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Conditional Marketing Authorisation

The National Academies of Sciences, Engineering, and Medicine

Workshop on FDA's Accelerated Approval Process for New Pharmaceuticals

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An agency of the European Union

Conditional Marketing Authorisation

Article 14-a of Regulation (EC)No 726/2004

Scope (at least one):

- Intended for treatment, prevention or diagnosis of **seriously debilitating diseases or life-threatening diseases**;
- To be used in **emergency situations**, in response to public health threats;
- Designated as **orphan** medicinal products.

Requirements (all):

- The **benefit-risk balance** is **positive**;
- It is **likely** that the applicant can **provide comprehensive clinical data**;
- **Unmet medical needs** will be fulfilled;
- The **benefit to public health of the immediate availability** of the medicinal product outweighs the risk inherent in the fact that additional data are still required.

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CMA framework

Early and temporary authorisation awaiting comprehensive available clinical data* that target seriously debilitating or life-threatening diseases

To balance this temporary uncertainty additional scrutiny

- 1-year validity - Annual renewal
- 6-monthly PSUR cycle

- Information to the public (Summary of Product Characteristics / Package Leaflet)
- MA subject to Specific Obligations (SOBs)

* *In emergency situations, also pre-clinical or pharmaceutical data may be less comprehensive*

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Specific Obligations (SOBs)

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- Substantive element -> grant of MA and post-MA
- Feasibility
- *Onus* on the applicant
- MAH has an annual submission to report on the progress of the SOBs and confirm the B/R based on new available data
- Final objective (average 4 years): get a comprehensive dossier – support the switch to standard MA
- Examples of SOBs:
  - Submission of final results from (ongoing) clinical studies:
    - Big majority
    - Mainly phase 3 studies
    - Objectives include efficacy and safety
  - Interim results of ongoing clinical studies
  - Additional analyses

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SOBs: Non-compliance

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Regulation (EC) No 726/2004

Article 20a

" Where the Agency concludes that a holder of a marketing authorisation granted pursuant to Article 14-a ***failed to comply with the obligations*** *laid down in the marketing authorisation, the Agency shall inform the Commission accordingly. The Commission shall adopt a decision to* ***vary, suspend or revoke*** *that marketing authorisation …"*

Commission Regulation (EU) No 488/2012

Concerning **financial penalties** for infringement of certain obligations in connection with Mas granted under Regulation No 726/2004

Articles 1(3) and 1(5)

"…rules concerning the application of financial penalties to the holders of marketing authorisations…in respect of infringements of the following obligations, ….

…the obligation to comply with conditions or restrictions included in the marketing authorisation with regard to the safe and effective use of the medicinal product…

…the obligation to supply …any information that may influence the evaluation of the risks and benefits of the product…"

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Procedural aspects

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- Applicant to consider early engagement with EMA, in particular
  - if certain tests or trials are to be omitted or if the development deviates from guideline requirements.
  - to discuss most suitable type of MA and post-authorisation studies/SOBs.
- 6-7 months before submission applicant to notify of intention to submit, including request for CMA (can also be requested at time of submission)
- Justification for request to be included in Module 1 of the dossier
- CHMP Rapporteurs assess justification provided
- New MAAs only; cannot be used for post-authorisation extensions

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CMA - examples

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Data that supported approval: The main efficacy data in support of the claimed indication based on a single pivotal trial …phase I/II, open-label, first-in-human, multi-cohort, single-arm trial…

Specific Obligations (data requested to switch to standard MA)

SOB1: *In order to further confirm the efficacy and safety … in the treatment of adult patients … the MAH should conduct and submit the results of a longer follow-up of efficacy evaluable patients (approximately 116 treatment-naïve patients and more follow-up of the 136 previously treated…) of study…, a Phase 1/2 Study*

SOB2: *In order to further confirm the efficacy and safety … in the treatment of adult patients with …, the MAH should submit the results of study …, a randomized, open-label, Phase 3 Study of … versus standard of care for first line treatment…*

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CMA – the challenges

- Correlation between surrogates and clinical endpoints may be challenging, leading to unexpected findings
- Identifying appropriate specific obligations:
  - What trials are feasible post-approval and still informative (bringing overall data to 'comprehensive' level) ?
- Is there enough information to make clinical and other decisions?

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CMA: Analysis of 10 years experience

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Analysis on **10 years (2006-2016) of experience** with CMA: **Key findings**

- 'Typical' CMA includes **evidence from 2 phase II or III studies** at the time of approval.
- For most CMAs, **specific obligations** were **fulfilled** in line with agreed scope and timelines.
- On average **within 4 years** CMAs were **converted** into standard MAs.
- **Pro-active use** by Applicants linked to shorter assessment periods.
- Most experience with CMAs in the **therapeutic areas of oncology and infectious diseases.**

[Conditional marketing authorisation - Report on ten years of experience at the EMA (europa.eu)]

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CMA: Moving forward

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Sponsors / Applicants

- More emphasis on early data generation within a comprehensive development
- Consider proactively how additional data can be best generated post-approval (SOB)
- Consider applying for Scientific Advice
- Consider engaging early with the Agency, in particular
  - if certain tests or trials are to be omitted or if the development deviates from guideline requirements
  - to discuss post-authorisation studies/SOBs.
- Exploring use in other therapeutic areas
  - identification of appropriate intermediate endpoints

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CMA: Moving forward

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- Pharma Package (future changes to legal framework in EU) – European Parliament Resolution of 24 November 2021:
  - *based on the experience of the authorisation of COVID-19 vaccines, … consider extending the application of rolling reviews to other emergency medicines…*
  - *Reassessment of the system which leads from CMA to standard MA*
- Involvement of other stakeholders e.g. HTA bodies (strengthened by HTA Regulation – Regulation (EU) 2021/2282)
- Role of RWE
- Role of patient data
- Modernise communication of benefits, harms, and uncertainties
  - Improve the way we describe effects and decision for other actors to decide
- International collaboration

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Early access tools: Accelerated assessment

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- For products of major interest from the point of view of **public health** and in particular from the viewpoint of **therapeutic innovation***
- Maximum active time reduced to **150 days**
- To establish major public health interest, the justification should address:
  - **unmet medical need** and the available methods,
  - extent to which the medicinal product is expected to **fulfil** the unmet medical need,
  - strength of **evidence**.
- Can **switch** back to a standard 210 day timetable
- Further information: CHMP Guideline on Accelerated Assessment

* Article 14 (9) of Regulation (EC) No 726/2004

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Early Access Tools: PRIME – PRIority MEdicines

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- Scheme launched 2016
- Aims to foster development of medicines with major public health interest, unmet medical need
- Offers dedicated and reinforced support throughout development and pre-authorization
  - Appointment of Rapporteurs
  - Kick-off meeting
  - EMA dedicated contact point
  - Scientific advice at key development milestones
- Enables accelerated assessment of medicines
- Makes better use of existing regulatory & procedural tools
- SMEs and academia, possible entry point at proof of principle

- Timely approval and patient access to important new medicines
- Builds on accelerated assessment criteria
- Promote better use of existing tools, such as Scientific Advice and Accelerated Assessment
- Early dialogue on manufacturing process and MAA requirements (stability and inspections)
- Optimises current regulatory tools by increasing efficiency of development and quality and robustness of data (incl. CMC data)

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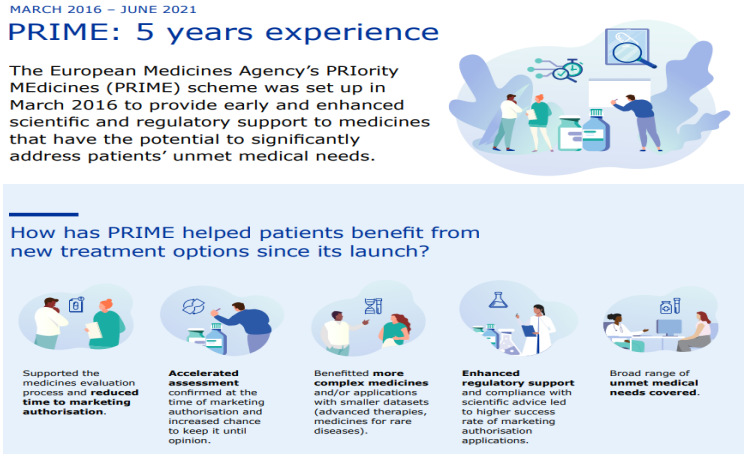
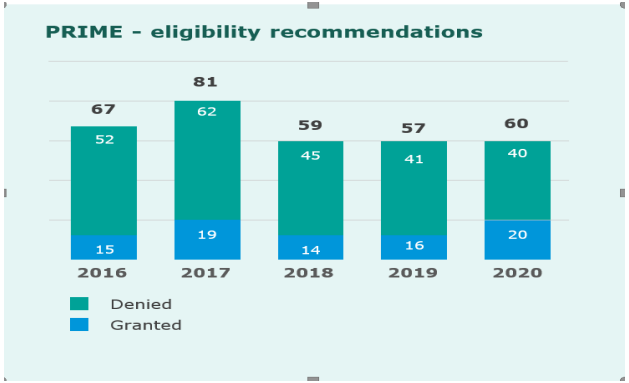
PRIME: 5 years experience

PRIME helped patients benefit from new treatment options since its launch:

- reduced time to marketing authorisation
- accelerated assessment facilitated
- more complex medicines covered
- enhanced regulatory support
- broad range of unmet medical needs.





[prime-5-years-experience_en.pdf (europa.eu)]

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Further information

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Data at the time of authorisation and generated later

- **50%** Of products had (some) results from **phase III**
- **59%** Of main/pivotal studies were **randomised** (34% single arm)
- **57%** Of main/pivotal studies were **open label**
- **53%** pre-defined **response rate** as primary endpoint

"Typical" CMA as **pivotal evidence** has 2 phase II or III studies, often open label, randomised and measuring a pre-defined response rate

Specific obligations typically were clinical studies that were already ongoing at the time of authorisation

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Specific obligations (SOs) imposed

- 72% **clinical study results**
- 62% Of imposed studies **ongoing**
- 52% **randomised** (36% single arm)
- 73% **open label**
- 31% **same primary endpoint** as main studies in MAA

"Typical" CMA **SOBs** required to conduct two phase II, III or IV efficacy and safety studies, which were open label, randomised or single arm, and measuring an endpoint often different from pivotal studies in CMA application

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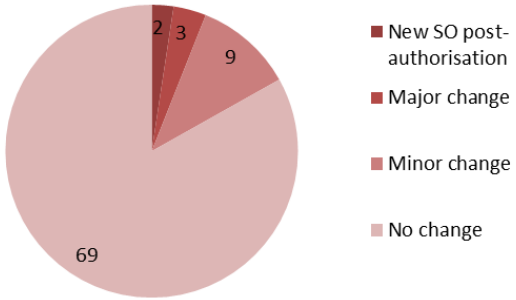
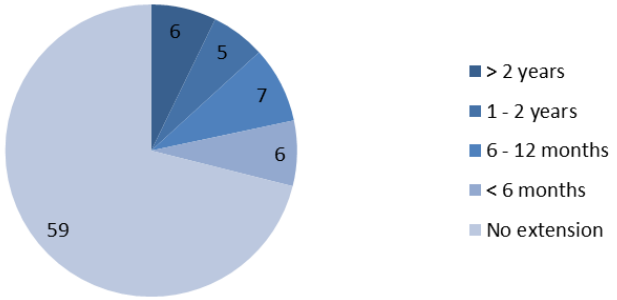
Changes to specific obligations

Changes to scope of specific obligations, all SOs completed or pending, N=83



Extensions of due dates for specific obligations, all SOs completed or pending (N=83)



Most specific obligations did not have any change to their scope and due dates. Only very few had major changes to the scope or extensions beyond one year.

Although often the changes in scope and timelines of specific obligations were related to difficulties in recruitment and study initiation or conduct, in some cases it was linked to better-than-expected outcomes (e.g. lower than expected incidence of metastases or longer overall survival).

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