EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6th Meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines

Accelerated Assessment and Conditional Marketing authorisation

30th June 2021

Presented by: Victoria Palmi / Caroline Pothet – EMA
Martina Schüssler-Lenz, Chair of Committee for Advanced Therapies

AA – Review of key "reversion" factors

Available pre-submission tools

CMA – Current state of art

Discussion

Accelerated Assessment

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

Major public health interest to be shown by demonstrating:

-Existence of **unmet medical need**(s)

-How the product could **address** the unmet medical need(s)

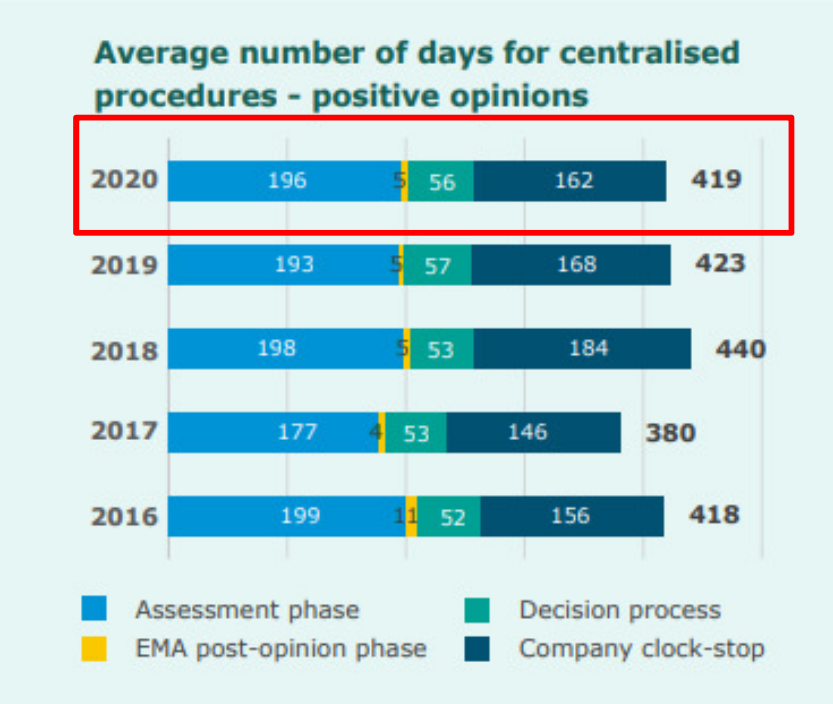
- **Strength of evidence** expected at time of MAA

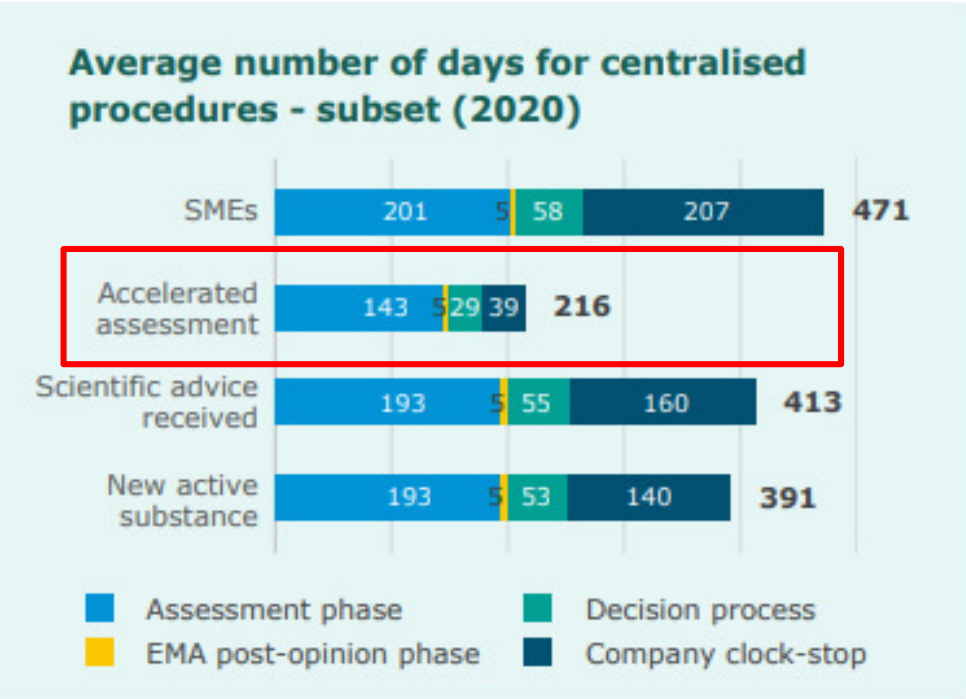
NEW! Revised AA request template

9. *When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of* ***major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation****, the applicant may request an* ***accelerated assessment procedure****. The request shall be duly substantiated.*

Feedback on new template welcome!

Accelerated Assessment *in practice*





Source: EMA 2020 Annual report

Accelerated Assessment *in practice for ATMPs*

- To date, CAT has adopted 9 opinion for products that started their assessment under AA.
- Only one product finalised its assessment within 150 days but 4 of them managed to conclude their assessment within 180 days.
- Even when reverting to standard time table, the total assessment time is, on average, faster than never having started it.
- Most applications had a positive opinion.
- A high number of PRIME submissions are *'expected'* in the coming years.
- Timelines are very challenging for applicants and for rapporteurs and a **robust data package** is key to maintain a fast review.

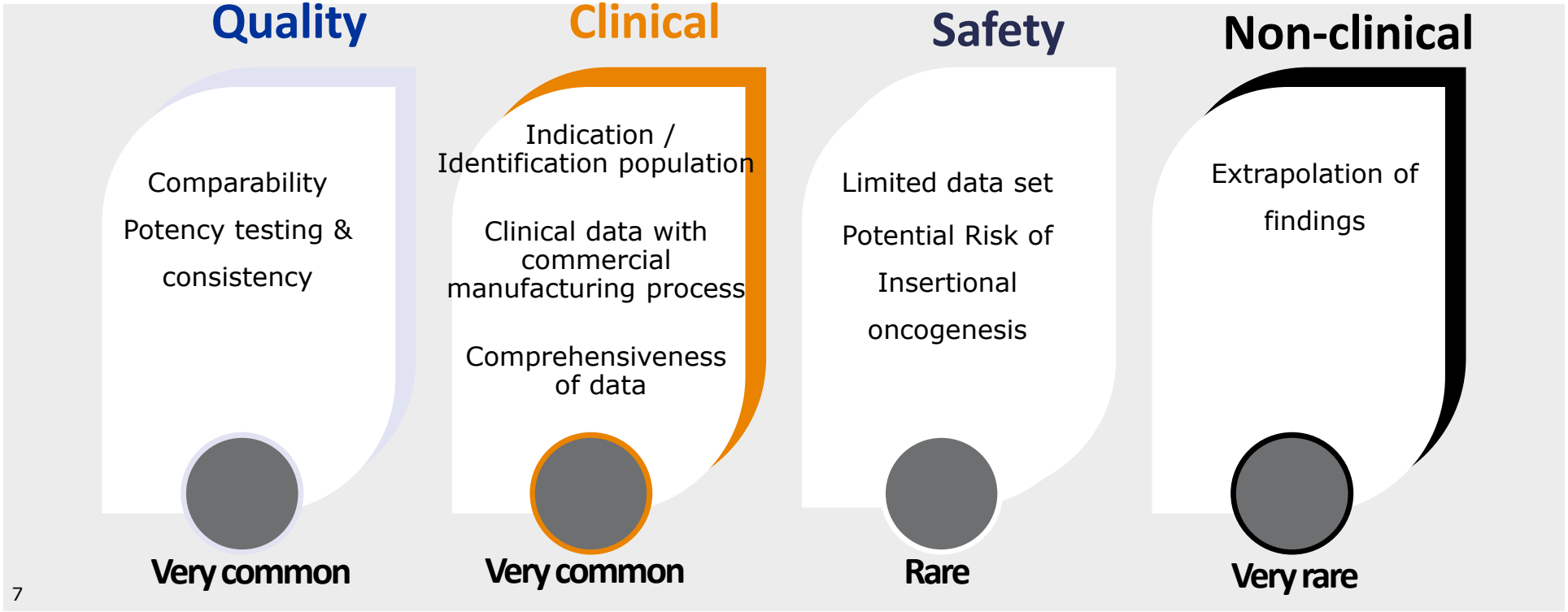
Understanding the barriers of Accelerated Assessment

For most applications the main reason to switch are:

- Major Objections not resolvable under accelerated assessment
- High number of other concerns

Major objections

Understanding previous experience to prepare a dossier fit for purpose



How do we ensure that submissions have the standards required for a shortened review?

The quality and manufacturing can be considered the most critical part of the assessment. Lack of demonstrated **comparability**, lack of experience with **commercial manufacturing process**, **potency** testing and variability of **starting materials** can lead to serious delay in approval.

- ***Quality toolbox***
- ***Certification***

How do we ensure that submissions have the standards required for a shortened review?

The **identification of the population** that will benefit the most /population for which the risk-benefit balance is positive (vs the studied population) is one of the biggest bottleneck in the assessment.

Reinforce pre-submission dialogue and discuss with the assessment team

- Data package expected at the start of the procedure
- The evidence supporting the claimed indication and extrapolations from clinical trials, effects in different severity stages, pre-symptomatic vs symptomatic patients, reliable diagnostic test, conditions with other options.
- Refer to the Guide on the Wording of the therapeutic indication

Development plans are critical when targeting a small number of patients globally

Under 50 patients in MAA in the EU - AA		Under 200 patients in MAA in the EU - AA	
Skysona	Cerebral adrenoleukodystrophy (CALD)	**Zolgensma**	Spinal Muscular Athropy (SMA)
Libmeldy	Metachromatic leukodystrophy (MLD)	**Tecartus**	Mantle cell lymphoma (MCL)
Strimvelis	Severe combined immunodeficiency	**Kymriah**	B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)
Zynteglo	Beta Thalassaemia	**Yescarta**	Large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL)
		Abecma	Relapsed and refractory multiple myeloma

Criteria to discuss comprehensiveness of clinical data in marketing authorisation applications

01 Quality of evidence (including feasibility considerations)

02 Efficacy: precision of effect size

03 Efficacy: clinical meaningfulness of the endpoint

04 Efficacy: duration of efficacy

05 Safety: exposure

06 Safety: length of follow-up.

07 Target population vs study population

08 Pharmacological rationale

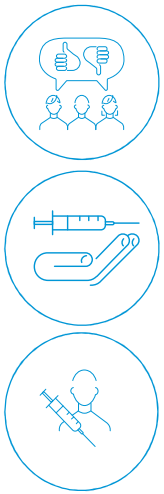
09 Natural history/ course of the disease

- AA – Review of key "reversion" factors
- **Available pre-submission tools**
- CMA – Current state of art
- Discussion

Available tools supporting innovation to advance patient access

GENERAL SUPPORT

- Innovation Task Force
- **Scientific advice**
- *Parallel consultation with HTAs or FDA*
- ATMP Classification procedure
- **ATMP Certification procedure**
- **PRIME (early access) – Quality toolbox**
- Qualification of novel methodologies, e.g., registries
- Paediatric and Orphan framework
- Scientific guidelines
- SME support
- Academia cooperation
- Fee incentives



AUTHORISATION

ACCESS DECISION

POST-LICENSING EVIDENCE

Scientific advice

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DOI: 10.1111/bcp.14672

ORIGINAL ARTICLE-THEMED ISSUE

Towards a better use of scientific advice for developers of advanced therapies

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Scientific advice (SA) is an important tool offered by regulators to help developers generate robust evidence on a medicine's benefits and risks. Drawing on accumulated experience and looking at the SA provided by the European Medicines Agency in 2018 to advanced therapy medicinal products originally developed by public bodies, we discuss most commonly raised issues and the complexity and timings of the questions posed. Earlier and more frequent SA could help advanced therapy medicinal product developers to pre-empt delays at the marketing authorisation stage. Carefully addressing quality and nonclinical issues before entering the pivotal phase of development will clear the path for a smooth clinical development and successful marketing authorisation.

KEYWORDS
advanced therapy medicinal products, drug development, drug regulation, scientific advice

1 | INTRODUCTION

Public bodies (including academic institutions, research organisations, hospitals), public–private partnerships and small and medium-sized enterprises (SMEs) represent an important source of innovative therapeutics.[1] This holds particularly true for the area of advanced therapy medicinal products (ATMPs), as research on these products and their initial development is conducted to a great extent by public bodies and SMEs.[2] This is confirmed by a recent survey, which concluded that the European ATMP field is still in early phase of maturity with a high representation of SMEs (65%) and 72% of reported therapeutics in early clinical development (phases I–II).[3]

Public bodies and SMEs tend to have limited resources to conduct late-stage clinical trials and the majority of authorised ATMPs in the EU needed collaboration of SMEs or public partners with large pharmaceutical companies (e.g. Strimvelis, Imlygic, MACI, Holoclar, Zolgensma). Moreover, academic institutions and SMEs may encounter more challenges in navigating—and complying with—regulatory requirements on various aspects of development compared with large pharmaceutical companies.[4] These challenges could cause delays at different stages of development and even lead to abandonment of potentially promising projects.

The scientific advice (SA) service is provided by regulators around the globe and is a useful tool to support the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. At the European Medicines Agency (EMA), this service is provided by the Scientific Advice Working Party supported by the Committee of Advanced Therapies.[5] This is, however, a voluntary procedure in which developers can ask the regulators' opinion on the most appropriate way to generate robust

(Tavridou, Rogers et al, *Br J Clin Pharmacol*, 2020)

1. Comparability and control strategy

2. Toxicity & bridging

3. Small patient population

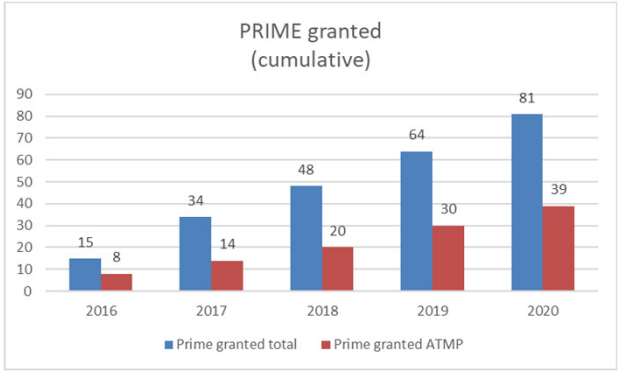
4. Study design

5. Data contextualisation

6. Follow-up

PRIority MEdicines (PRIME)

Reinforcing the concept of Accelerated Assessment



- ***Identifying products fulfilling the criteria for AA earlier***

  - Entry to scheme at two different stages in development:
    - at the earlier stage of **proof of principle** (prior to phase II/exploratory studies) focusing on SMEs.
    - at **proof of concept** (prior to phase III/confirmatory studies).
  - Must be based on adequate data to justify a potential major public health interest.

- ***Enhanced support, e.g., through timely appointment of Rapporteurs and iterative scientific advice***
  - Confirmation of eligibility to AA prior to submission.

Applicants not eligible to PRIME can still request accelerated assessment.

Go to https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines for more information.

5-year review ongoing

Joint EMA-FDA workshop on quality support to PRIME & Breakthrough

Key conclusions -areas for further reflection

Published 31st July 2019

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https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough

1. EU toolbox guidance

- To summarise the identified scientific elements/regulatory tools already available in the EU to address some of the challenges faced and generation of robust quality packages.
- Applicable to small molecules, Biologicals/Biotechnological products and ATMPs
- Living document – to be updated as experience evolves.

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2 February 2021
EMA/CHMP/BWP/QWP/IWG/694114/2019
Committee for Human Medicinal Products (CHMP)

Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications

Consultation with BWP, QWP, IWG and CAT	September 2020
Draft adopted by BWP, QWP, IWG and CAT	December 2020
Draft adopted by CHMP for release for consultation	29 January 2021
Start of public consultation	2 February 2021
End of consultation (deadline for comments)	31 July 2021

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	***Priority Medicines (PRIME), quality development, Module 3, data, scientific elements, regulatory tools, flexibility, benefit-risk***

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Content:

Scientific tools

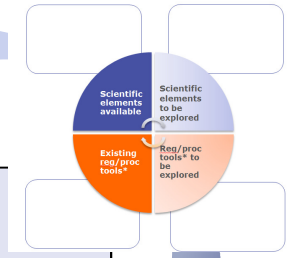
- General **scientific tools** (e.g. Prior knowledge, RA)
- Scientific tools related to **process validation** (e.g. protocols, concurrent PV)
- Scientific tools related to **control strategy** (e.g. in silico models)
- Scientific tools related to **GMP compliance** (e.g. launch from IMP site)
- Scientific tools related to **stability** (e.g. models)
- Scientific tools related to **comparability** (biologicals) (e.g. risk-based)

Regulatory tools

- Regulatory tools to **manage flexibility** (e.g. PACMP, CMA)

EMA toolbox guidance- approach

Scientific/regulatory tool (e.g. concurrent process validation)



- description of the application of the scientific tool
- reference to where it is described/referenced in the guidance/legislation/EMA communications
- where possible, illustration with an example

UNDER CONSULTATION - Feedback welcome

Certification procedure (for SMEs) – Art 14 of REG (EC) 1394/2007

- Scientific evaluation of quality and/or non-clinical data (Modules 3 and 4)
  - See guideline for minimal content
- Stand alone evaluation - not legally binding for any future application
- Not scientific advice : Is my product development on track for a future MAA?
- Submission via EMA Service Desk followed by Eudralink
- 90 days procedure (if no clock stop required); potential for site visits
- The applicant obtains a Certificate and a List of Deficiencies

For further details: Certification procedures for micro-, small- and medium-sized enterprises (SMEs) webpage

Potential Benefits of CAT certification

- Offers an early **strategic dialogue between the SMEs and regulators**
- **Facilitates the preparation of a MAA** with a view to simplify the future filing / assessment => Potential to lead to early access to market
- Clarify regulatory requirements and provide **feedback on the quality and completeness** of the CMC/NC package
- Only 14 procedures completed so far – Feedback welcome !

- AA – Review of key "reversion" factors
- Available pre-submission tools
- **CMA – Current state of art**
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Conditional Marketing Authorisation (CMA)

Pragmatic tool for early approval of products that target a high unmet need around seriously debilitating diseases or life-threatening diseases – pending comprehensive clinical data.

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

CMA is valid for 1 year (renewable) and is subject to specific obligations (including conduct of study/-ies).

When comprehensive data confirms positive B/R balance, the CMA can be converted into a standard MA.

Criteria:

- the **risk-benefit balance is favourable**;
- the applicant is likely to be **able to provide comprehensive data**;
- **unmet medical needs** of patients will be met;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

Articles 14-a and 20a of Regulation (EC) No 726/2004 and Regulation (EC) No 507/2006

CMA – 2020 at a glance

Thirteen medicines received a recommendation for a **CMA**, one of the possibilities in the EU to give patients early access to new medicines: **Adakveo**, **Ayvakyt**, **Blenrep**, **Comirnaty**, **Enhertu**, **Hepcludex**, **Idefirix, Dovprela**, **Retsevmo**, **Rozlytrek**, **Tecartus**, **Veklury** and **Zolgensma**

CMA and switch to standard marketing authorisation (excluding withdrawals)					
	2016	2017	2018	2019	2020
Positive opinions for CMAs	8	3	1	8	13
Opinions recommending switch of CMA to standard marketing authorisation	2	5	2	1	2

- **Blenrep & Enhertu MAA CHMP opinion issued under AA.**
- **Five (including 2 ATMPs) of the CMAs started under AA.**
- **Amongst those 13, 10 requested CMA at initial submission.**

Source: 2020 EMA Annual report

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EUROPEAN MEDICINES AGENCY

Thank you for your attention.

Acknowledgments:

Patrick Celis, Ana Hidalgo-Simon, Dolca Rogers, Klara Tiisto, Veronika Jekerle, Dolores Hernan.

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