under which products at a **later stage of development** could be considered for PRIME eligibility, e.g. when substantial improvements are still possible in a PASS/PAES or in the context of engagement with HTAs. Guidance could be published outlining the justification expected from the applicant to support the request, including the planned interactions.
- In addition to the existing possibility of participation to Scientific Advice, consider **patient involvement** in the cases when the determination of UMN existence is a deciding factor for granting PRIME, and in the kick-off meeting discussions.

The industry request to extend PRIME to **extensions of indications** of authorised products is not considered a priority at this timepoint, as it remains unclear what added value such additional support would provide, considering also the fact that once the product is authorised companies do have access to the rapporteur teams. Resources should be directed towards more effective measures.

## **2. Flexibility of SA provision for PRIME**

**To allow for more flexibility in the provision of scientific advice in the context of PRIME, EMA will:**

- build synergies with the ongoing initiatives of strengthening the Scientific Advice framework, in line with EMA's Regulatory Science Strategy;
- increase flexibility in a transparent manner, develop guidance clarifying rules of engagement with the Agency, Rapporteurs and under which situations increased flexibility in terms of scientific advice provision could be considered;
- give due consideration to the possibility of regular involvement of the Rapporteur team in scientific advices. The most appropriate experts for a given question at a given point in time should be involved. Support strong and collegial knowledge building across the network, see point below.

## **3. Knowledge building to support AA**

### ***Product development tracker***

The annual update on the ongoing development of PRIME product provided by the company, as it exists today, is seen as an important area for improvement to support the Rapporteur team in their assessment work, both during development and in the run-in to the MAA submission.

EMA will look into the development of a product development tracker, which would form the basis for interactions with the company at certain milestones and whenever key updates to the development programme are envisaged, to provide the most up-to date snapshot of the development status and indexing previous discussions with regulators.

The document would, amongst others:

- cover the key development areas identified in the SA/MO analysis, to support proactive

identification of the areas of input in the development plan,

- record and provide a link to all forms of rapporteur and EMA engagement (advices, letters) to contribute towards the knowledge building of the progress of the PRIME product development
- note outcome of discussions or completed studies (in line with EMA advice, divergent),
- allow, in the absence of updates, to identify programs that have stalled or companies that are not effectively using opportunities for support, hence allowing to focus resources on developments that would most benefit from input.
- serve as a guidance for the discussion at a dedicated meeting (the submission readiness meeting).

### ***Submission readiness' meeting***

In terms of possible areas for enhancement of support to PRIME products, the surveys to Industry and to Regulators conducted by the Agency identified the possibility to strengthen engagement between the kick-off meeting and the submission of the marketing authorisation application.

It is also noted that whilst the vast majority of PRIME products for which a marketing authorisation application was submitted started their regulatory review under accelerated assessment, a significant proportion of PRIME applications still reverted to standard timetable (approximately 56%). This shows that there is room to optimise current interactions to support the necessary knowledge acquisition throughout development and thus facilitate accelerated assessment. Furthermore, there are currently no means for regulators to ensure that the application is mature enough/addresses relevant points discussed during development ahead of the submission of the marketing authorisation application.

A **submission readiness** meeting reviewing the status of key development discussions and the implementation of advices would strengthen the upcoming MAA assessment. It would also assess the realistic chance of obtaining and maintaining an accelerated assessment timetable by avoiding the submission of premature applications.

The submission readiness meeting would be envisaged as a “closing kick-off meeting”, in order to review the main areas of development of the product identified at the kick-off meeting and discussed in the context of scientific advice and specifically to advise on any key deficiencies or submission planning approaches. While applicants remain free to choose their submission strategy and timing, the development of the future framework for such meetings would need to keep a balanced approach between advising on submission readiness and sufficiency of the data to support an MAA.

Therefore, EMA will consider together with the network suitability of organising ‘Submission readiness’ meetings towards the end of the development programme, ahead of a potential marketing authorisation application.

## 6. Conclusion and next steps

PRIME exists to support the development of promising medicines that target an area of unmet medical need and have therefore the potential to be of significant clinical value for public health.

It is in the interest of patients that available resources from regulators and developers are invested effectively and wisely, so that the efforts invested in PRIME have a tangible impact on rapid access to safe, transformative medicines, and make a real difference to the lives of patients.

Many important and innovative medicines are under development, which would not benefit from PRIME, as their development plans are finalised and already in progress, or the company has sufficient expertise and assurance to design their studies.

On the basis of the available experience during the first five years of operation of the PRIME scheme, all parameters suggest a trend for a positive impact of PRIME on evaluation times, which is more pronounced for SMEs and ATMPs. The majority of PRIME products are also orphan-designated. It would therefore appear that the scheme is well placed to have a positive impact on products that hold the potential to address an unmet medical need. This review also re-confirmed that provision of advice, and compliance of the company with that advice, enhances the MAA success rate.

PRIME currently offers additional support in the form of a dedicated contact point at EMA, early rapporteur appointment and consolidated development overview via a kick-off meeting. The possibility for adjustments and efficiency gains was identified in three areas:

- PRIME eligibility: scope and timing
- Flexibility of Scientific Advice provision for PRIME
- Knowledge building to support accelerated assessment

The report makes recommendations on scientific and procedural changes that will be taken forward,

with a view to give a clear indication of expectations in terms of evidence, knowledge gain during development, and prepare for later MAA submission and assessment.

Based on these findings and recommendations, concrete activities to further strengthen the scheme will be established, including, as appropriate, development and/or update of relevant guidance on PRIME.

This will consider, and exploit synergies with other initiatives, including changes to the Scientific Advice process and learnings from recent rapid product development support initiatives in the context of the COVID-19 pandemic, and leveraging changes to the legal European regulatory framework. Furthermore, engagement with other European and international decision makers should be strengthened.



The PRIME scheme established by EMA is a tool that has the patients and their interests at the very core of its rationale. Patients living with spinal muscular Atrophy (SMA) have benefited from it in a number of times since its creation as different therapies that are addressing unmet needs of our community have been accepted for PRIME. This has meant, not only that the development and assessment of these therapies will be carefully supported and accelerated, so that they can reach us in a timely manner, but also that the patient voice has been heard, and our continued need for more treatment options has been taken onboard by the EMA.

---

*Mencía de Lemus  
(SMA Europe)*

## 7. Annexes

### 7.1 Information on PRIME products that have received a marketing authorisation

### 7.2 Survey questions

7.2.1. Survey to Industry from EMA on PRIME products with an MAA

7.2.2. Survey to Industry from EMA on PRIME products without an MAA

7.2.3. Survey to Regulatory partners from EMA

7.2.4. Survey to Industry from industry associations

**Table 2.** Information on PRIME products that have received a marketing authorisation

Product name (INN)	Type of product	ODD	SME status at time of MAA	Therapeutic area	Therapeutic indication granted	MAA evaluation start date	Date of CHMP opinion	AA at start of evaluation /time of opinion	Outcome of MAA	SA/PA
Abecma (Idecabtagene vicleucel)	ATMP	Yes	No	Oncology	Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.	21/05/2020	24/06/2020	Yes/No	CMA	6
Blenrep (Belantamab mafodotin)	Biological	Yes	No	Oncology	Monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.	30/01/2020	23/07/2020	Yes/Yes	CMA	7
Bylvay (Odevixibat)	Chemical	Yes	Yes	Gastroenterology /hepatology	Treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.	26/11/2020	20/05/2021	Yes/Yes	MA under EC	4
Ervebo (Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live))	Biological	No	No	Infections	Active immunization of individuals 18 years of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus. The use of Ervebo should be in accordance with official recommendations.	28/03/2019	17/10/2019	Yes/Yes	CMA	2

Product name (INN)	Type of product	ODD	SME status at time of MAA	Therapeutic area	Therapeutic indication granted	MAA evaluation start date	Date of CHMP opinion	AA at start of evaluation /time of opinion	Outcome of MAA	SA/PA
Evrysdi (Risdiplam)	Chemical	Yes	No	Neurology	Treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.	13/08/2020	25/02/2021	Yes/Yes	Standard MA	5
Givlaari (Givosiran)	Chemical	Yes	No	Endocrinology - Gynaecology - Fertility - Metabolism	Treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older.	18/07/2019	30/01/2020	Yes/Yes	Standard MA	3
Hepcludex (Bulevirtide)	Chemical	Yes	Yes	Infections	Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.	31/10/2019	28/05/2020	Yes/No	CMA	2
Idefixir (Imlifidase)	Biological	Yes	Yes	Immunology - Rheumatology - Transplantation	Desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefixir should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.	28/02/2019	13/07/2020	No/N.A.	CMA	1
Imcivree (Setmelanotide)	Chemical	Yes	Yes	Endocrinology - Gynaecology - Fertility - Metabolism	Treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.	16/07/2020	20/05/2021	Yes/No	Standard MA	3
Kymriah (Tisagenlecleucel)	ATMP	Yes	No	Oncology	Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	23/11/2017	26/07/2018	Yes/No	Standard MA	6

Product name (INN)	Type of product	ODD	SME status at time of MAA	Therapeutic area	Therapeutic indication granted	MAA evaluation start date	Date of CHMP opinion	AA at start of evaluation /time of opinion	Outcome of MAA	SA/PA
Oxlumo (Lumasiran)	Chemical	Yes	No	Uro-nephrology	Treatment of primary hyperoxaluria type 1 (PH1) in all age groups.	23/04/2020	15/10/2020	Yes/Yes	Standard MA	2
Polivy (Polatuzumab vedotin)	Biological	Yes	No	Oncology	Treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant, in combination with bendamustine and rituximab.	25/01/2019	14/11/2019	Yes/No	CMA	7
Rozlytrek (Entrectinib)	Chemical	No	No	Oncology	Monotherapy for the treatment of adult and paediatric patients 12 years of age and older, with solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options (see sections 4.4 and 5.1). Monotherapy for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.	30/01/2019	28/05/2020	No/N/A	CMA	7
Skysona (Elivaldogene autotemcel)	ATMP	Yes	No	Neurology	Treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA)-matched sibling haematopoietic stem cell (HSC) donor is not available	01/10/2020	20/05/2021	Yes/No	Standard MA	6

Product name (INN)	Type of product	ODD	SME status at time of MAA	Therapeutic area	Therapeutic indication granted	MAA evaluation start date	Date of CHMP opinion	AA at start of evaluation /time of opinion	Outcome of MAA	SA/PA
Tecartus (Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured)	ATMP	Yes	Yes	Oncology	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor	28/01/2020	15/10/2020	Yes/No	CMA	4
Yescarta (Axicabtagene ciloleucel)	ATMP	Yes	Yes	Oncology	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	17/08/2017	26/07/2018	Yes/No	Standard MA	3
Zolgensma (Onasemnogene abeparvovec)	ATMP	Yes	No	Neurology	Treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	01/11/2018	26/03/2020	Yes/No	CMA	3
Zynteglo (Betibeglogene autotemcel)	ATMP	Yes	No	Haematology - Hemostaseology	Treatment of patients 12 years and older with transfusion-dependent $\beta$ thalassaemia (TDT) who do not have a $\beta^0/\beta^0$ genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.	04/10/2018	26/04/2019	Yes/Yes	CMA	5



# Survey for PRIME designated medicinal products, which have submitted a MAA

Fields marked with \* are mandatory.

## Survey for PRIME designated medicinal products, which have submitted a marketing authorisation application

To companies granted PRIME and that went through the marketing authorisation regulatory process; please complete one questionnaire per product

This survey is part of the 5-year analysis of the PRIME scheme and its goal is to inform the review of the performance of the scheme, to ensure that it delivers the expected impact on public health and adapt its scope and features, if applicable.

This survey will be open for input until **30 June 23:59 CET**.

Your Company will also receive a general Industry survey, to capture Industry's views on the PRIME scheme at Company level, which is complementary to this product specific survey.

### **Data Protection Statement**

#### **Collection of data**

In this survey EMA does not collect or process personal data. Therefore, please make sure that you do not reveal your identity or include other personal data in the free text answers. The survey is designed to collect the answers only in an aggregate and anonymous format. The responses will only be evaluated and the results shared in an aggregate way.

For the collection of data in this Survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: <https://ec.europa.eu/eusurvey/home/privacystatement>.

The EU Survey external system uses:

- Session "cookies" in order to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey in order to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request. Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

### **Purpose of data processing**

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the particular subject-matter of the survey.

### **Location of data storage**

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

### **Publication of data**

Data collected in this survey will not be published, but aggregated survey results may be shared with third parties.

## **1 Applicant and background**

---

\* 1.1 Are you an SME:

- Yes  
 No

\* 1.2 Type of product:

- Chemical  
 Biological  
 Advanced Therapy Medicinal product (ATMP)

1.3 Additional details (optional)

\* 1.4 What is your company's overall experience with the European Medicines' Agency (EMA) Priority Medicines (PRIME) scheme? (tick all that apply)

- Multiple PRIME-designated products  
 A single PRIME-designated product

- PRIME applications submitted and rejected
- PRIME applications submitted and pending decision
- Marketing authorization for PRIME product granted
- Marketing authorization for PRIME product withdrawn
- Marketing authorization for PRIME product refused
- Marketing authorisation application for PRIME product under assessment

## 2 Experience with the PRIME scheme during development

---

2.1 How much did the PRIME interactions support your development program on (rate lowest 1 to highest 5 or N/A):

*at least 5 answered row(s)*

	1	2	3	4	5	n /a
* Scientific aspects - Quality	<input type="radio"/>					
* Scientific aspects - Non-clinical	<input type="radio"/>					
* Scientific aspects - Clinical	<input type="radio"/>					
* Procedural/regulatory aspects	<input type="radio"/>					
* Subsequent EMA interactions (e.g. on paediatric, orphan, scientific advice)	<input type="radio"/>					
* Other? Please specify:	<input type="radio"/>					

2.2 Other? Please specify:

2.3 How useful was the support offered by EMA (rate lowest 1 to highest 5 or N/A):

*at least 5 answered row(s)*

	1	2	3	4	5	n/a
* Clarity of guidance documents on EMA website	<input type="radio"/>					
* In-person pre-submission discussion	<input type="radio"/>					
* Communication with the agency ahead of the kick-off meeting	<input type="radio"/>					
* At the kick-off meeting	<input type="radio"/>					
* Between the kick-off meeting and MAA submission	<input type="radio"/>					

2.4 Further comments

2.5 How useful was the support offered by the rapporteur team (rate lowest 1 to highest 5)?

	1	2	3	4	5	n/a
At the kickoff meeting	<input type="radio"/>					
Between the kickoff meeting and MAA submission	<input type="radio"/>					

2.6 Further comments on the support offered by EMA or Rapporteur team (optional)

2.7 Did PRIME facilitate your product development (rate lowest 1 to highest 5)?:

*at least 5 answered row(s)*

	1	2	3	4	5	n/a
* By accelerating development timelines	<input type="radio"/>					
* By facilitating the regulatory review process	<input type="radio"/>					
* By facilitating maintenance of accelerated assessment during evaluation	<input type="radio"/>					
* By facilitating planning for post-authorisation safety and efficacy follow-up	<input type="radio"/>					

2.8 Further comments

2.9 Do you think PRIME designation facilitated global development of your product? (rate lowest 1 to highest 5)

2.10 Do you think PRIME designation facilitated global of your product convergence of regulatory requirements? (rate lowest 1 to highest 5)

2.11 How supportive would you be of strengthened dialogue with international regulators (e.g. FDA) to support global development as part of PRIME interactions? (rate lowest 1 to highest 5)

2.12 Further to 2.25, please provide further comments below, if necessary:

2.13 Do you have any ATMP-specific development considerations you would like to share (comment):

- Quality
- Non-clinical
- Clinical
- Post-authorisation safety and efficacy follow-up
- Other

\* 2.14 Are you aware of the Quality toolbox currently in public consultation?

Please find the link below to the Quality toolbox: <https://www.ema.europa.eu/en/toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime-marketing>

- Yes
- No

### 3 PRIME and downstream decision makers

---

\* 3.1 Access facilitation: do you think that PRIME designation supported an easier or expedited evaluation by HTAs and Payers?

- Yes
- No

\* 3.2 If yes, please select any of the following (multiple possible)

- By supporting the design of studies satisfying multiple stakeholder requirements
- by showing the importance of the product to address an unmet need
- By enhancing the willingness to organise parallel EMA/HTA advice
- By facilitating getting reimbursement
- Other (specify)

\* 3.3 If no, please select any of the following (multiple possible)

- Downstream decision makers had different evidence needs
- Additional studies were requested for HTA purposes
- By the time we were granted PRIME the HTA advice had already been given

We requested but were not granted parallel EMA/HTA discussion

Other (specify)

3.4 Yes - Other (specify)

3.5 No - Other (specify)

3.6 Post MAA interactions: to improve the PRIME procedure and support an evidence generation continuum, we would be extremely grateful to understand which HTA interactions you have had so far and in the context of relative effectiveness assessment to inform pricing and reimbursement decisions. This information will be commented in the reports only in an aggregated manner and after your consent on the text.

Please fill in the table below:

	HTA/Payer agency contacted	Month/year (field)	Time in months) for an HTA decision outcome (field)	Outcome of the HTA decision (added benefit; no added benefit; no conclusion on added benefit; other (please explain)	Do you feel that PRIME has influenced the relative effectiveness assessment timeline by making it (shorter ; longer ; the same)	New issues were identified not covered by regulatory development support and/or marketing authorization decision, requiring additional studies (y/n)	PRIME helped to support the discussion on addressing unmet medical needs (UMN) (1-5)	Other comments
HTA 1								
HTA 2								
HTA 3								
HTA 4								
HTA 5								
HTA 6								
HTA 7								
HTA 8								
HTA 9								
HTA 10								

## 4 Closing question on experience with the PRIME scheme

---

4.1 Please indicate your (rate lowest 1 to highest 5) overall satisfaction with the support received by the Agency/Assessment teams\* (mandatory)

4.2 Please indicate your (rate lowest 1 to highest 5) your likelihood to use PRIME scheme for future developments\* (mandatory)

\* 4.3 If you could suggest one improvement to PRIME, what would it be?



# Survey for PRIME designated medicinal products, which have not submitted a marketing authorisation application

Fields marked with \* are mandatory.

## Survey for PRIME designated medicinal products, which have not submitted a marketing authorisation application

To companies granted PRIME and that did not go through MAA approval process; please complete one questionnaire per product

This survey is part of the 5-year analysis of the PRIME scheme and its goal is to inform the review of the performance of the scheme, to ensure that it delivers the expected impact on public health and adapt its scope and features, if applicable

This survey will be open for input until **30 June 23:59 CET**.

Your Company will also receive a general Industry survey, to capture Industry's views on the PRIME scheme at Company level, which is complementary to this product specific survey.

### Data Protection Statement

#### **Collection of data**

In this survey EMA does not collect or process personal data. Therefore, please make sure that you do not reveal your identity or include other personal data in the free text answers. The survey is designed to collect the answers only in an aggregate and anonymous format. The responses will only be evaluated and the results shared in an aggregate way.

For the collection of data in this Survey, EMA relies on the EU Survey external system. For more

information on how EU Survey processes personal data, please see: <https://ec.europa.eu/eusurvey/home/privacystatement>.

The EU Survey external system uses:

- Session "cookies" in order to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey in order to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers. IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

### **Purpose of data processing**

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the particular subject-matter of the survey.

### **Location of data storage**

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

### **Publication of data**

Data collected in this survey will not be published, but aggregated survey results may be shared with third parties.

## **1 Applicant and background**

---

\* 1.1 Are you an SME:

- Yes
- No

\* 1.2 Type of product:

- Chemical
- Biological
- Advanced Therapy Medicinal product (ATMP)

\* 1.3 What is your company's overall experience with the European Medicines' Agency (EMA) Priority Medicines (PRIME) scheme? (tick all that apply)

- Multiple PRIME-designated products
- A single PRIME-designated product
- PRIME applications submitted and rejected
- PRIME applications submitted and pending decision

- Marketing authorization application for PRIME product under assessment
- Marketing authorization for PRIME product granted
- Marketing authorization for PRIME product withdrawn
- Marketing authorization for PRIME product refused

## 2 Experience with the PRIME scheme during development

2.1 How much did the PRIME interactions support your development program on (rate lowest 1 to highest 5 or N/A):

*at least 5 answered row(s)*

	1	2	3	4	5	n/a
* Scientific aspects - Quality	<input type="radio"/>					
* Scientific aspects - Non-clinical	<input type="radio"/>					
* Scientific aspects - Clinical	<input type="radio"/>					
* Procedural/regulatory aspects	<input type="radio"/>					
* Subsequent EMA interactions (e.g. on paediatric, orphan, scientific advice)	<input type="radio"/>					
* Other? Please specify:	<input type="radio"/>					

2.2 Other? Please specify:

2.3 How useful was the support offered by EMA (rate lowest 1 to highest 5 or N/A):

*at least 5 answered row(s)*

	1	2	3	4	5	n/a
* Clarity of guidance documents on EMA website	<input type="radio"/>					
* In-person pre-submission discussion	<input type="radio"/>					
* Communication with the agency ahead of the kick-off meeting	<input type="radio"/>					
* At the kickoff meeting	<input type="radio"/>					
* Between the kickoff meeting and present	<input type="radio"/>					

2.4 Further comments

2.5 How useful was the support offered by the rapporteur team (rate lowest 1 to highest 5 or N/A)?

*at least 2 answered row(s)*

	1	2	3	4	5	n/a
* At the kickoff meeting	<input type="radio"/>					
* Between the kickoff meeting and present	<input type="radio"/>					

2.6 Further comments on the support offered by EMA or Rapporteur team (optional)

2.7 Do you expect that PRIME may facilitate your product development (rate lowest 1 to highest 5)?

	1	2	3	4	5	n/a
* By accelerating development timelines	<input type="radio"/>					
* By facilitating the regulatory review process	<input type="radio"/>					
* By facilitating maintenance of accelerated assessment during evaluation	<input type="radio"/>					
* By facilitating planning for post-authorisation safety and efficacy follow-up	<input type="radio"/>					

2.8 Further comments

2.9 Do you think PRIME designation may facilitate global development of your product? (rate lowest 1 to highest 5)

2.10 Do you think PRIME designation may facilitate convergence of regulatory requirements? (rate lowest 1 to highest 5)

2.11 How supportive would you be of strengthened dialogue with International Regulators (e.g. FDA) to support global development? (rate lowest 1 to highest 5)

2.12 Further to 2.24, please provide further comments below, if necessary:

2.13 Do you have any ATMP-specific development considerations you would like to share (comment):

- Quality

- Non-clinical
- Clinical
- Post-authorisation safety and efficacy follow-up
- Other

2.14 Are you aware of the Quality toolbox currently in public consultation?

Please find the link to the Quality toolbox: <https://ec.europa.eu/eusurvey/runner/PRIMEgrantedNoMAA>

- Yes
- No

### 3 PRIME and downstream decision makers

---

3.1 Access facilitation: do you think that PRIME designation might support an easier or expedited evaluation by HTAs and Payers?

- Yes
- No

\* 3.2 If yes, please select as many options (multiple answers possible):

- By supporting the design of studies satisfying multiple stakeholder requirements
- By showing the importance of the product to address an unmet need
- By enhancing the willingness to organise parallel EMA/HTA advice
- By facilitating getting reimbursement
- Other (specify)

\* 3.3 If no please select as many options (multiple answers possible):

- Downstream decision makers had different evidence needs
- Additional studies were requested for HTA purposes
- By the time we were granted PRIME the HTA advice had already been given
- We requested but were not granted parallel EMA/HTA discussion
- Other (specify)

3.4 Yes - Other (specify)

3.5 No - Other (specify)

3.6 **HTA interactions:** to improve the PRIME procedure and support an evidence generation continuum, we would be extremely grateful to understand which HTA interactions you have had so far to prepare for relative effectiveness assessment to inform pricing and reimbursement decisions. This information will be commented in the reports only in an aggregated manner and after your consent on the text.

Please fill in the table with the required information:

	HTA/Payer agency contacted	Month/year (field)	New issues were identified not covered by regulatory development support, requiring additional studies (y/n)	PRIME helped to support the discussion on addressing unmet medical needs (UMN) (1-5)	Other comments
HTA 1					
HTA 2					
HTA 3					
HTA 4					
HTA 5					
HTA 6					
HTA 7					
HTA 8					
HTA 9					
HTA 10					

## 4 Closing question on experience with the PRIME scheme

---

4.1 Overall satisfaction with the support received so far by the Agency/Rapporteur team\* (mandatory)

4.2 Likelihood to use PRIME scheme for future developments\* (mandatory)

\* 4.3 If you could suggest one improvement to PRIME, what would it be?

# Survey to regulatory partners

Fields marked with \* are mandatory.

## Survey to regulatory partners

---

This survey is part of the 5-year analysis of the PRIME scheme and its goal is to inform the review of the performance of the scheme, to ensure that it delivers the expected impact on public health and adapt its scope and features, if applicable.

Any proposed changes to the scope and features of PRIME will be discussed with the PRIME oversight group and the EU regulatory network, including relevant Scientific Committees.

This survey will be open for input until 30 September 2021.

## Data Protection Statement

---

### Collection of data

In this survey EMA does not collect or process personal data. Therefore, please make sure that you do not reveal your identity or include other personal data in the free text answers. The survey is designed to collect the answers only in an aggregate and anonymous format. The responses will only be evaluated and the results shared in an aggregate way.

For the collection of data in this Survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: <https://ec.europa.eu/eusurvey/home/privacystatement>.

The EU Survey external system uses:

- Session "cookies" in order to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey in order to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers. IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

### Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the particular subject-matter of the survey.

### Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

### Publication of data

Data collected in this survey will not be published, but aggregated survey results may be shared with third parties.

## 1. Your experience with PRIME

---

\* 1.1 Your experience with PRIME is as follows (tick all that apply):

- Regular participant to PRIME kick-off meetings
- Rapporteur of PRIME products in pre-submission phase
- Rapporteur of PRIME products that have submitted a marketing authorization application
- SAWP Reviewer of PRIME eligibility requests

## 2. Products in PRIME

---

\* 2. 1 Do you think we are getting the right products into PRIME in terms of their potential to address major public health needs?

- Yes
- No (specify)

\* 2.2 No (specify)

2.3 Further comments

\* 2.4 Do you think we are getting the PRIME products at the right stage of development?

- Yes
- No

\* 2.5 If no, please tick all that apply:

- We should accept earlier entry for promising medicines (beyond SMEs)
- We should accept promising products in late stage development in need of specific support (e.g. important PASS/PAES advice, engagement with HTAs, engagement with international regulators)
- Other reasons (specify)

\* 2.6 No, other reasons (specify)

## 2.7 Further comments

## 3. Engagement during development

---

### \* 3.1 How closely should we follow the PRIME product development?

- More closely
- Less closely
- The current level of interaction is about right

### \* 3.2 If more closely, please tick all that apply:

- By being given access to a rolling update that summarises the most recent development updates, instead of an annual update
- By having more frequent meetings with the company
- With specific follow ups for certain complex products (e.g. ATMPs)
- Other (specify)

### \* 3.3 If less closely, please please tick all that apply:

- The current annual updates are not useful
- I am interested only to be involved in the SA
- Other (specify)

### 3.4 More closely - Other (specify)

### 3.5 Less closely - Other (specify)

### 3.6 How useful is the kick-off meeting in terms of establishing an interaction plan for subsequent follow-up? (rate lowest 1 to highest 5)

### \* 3.7 Companies contact. We would like to understand how often you are directly contacted once appointed as PRIME Rapporteur, and what your preference is (tick all that apply)

- In the majority of cases, companies contact me directly when they have a question, without going via the EMA
- In the majority of cases, companies contact EMA PRIME coordinator first, and EMA filters the issues that need to be brought to my attention
- I would prefer that it is made clearer that companies should always go via EMA first

### 3.8 Further comments

\* 3.9 Would you see any opportunities to strengthen interaction with Rapporteur between the kick-off meeting and submission of MAA?

\* 3.10 What would help you in preparing for evaluation of the marketing authorization application for a PRIME product?

## 4. Impact of PRIME in the marketing authorisation evaluation process

---

4.1 To what extent do you think PRIME facilitates the marketing authorization evaluation process (rate lowest 1 to highest 5):

	1	2	3	4	5	N/A
* Scientifically - Quality	<input type="radio"/>					
* Scientifically - Non-Clinical	<input type="radio"/>					
* Scientifically - Clinical	<input type="radio"/>					
* Procedurally/regulatory	<input type="radio"/>					
* By facilitating maintenance of accelerated assessment	<input type="radio"/>					
* By facilitating planning for post-authorisation safety and efficacy follow-up	<input type="radio"/>					
* Other (specify)	<input type="radio"/>					

4.2 Other (specify)

4.3 Further comments

## 5. Possible changes to support offered to PRIME products

---

5.1 How supportive would you be to introduce any of the following changes to the support offered for products in PRIME (rate lowest 1 to highest 5):

	1	2	3	4	5
* More flexibility in scientific advice for PRIME products	<input type="radio"/>				
* Possibility of rolling review to enable earlier submission and facilitate maintenance of accelerated assessment	<input type="radio"/>				
* Additional interaction with Applicant at certain key milestones and before submission of the MAA (e.g. submission readiness)	<input type="radio"/>				
* Early entry to PRIME for non-SMEs	<input type="radio"/>				
* Widening of scope of PRIME to new therapeutic indications of existing products	<input type="radio"/>				
* Further engagement with International regulators (e.g. FDA) for PRIME products	<input type="radio"/>				
* Further engagement with HTAs	<input type="radio"/>				

\* 5.2 If you could suggest one improvement to PRIME, what would it be?

# Industry Survey on PRIME

This survey is a general survey intended to capture Industry's views on the PRIME scheme, conducted at company level and which is complementary to a survey conducted by EMA for the medicinal products designated with PRIME. Its goal is to inform the review of the performance of the scheme, to ensure that it delivers the expected impact on public health and adapt its scope and features, if applicable.

A single company response to this survey is to be submitted.

The survey will be open for input until 30 June 23:59 CET.

Important note: in case you have received a PRIME designation, you will also receive another survey from the Agency to capture specific PRIME experience feedback related to that designation. If you have not received a PRIME designation questionnaire for a product granted PRIME, you should contact: [PRIME@ema.europa.eu](mailto:PRIME@ema.europa.eu).

If you have any questions or challenges filling out this questionnaire, please reach out to your trade association representative or send an e-mail to [IAI.PRIME.Industry@gmail.com](mailto:IAI.PRIME.Industry@gmail.com).

In the context of the General Data Protection Regulation (GDPR), no personal data is expected to be collected via this survey and as such respondents should endeavor to avoid including any identifiable information related to companies or products.

---

**\*Required**

## General Questions

1. Is your company a Small & Medium Enterprise (SME)? \*

*Mark only one oval.*

Yes

No

## 2. What type of products does your company develop? \*

*Tick all that apply.*

- Chemicals
- Biologics
- Advanced Therapy Medicinal Products (ATMPs)

Other:  \_\_\_\_\_

## 3. Does your company have products that have received a PRIME-designation? \*

*Mark only one oval.*

- Yes    *Skip to question 9*
- No

## Feedback from industry with no PRIME scheme experience

## 4. Which below option(s) describe best the reason why you did not take part in the PRIME scheme? \*

*Tick all that apply.*

- The company does not investigate eligible products that can be considered within the scope of the scheme
- The company is NOT interested in applying to the scheme
- The company is interested BUT still does not have enough clinical evidence to request it
- The Company has applied to PRIME and the designation has not been granted

Other:  \_\_\_\_\_

## 5. Have you ever submitted a PRIME designation application that was rejected? \*

*Mark only one oval.*

- Yes
- No    *Skip to question 9*

### Feedback from industry with rejected PRIME scheme applications

6. Please rate the clarity of grounds for refusal in the letter \*

*Mark only one oval.*

	1	2	3	4	5	
Least clear	<input type="radio"/>	Most clear				

7. Please add any observations from the refusal that you find relevant for your experience (e.g. how it helped further development, thoughts on claimed reasons for refusal, etc.).

---

---

---

---

---

8. Despite the rejection, are you still considering using the scheme in the future? \*

*Mark only one oval.*

Yes

No

### Feedback from industry on the PRIME scheme generally

9. What is your company's overall experience with the European Medicines' Agency (EMA) Priority Medicines (PRIME) scheme? \*

*Tick all that apply.*

- Multiple PRIME-designated products
- A single PRIME-designated product
- PRIME applications submitted and rejected
- PRIME applications submitted and pending decision
- Marketing authorization for PRIME product granted
- Marketing authorization for PRIME product refused
- Marketing authorization application for PRIME product withdrawn
- No PRIME designation requests submitted

10. What were the reasons that made you not apply for PRIME or not consider it as part of your regulatory strategies for some or all assets so far? \*

*Tick all that apply.*

- We did not know it existed
- We do not consider the scheme helpful to support development
- Lack of resources to manage the application
- Unclear benefit or value from the scheme
- My product was too late in development
- Belief that although products were fulfilling the criteria, the designation would not be granted
- Concerns about transparency in case of non-eligibility
- Based on precedent, submission was internally discouraged
- Based on initial pre-submission discussion with EMA
- Not applicable

Other:  \_\_\_\_\_

11. Would you say that your company: \*

*Mark only one oval.*

- Is actively considering PRIME for assets in the future;
- Is generally interested in PRIME but not actively considering;
- Is not interested in PRIME in the future.

12. Please elaborate on possible reasons for your answer above.

---

---

---

---

---

13. For potentially eligible assets would you say your company sees PRIME as: \*

*Mark only one oval.*

- A regular part of a global expedited pathway strategy;
- Considered to expedite certain global submissions, but not regularly used;
- Rarely or never considered as part of an expedited strategy.

14. What is your opinion of potential advantages offered by PRIME (rank below from 1 as lowest opinion to 5 as highest opinion)? \*

Mark only one oval per row.

	1	2	3	4	5
Acceleration of development timelines	<input type="radio"/>				
Early rapporteur appointment	<input type="radio"/>				
Dedicated EMA contact point	<input type="radio"/>				
Strengthened development support	<input type="radio"/>				
Expedited regulatory review process	<input type="radio"/>				
Facilitating global development	<input type="radio"/>				
Support of HTA evidence package generation	<input type="radio"/>				
Facilitate planning for post-authorisation safety and efficacy follow-up	<input type="radio"/>				

15. Are there other reasons to the ones listed in the question above?

---

---

---

---

---

16. Please rate the following based on your experience in considering PRIME (rank below from 1 as lowest opinion to 5 as highest opinion)? \*

*Mark only one oval per row.*

	1	2	3	4	5
Clarity of guidance documents on EMA website	<input type="radio"/>				
In-person pre-submission discussion	<input type="radio"/>				

### PRIME and other global expedited pathways

17. Did your company apply for any of the following global expedited pathways? \*

*Tick all that apply.*

- US FDA Breakthrough Therapy designation (BTD)
- Regenerative Medicine Advanced Therapy (RMAT)
- Japan's MHLW Sakigake
- MHRA's Innovative Licensing and Access Pathway (ILAP)
- China NMPA Breakthrough Therapy Drug Procedure
- None / Not applicable

Other:  \_\_\_\_\_

18. If yes to the question above, would your company typically apply for PRIME designation at around the same time? \*

*Mark only one oval.*

- Yes
- No
- Not applicable

19. When considering global expedited pathways as the ones listed above, what could be the possible reasons for choosing a different strategy on the use of PRIME in Europe as compared to other schemes?

---

---

---

---

---

20. How supportive would you be of strengthened dialogue with FDA and other regulators to support global development as part of PRIME interactions? \*

*Mark only one oval.*

	1	2	3	4	5	
Least supportive	<input type="radio"/>	Most supportive				

21. Please elaborate on possible reasons for the answer above.

---

---

---

---

---

### Refinements on the PRIME scheme

22. What would make you more likely to submit a PRIME application in the future?

---

---

---

---

---

23. If you could suggest one improvement to PRIME (that would not require a legislative change) what would it be?

---

---

---

---

---

---

This content is neither created nor endorsed by Google.

Google Forms

## European Medicines Agency

Domenico Scarlattilaan 6  
1083 HS Amsterdam  
The Netherlands

**Telephone** +31 (0)88 781 6000

**Send a question:** [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact)

[www.ema.europa.eu](http://www.ema.europa.eu)

### **PRIME: Analysis of the first 5 years' experience**

Findings, learnings and recommendations  
EMA/587035/2021

© European Medicines Agency, 2022.

Reproduction is authorised provided the source is acknowledged.

