PRIME Turns One

PRIME and Other Early Access Tools

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The European Medicines Agency's (EMA) PRIority MEdicines Scheme (PRIME) turned one year old in March 2017.[1] PRIME supports the development of medicines addressing unmet medical needs and medicines that provide a therapeutic advantage over existing treatments. This is achieved by offering the sponsor early, proactive, and enhanced support, which builds on the existing regulatory framework and tools to enable early patient access to innovative medicines.[2] This newest scheme provides some clear advantages over other programs, such as accelerated assessment, conditional marketing approval, and compassionate use, and can be used in conjunction with these programs. Other initiatives such as Adaptive Pathways and EMA-HTA (Health Technology Assessment) Parallel Scientific Advice also support clinical program development geared toward early patient access to innovative medicines.

"PRIME fosters the efficient development of medicines by reinforcing scientific and regulatory advice provided at various stages of the development program, and enhances communication between the sponsor and the EMA through the assigned contact points."

PRIME was originally proposed in a Reflection Paper in 2015 and then launched in March 2016.[3,4] In the first year, the EMA evaluated 91 applications and accepted 19 products into the program with one program discontinuation (five applications were considered to be out of scope).[5] The majority of products (56%) are advanced therapy medicinal products (i.e., tissue-engineered products, gene and cell therapies), with chemical drugs being the second largest group *(Figure 1)*. Although the scheme aims to support academic research groups and small to medium-sized enterprises (SMEs) specifically, only 42% of successful applications stemmed from SMEs with no applications thus far from academic institutions *(Figure 2)*.

To be eligible for PRIME, the proposed treatments generally must meet the eligibility criteria for accelerated assessment, i.e., they are medicinal products of substantial public health interest, particularly from the perspective of therapeutic innovation. A strongly substantiated mechanism of action, supportive preclinical data, and first-in-human (FIH) tolerance data, at a minimum, should be available. However, for candidates from small and medium-sized businesses and academia,

entry prior to the collection of human tolerance data may be possible according to the guidance.[7] However, clinical data at the exploratory stage generally is expected and significantly increases the chances of acceptance. Benefits for eligible sponsors include the following:

- Expected eligibility for accelerated assessment for the marketing authorization application
- Early appointment of a Committee for Medicinal Products for Human Use (CHMP) or Committee for Advanced Therapies (CAT - for Advanced Therapy Medicinal Products [ATMP]) Rapporteur
- Scientific advice on the overall development plan and at key developmental milestones with the involvement of appropriate stakeholders (e.g., regulators, HTA agencies, patients)
- Kickoff meeting to understand the development program and obtain preliminary guidance on the requirements for the marketing authorization application
- Dedicated contact point at the EMA

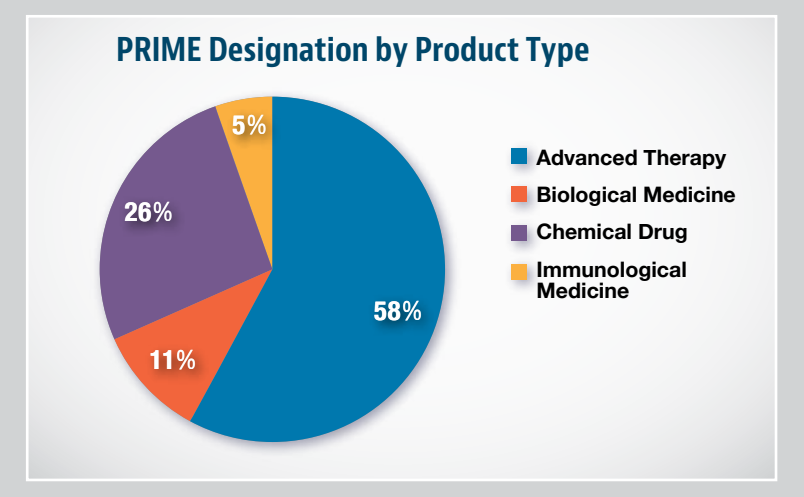
Some benefits will be delayed for sponsors entering with very limited or no clinical data. Only one of the 19 PRIME designated products provided only nonclinical and tolerability FIH data: A4250, a selective inhibitor of the ileal bile acid transporter for the treatment of progressive familial intrahepatic cholestasis by Albireo.[6]

PRIME fosters the efficient development of medicines by reinforcing scientific and regulatory advice provided at various stages of the development program, and enhances communication between the sponsor and the EMA through the assigned contact points. The support and guidance provided allow for an optimized and efficient development program for the generation of robust data supporting marketing authorization. Eligibility for accelerated assessment will be confirmed during the development program and further enabled through the sponsor-agency interactions.

There are several other early access tools for sponsors of medicines addressing unmet medical needs: accelerated assessment,[8] conditional marketing authorization (CMA),[9] and compassionate use[10] at the European Union (EU) level with some supplemental national programs *(Figure 3)*. Generally, programs can be used in combination, e.g., PRIME already rolls accelerated assessment into the advantages of the designation.

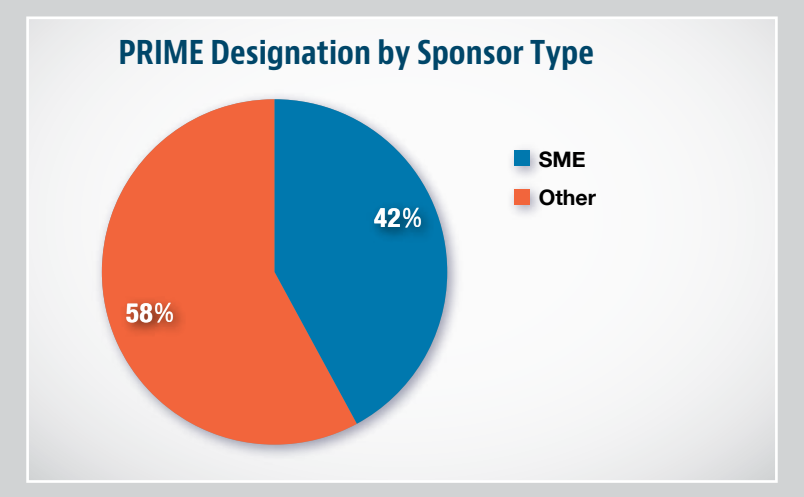
Accelerated assessment reduces the evaluation of a centralized marketing authorization application to 150 days.[8] The standard timeframe could be as much as 210 days depending on clock-stops initiated by requests for further information. Accelerated assessment is, itself, a program facilitating early access to medicines for patients. Sponsors would generally apply at least

Figure 1. PRIME Designation by Product Type



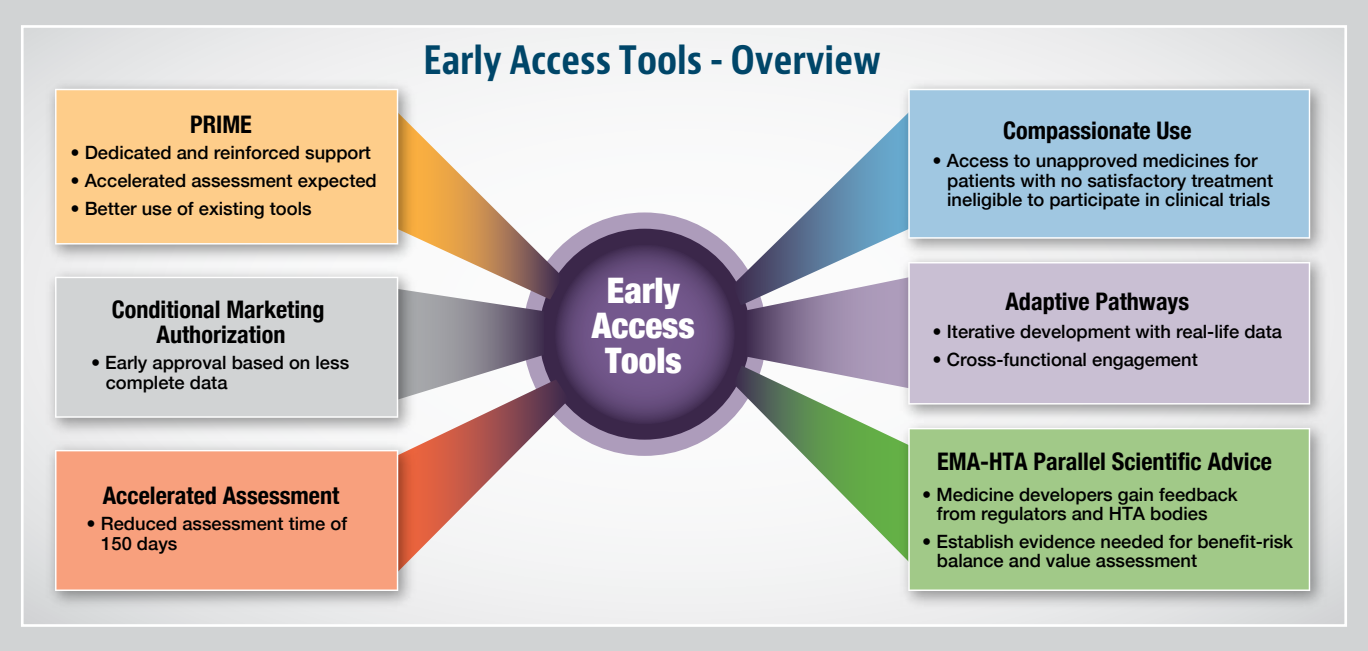
Percent of designations per product type of advanced therapy, biological, chemical, and immunological medicines of the total of 19 granted designations up to 23 March 2017.[6]

Figure 2. PRIME Designation by Sponsor Type



PRIME was implemented to support academic research groups and smaller biotechnology companies in particular; nonetheless, only 42% of the 19 designations were from SME applicants. However, including the declined applications, 46 applications (50%) came from SMEs, including one from an academic institution, and 40 applications (43%) from others.

Figure 3. Early Access Tools



Several early access tools are available within the European Union to support faster patient access to therapies for unmet medical needs in serious and life-threatening diseases.

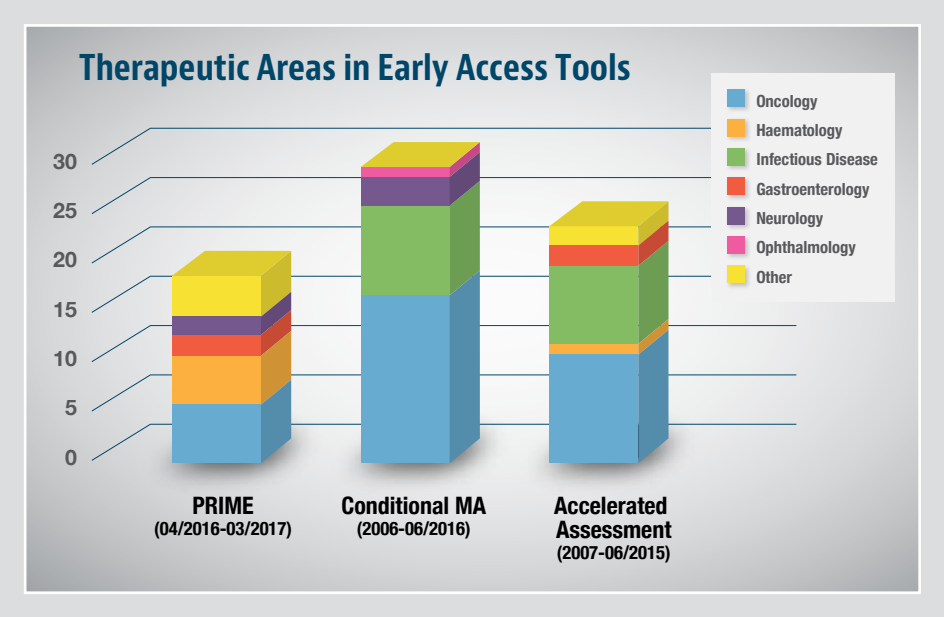
two to three months before the intended filing date for the marketing authorization to determine eligibility for accelerated assessment. However, the EMA strongly recommends a pre-submission meeting six to seven months in advance of filing to discuss the sponsor's intentions. The justification for eligibility for accelerated assessment must show that the medicinal product is of major health interest and an innovative therapeutic. Products accepted into the PRIME scheme generally are expected to qualify for accelerated assessment.

CMA may be granted for medicines that address an unmet medical need, where the immediate availability to patients outweighs the risk of the less comprehensive data available.[9] To qualify, medicines must belong to at least one of three categories: a) treat, prevent, or diagnose a seriously debilitating or life-threatening disease; b) intended for emergency use; or, c) designated as an orphan medicine. CMA is granted with specific obligations attached that ensure that comprehensive data will be available for the medicine in due course and the conditional approval can be converted into full approval. CMA is valid for one year and can be renewed with the aim to receive full marketing authorization by providing comprehensive data collected by completing the specific obligations.

The EMA published a 10-year report assessing the program from July 2006 to June 2016.[11] During that time, 30 medicines received CMA (6 additional applications received a positive recommendation from CHMP for CMA, but were not yet authorized at the time of data lock for the report and were therefore not included in the overall calculations). The average time to receive full marketing authorization was 4 years (0.48 to 7.12 years). Two-thirds of CMA applications were justified by 'no approved satisfactory treatment' (11) and 'improved treatment effect and/or safety vs. available therapies' (9). Only 14 marketing authorization applications contained the request for CMA consideration in the initial request, which may indicate a certain reluctance by sponsors to apply for this pathway. The consideration of CMA during the review procedure (14) or re-examination (2) generally led to longer review times due to clock-stops. Fifty-eight pivotal studies were identified and 31 of these were Phase II (including Phase I/II and IIb), with 21 pivotal Phase III studies. Almost two-thirds of applications receiving CMA (18) had prior scientific advice or protocol assistance. Eleven of the products converted their CMA to a full marketing authorization, 2 were withdrawn, and the remaining are still CMAs with less than 5 years of authorization. Over the past 10 years, there were only 22 unsuccessful applications for CMA (negative CHMP opinion or withdrawal by sponsor). Although there was a slight uptick in the applications for 2014 and 2015, no clear trend is discernible. Compared to the PRIME designation, very few requests have been received over the past 10 years. The appropriateness of considering a CMA for a PRIME-granted product should be addressed during one of the scientific advice meetings at key development milestones.

Generally, therapeutics for oncology indications made up the majority of products being eligible for an early access tool. Infectious disease products also played a major role for CMA (new chemical entities only) and accelerated assessment. However, none of the seven PRIME applications for a product to treat an infectious disease were successful. The remainder of granted applications were for a variety of therapeutic areas *(Figure 4)*.

Figure 4. Early Access Tool Utilization by Therapeutic Area



Number of applications granted for PRIME,[5] CMA[11] and accelerated assessment[12] for the timeframes, as indicated, as they address different therapeutic areas. There were a total of 19 PRIME designations, 30 CMA, and 24 accelerated assessment applications granted.

Compassionate use is an EU-wide program, which permits unauthorized medicines to become available to groups of patients under very specific and strict conditions. Compassionate use only applies to life-threatening, long-lasting, or seriously debilitating illnesses that cannot be treated with existing authorized medicines. Contrary to other early access programs, the use of a medicine in the compassionate use setting needs to be initiated by the national competent authority wishing to make the medicine available before authorization. Generally, the medicine must be undergoing clinical trials, and the EMA will offer an opinion on compassionate use. Currently, only four products have an opinion on their use under the program: Ledipasvir/Sofosbuvir, Daclatasvir, Sofosbuvir Gilead, and IV Zanamivir.[10] Three of those products are for the treatment of Hepatitis C, with the fourth for life-threatening influenza Virus A or B. Appropriateness of compassionate use should be determined at one of the sponsor meetings with the EMA.

Adaptive Pathways[13] is another of EMA's schemes to accelerate patient access to new innovative medicines. A pilot was initiated in 2014 for two years and 18 proposals were accepted for the initial face-to-face meeting to discuss the pathway. Adaptive Pathways is based on three principles: 1) iterative development including CMA and compassionate use; 2) real-life use to supplement clinical trial data through patient registries and pharmacovigilance; and, 3) early involvement of other stakeholders such as patients and HTA bodies (also see "EMA-HTA Parallel Scientific Advice" article in this issue). The key takeaway points from the pilot include that adaptive pathways can foster a multi-stakeholder communication to: 1) agree on a development program optimizing and aligning requirements as much as possible; 2) provide information for prospective planning of the development program; 3) aim to generate data for a common evidence base to address different stakeholders needs; and, 4) support evidence generation in challenging therapeutic areas.[14] However, the program is not for all products and needs to be carefully evaluated. Also, the involvement of patients, healthcare professionals, and payers in advice procedures needs further optimization. The EMA continues to explore the adaptive pathways approach, particularly in respect to parallel advice from EMA and HTA, and issued guidance for potential applicants.

The United Kingdom (UK) implemented the Early Access to Medicines Scheme (EAMS) in 2014, allowing the availability of promising new unlicensed medicines to treat high unmet medical needs to UK patients without delay.[15] The voluntary scheme follows a two-step evaluation: 1) assessment of clinical data to determine if the medicine would qualify as a Promising and Innovative Medicine (PIM); and, 2) scientific opinion assessing the benefit-risk ratio on the application by the Medicines and Healthcare Products Regulatory Agency (MHRA). Application for the EAMS requires sponsors to engage early with relevant decision bodies, including payers. All EAMS medicines are provided to the National Health Service (NHS) free of charge until a positive funding policy can be reached by the HTA.

PRIME has been likened to the U.S. Breakthrough Therapy Designation (BTD) that has been available as

an early access tool for the past five years.[16] The BTD is designed to expedite the development and review of drugs for serious conditions and life-threatening diseases that show preliminary clinical evidence indicating a substantial improvement on a clinically significant endpoint. Generally, clinically significant endpoints include those that measure an effect on irreversible morbidity or mortality, or symptoms that are serious consequences of the disease. A drug development program that receives BTD status will be eligible for other early access tools including fast-track designation (including priority review), intensive guidance during the development program, and an organizational commitment to involve senior U.S. Food and Drug Administration (FDA) managers. The BTD designation was implemented in July 2012 as part of the FDA Safety and Innovation Act (FDASIA) and guidance was published in May 2014.[17] From the implementation in 2012 through 30 September 2016, the FDA received 392 applications of which 141 designations were granted and 195 denied.[16] Twelve of the PRIME designated products have also publicly disclosed that they received BTD.[18] However, that does not mean that the other seven PRIME products do not qualify for BTD; there may be simple strategic considerations that offset the timing of applications. Both programs attract very similar product categories, while PRIME allows for candidates with less clinical experience and attracts more advance therapies. Additionally, PRIME allows for the early engagement with HTA bodies which ultimately make the market access decisions while the BTD does not engage in these discussions.

Choosing to apply for the PRIME scheme is a viable option for consideration for medicines that address an unmet medical need at an early clinical stage. The scheme provides consistent regulatory support through the assignment of a rapporteur, a dedicated contact point at the EMA to facilitate all interactions and enhanced interactions, including scientific and product development advice from multiple stakeholders, such as payers and/or patients. The scheme aims to optimize evidence collection to allow for faster patient access by including payers and other stakeholders in the clinical development program discussion. Products chosen for PRIME also may benefit from reduced review times through accelerated assessment. Should the EMA decide a potential medicine is not eligible for PRIME, the decision is made without prejudice and only minimal information is published by EMA. The sponsor can reapply once additional supportive clinical information becomes available. Additionally, access to the other early access tools mentioned here is not prevented due to ineligibility for PRIME. Each early access tool addresses a particular facet and the sponsor should consider capitalizing on these other tools. The applications for the PRIME scheme are short (less than 30 pages) and a decision is reached quickly (within 40 days). The benefits of acceptance into the scheme are likely to maximize the use of sponsor resources during clinical research, resulting in cost- and time-efficient drug development for much needed innovative medicines addressing unmet medical need. ■

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REFERENCES

[1] European Medicines Agency: First Anniversary of PRIME – Experience So Far. Press release 22 March 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/03/news_detail_002716.jsp&mid=WC0b01ac058004d5c1. Accessed 31 March 2017.

[2] European Medicines Agency: PRIME – PRIority MEdicines. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp. Accessed 30 March 2017.

[3] European Medicines Agency: Reflection Paper on a Proposal to Enhance Early Dialogue to Facilitate Accelerated Assessment of Priority Medicines (PRIME). EMA/CHMP/57760/2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/10/WC500196065.pdf. Accessed 31 March 2017.

[4] European Medicines Agency: Launch of PRIME – Paving the Way for Promising Medicines for Patients. Press release 7 March 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002484.jsp&mid=WC0b01ac058004d5c1. Accessed 31 March 2017.

[5] European Medicines Agency: Recommendations on Eligibility to PRIME Scheme. EMA/668812/2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Annex_to_CHMP_highlights/2017/03/WC500224565.pdf. Accessed 31 March 2017.

[6] European Medicines Agency: List of Products Granted Eligibility for PRIME. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439. Accessed 29 March 2017.

[7] European Medicines Agency: European Medicines Agency Guidance for Applicants Seeking Access to PRIME Scheme. EMA/191104/2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500202630.pdf. Accessed 31 March 2017.

[8] European Medicines Agency: Accelerated Assessment. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a. Accessed 31 March 2017.

[9] European Medicines Agency: Conditional Marketing Authorisation. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b. Accessed 31 March 2017.

[10] European Medicines Agency: Compassionate Use. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c. Accessed 31 March 2017.

[11] European Medicines Agency: Conditional Marketing Authorisation. Report on Ten Years Experience at the European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf. Accessed 31 March 2017.

[12] Boucaud-Maitre D, Altman JJ. (2016): Do the EMA Accelerated Assessment Procedure and the FDA Priority Review Ensure a Therapeutic Added Value? 2006 – 2015: A Cohort Study. *Eur J Clin Pharmacol*. 2016 Oct; 72(10):1275–1281. doi:10.1007/s00228-016-2104-3.

[13] European Medicines Agency: Adaptive Pathways. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce. Accessed 31 March 2017.

[14] European Medicines Agency: Final Report on the Adaptive Pathways Pilot. EMA/276376/2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf. Accessed 31 March 2017.

[15] Medicines and Healthcare Products Regulatory Agency: Early Access to Medicines Scheme (EAMS): How the Scheme Works. Available at: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works. Accessed 31 March 2017.

[16] U.S. Food and Drug Administration: Breakthrough Therapy. Available at: https://www.fda.gov/forpatients/approvals/fast/ucm405397.htm. Accessed 31 March 2017.

[17] U.S. Food and Drug Administration Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf. Accessed 31 March 2017.

[18] Mullard A. PRIME Time at the EMA. *Nat Rev Drug Discov*. 2017 Mar 30; 16(4): 226-228. doi:10.1038/nrd.2017.57.