EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Accelerating patients' access to medicines that address unmet medical needs.

- **Updated review of the accelerated assessment tool**

Presented by Victoria Palmi & Caroline Pothet - EMA
(with input from Christelle Bouygues)

Agenda

- Analysis of Requests for accelerated assessment
- Analysis of MAA under accelerated assessment
- Next steps to continue fostering innovation and early access to patients

Analysis of AA requests concluded between 2016 and October 2020

Caroline Pothet

Key principles of Accelerated Assessment

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

Request **at least 2-3 months before MAA** submission (when high level results from pivotal studies available)

Justification to be provided by the applicant (**onus on the applicant** to substantiate the claim)

Major public health interest **typically** 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

PRIority MEdicines (PRIME)

Reinforcing the concept of Accelerated Assessment

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

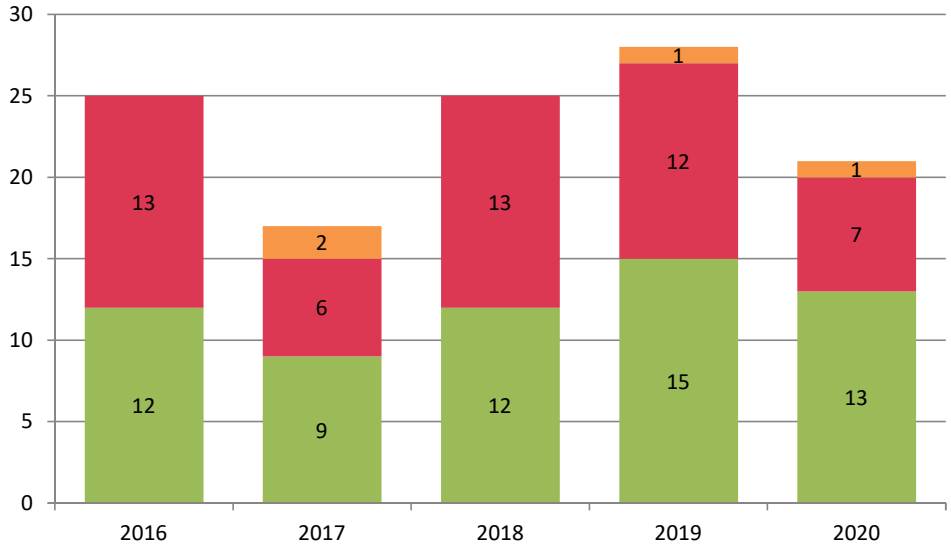
  - Entry to scheme at two different stages in development:
    - at the earlier stage of **proof of principle** (prior to phase II/exploratory studies) focusing on SMEs.
    - at **proof of concept** (prior to phase III/confirmatory studies).
  - Must be based on adequate data to justify a potential major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

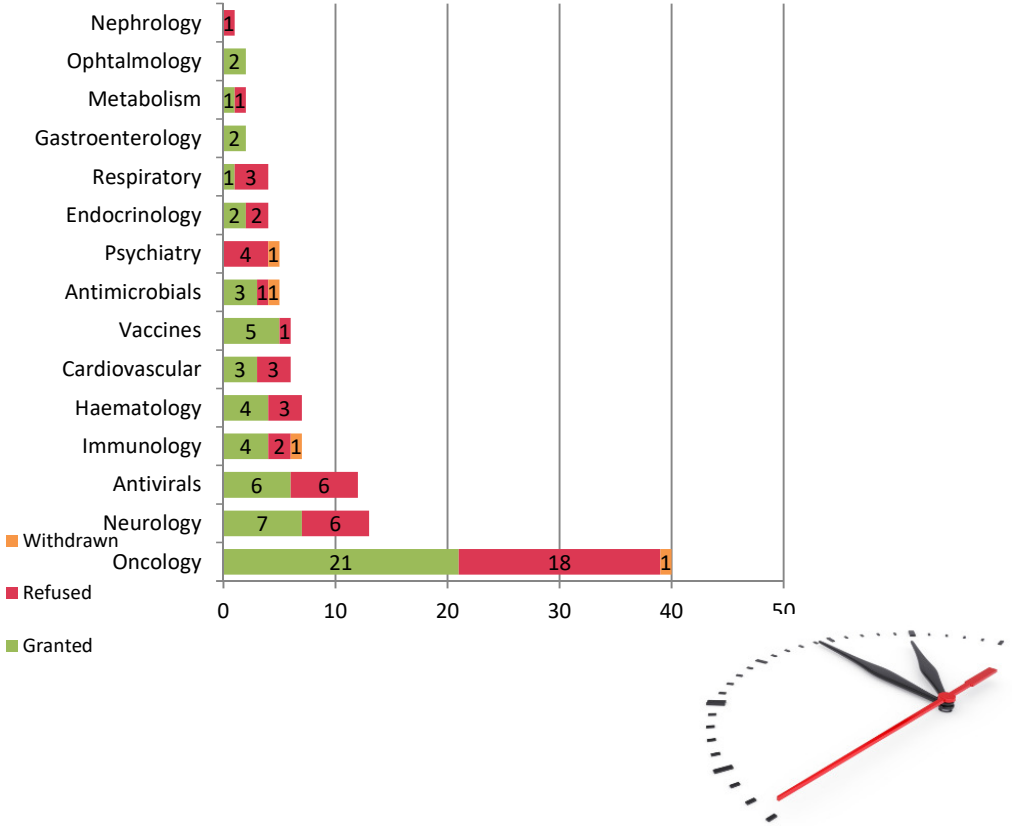
- ***Enhanced support, e.g. through iterative scientific advice and timely appointment of Rapporteurs***
  - Confirmation of eligibility to AA prior to submission.

Applicants not eligible to PRIME can still request accelerated assessment.

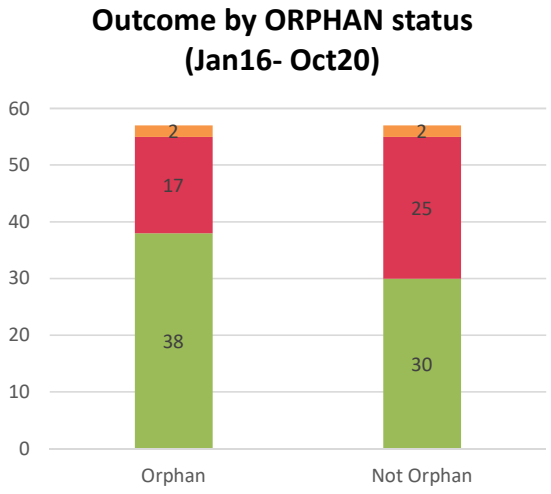
Go to https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines for more information.

AA requests (Jan16-Oct20)

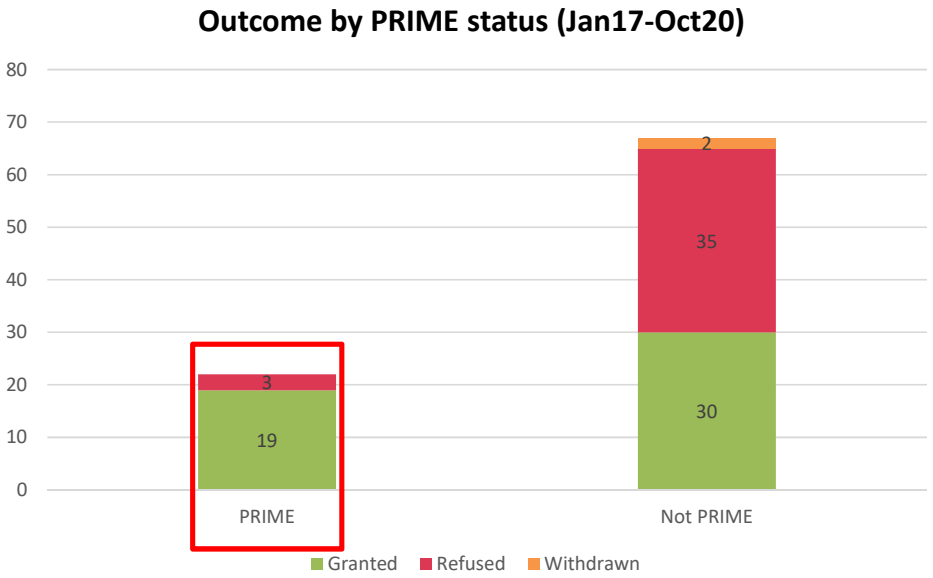


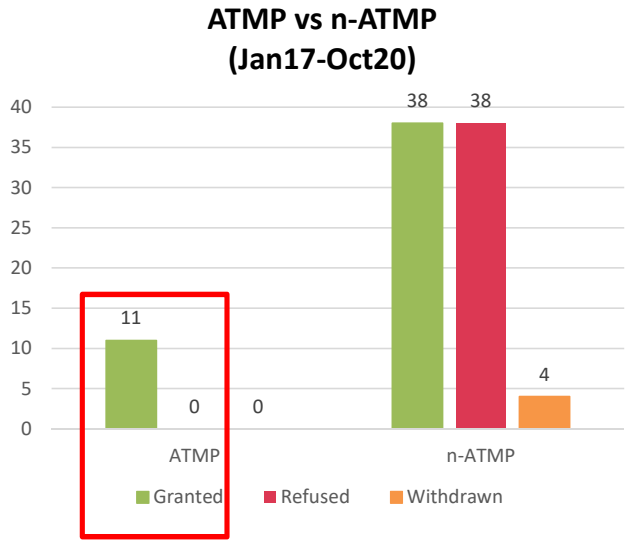


Outcome by type of products

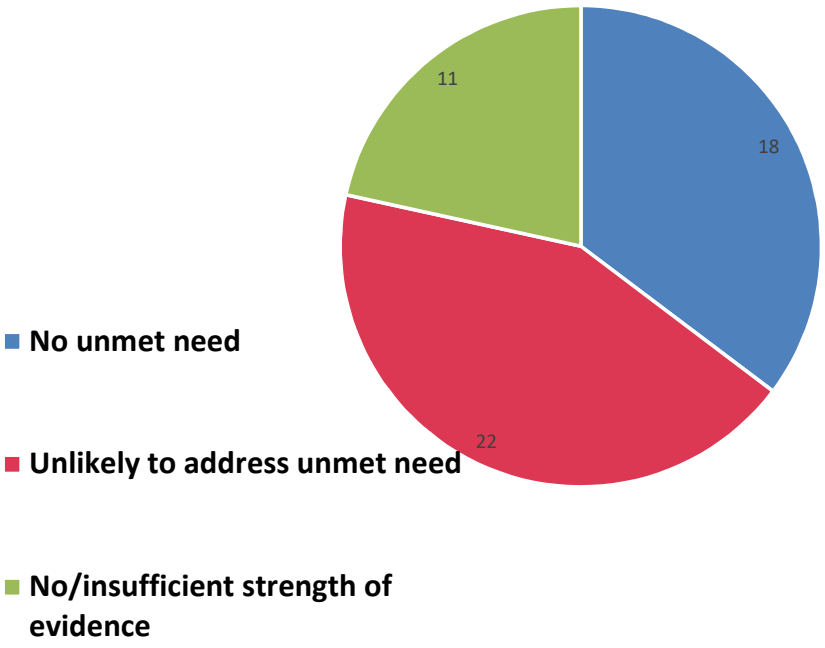


2 not included:
an Art. 58 application and an ancillary medicinal
substance in a device





Reasons for rejection (n=51)



- Unmet medical need:
  - The product **doesn't address an unmet medical** need (e.g. non-curative, relevant subset not studied)
  - The applicant **fails to demonstrate what the unmet need is** and/or how the product will address it.

- Strength of evidence:
  - Concerns with the evidence to be made available in the **proposed indication** at submission (e.g. dose, study design, study integrity, program size)
  - **Dossier completeness** (e.g. interim data)
  - GCP or GMP considerations

Key observations

- **Most PRIME assets confirmed AA prior to filing (~ 40% of granted requests)**
- **Target patient population and potential effects of the product** key in the acceptability of AA criteria.
  - Therapeutic innovation not sufficient but PRIME/ATMPs more likely to meet the criteria
- **Strength of evidence and transparency about potential challenges paramount to a successful outcome!**
  - Data maturity critical for all MAAs – Products under PRIME/ATMP/AA are no exception
  - Complex data/outcomes not always compatible with AA (e.g. more than 1 indication proposed, inconsistency in the studies' outcome, quality issues foreseen)
- **Additional indications not fulfilling AA criteria not a showstopper**
- **Overlap in current AA request template sections 3 and 4/5**

Next? Revised AA request guidance template…

Revision (2020)	Amendments
Product background	**New** section
Description of "**unmet medical need"**	Sections (existing treatment and unmet medical need) **merged** - Duplication reduced - Flow improved
Fulfilment of UMN = **"claims"**	Guidance **enhanced** - What does the product expect to do?
Strength of evidence = **"data"**	Guidance **enhanced** - Deeper dive into the data - Potential challenges (Q/E/S)
Conclusions on claims of major public health interest and therapeutic innovation	**No change** - High level overview

…and process optimised

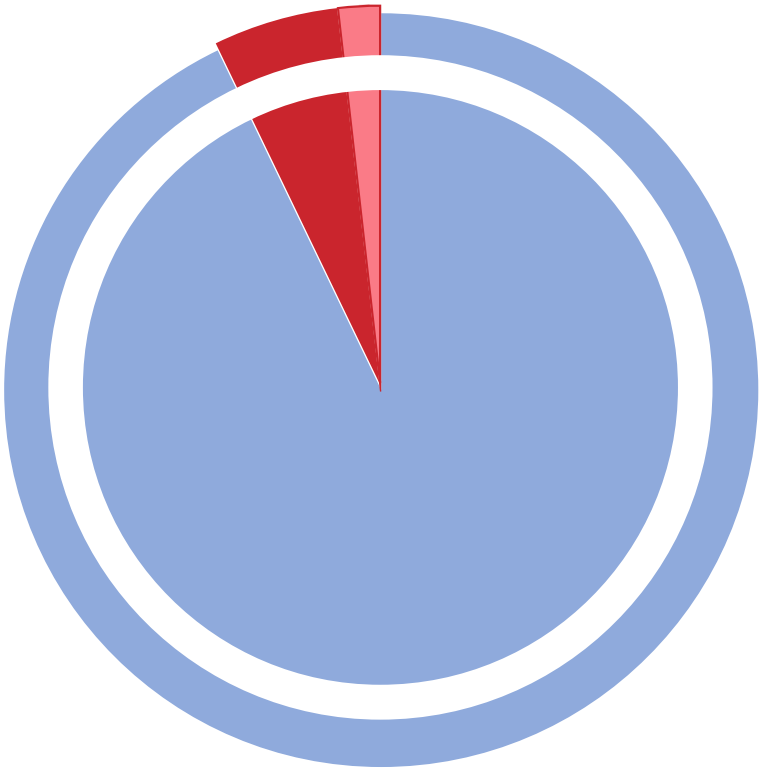
Request for AA [Applicant] + Briefing note & recommendations [Assessors] = One common template

- No need to “copy and paste” between templates
- Common understanding of information needed
- Improved consistency between applications

Evaluation of medicines under AA
Opinions concluded between Jan 2016 and October 2020

Victoria Palmi

Promising new medicines are reaching the patients



52 **Positive opinion**

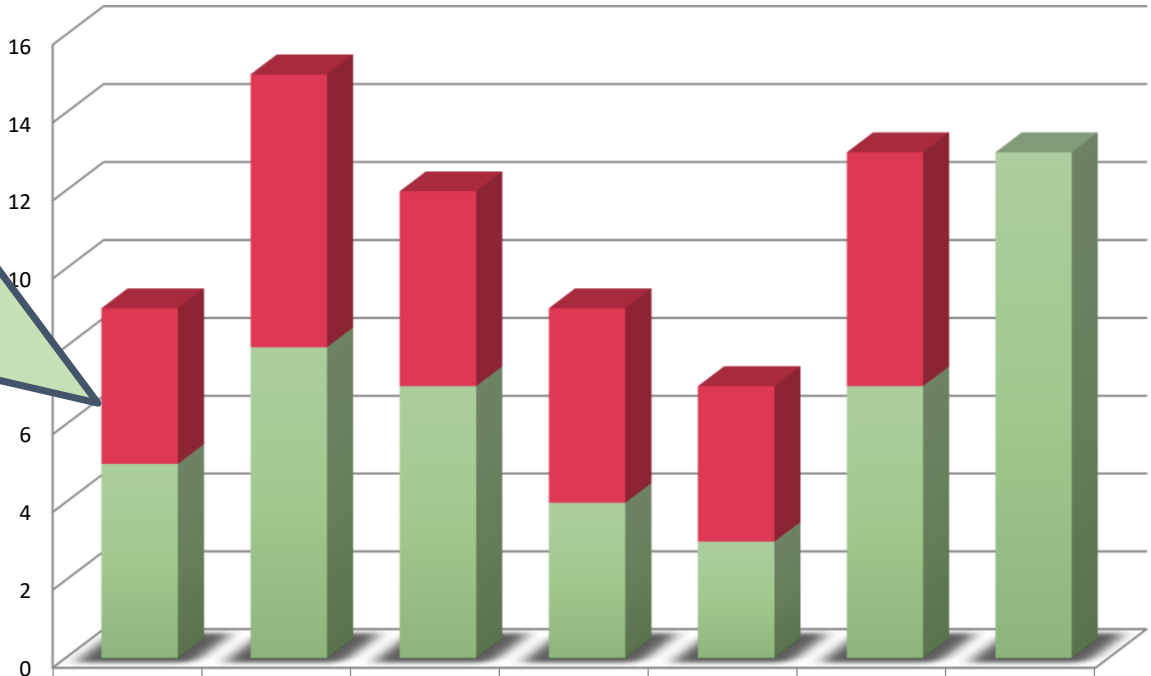
The majority of these applications targeting an unmet medical need had a positive opinion.

3 **Negative opinion**

1 **Withdrawn**

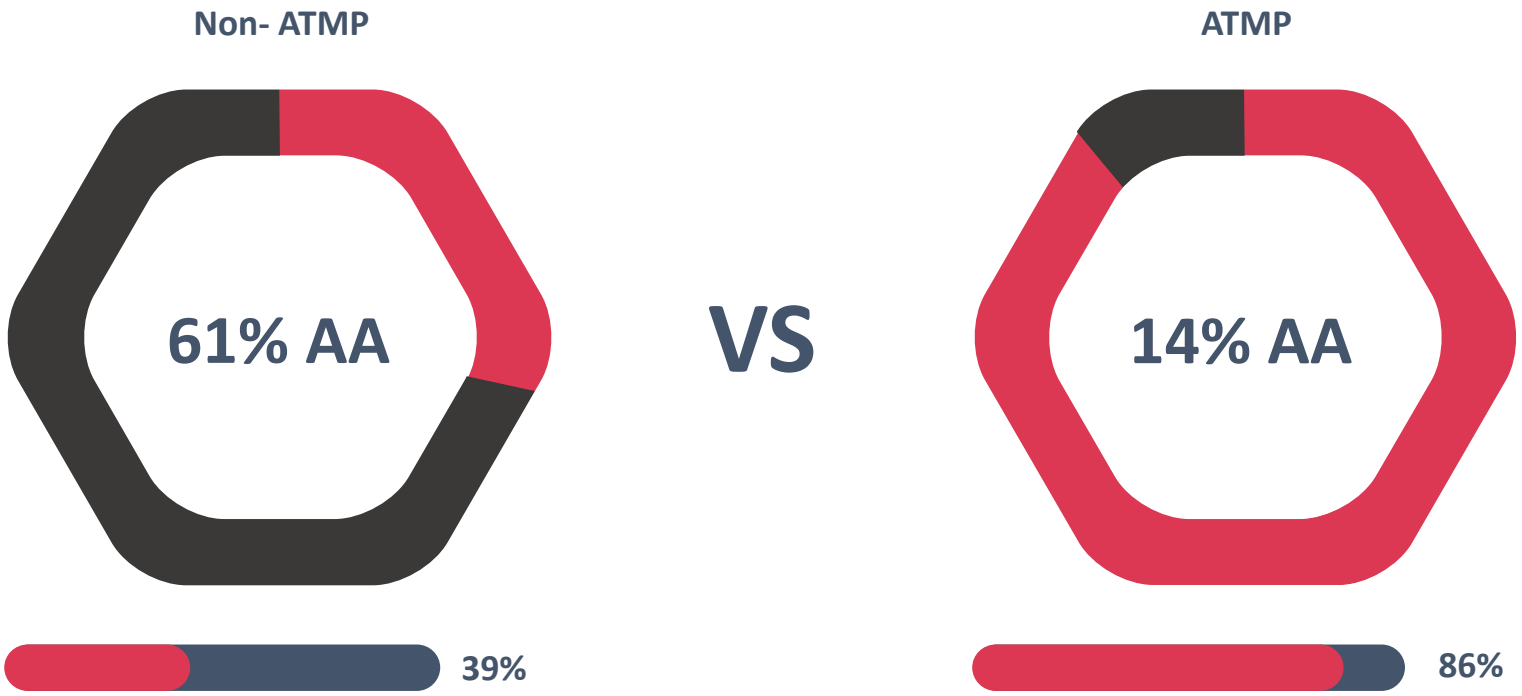
Maintenance of AA

- 54% accelerated review.
- 3 medicines were recommended for approval in **120 days.**
- 9 medicines were recommended for approval in **180 days.**



	2015	2016	2017	2018	2019	2020	Ongoing
Switch to standard TT	4	7	5	5	4	6	
Accelerated review	5	8	7	4	3	7	13

Maintenance of AA by type of product



27 medicines finalized their assessment under AA

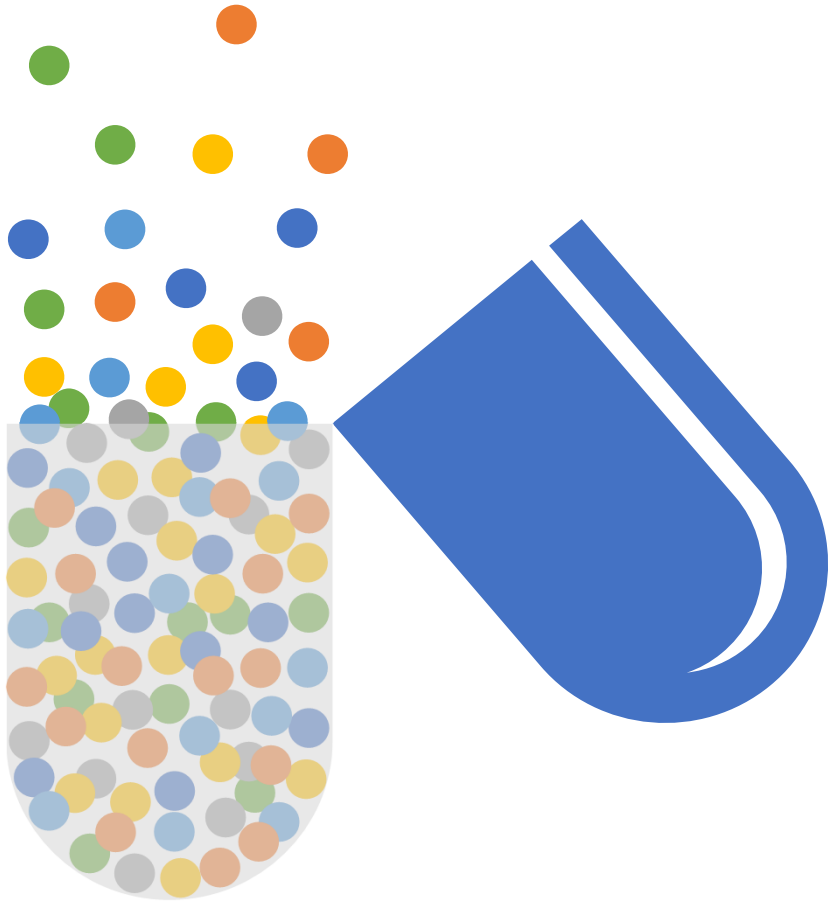
Only 1 out of 7 ATMPs finalized its assessment under AA

ATMPs are more complex and more difficult to assess under AA

Understanding the barriers of Accelerated Assessment

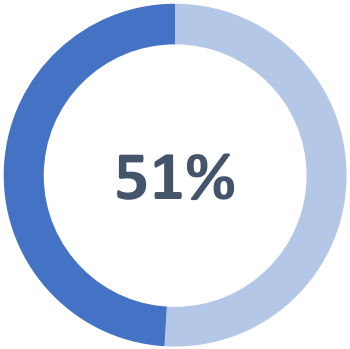
For most applications the main reason to switch are

Major Objections not resolvable under accelerated assessment



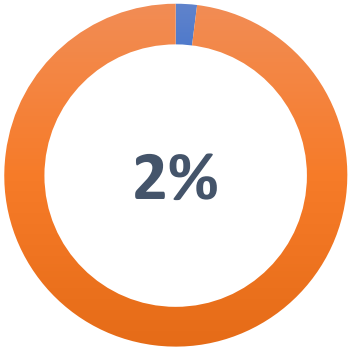
MAJOR OBJECTIONS RAISED DURING ASSESSMENT

FOR NON-ATMP

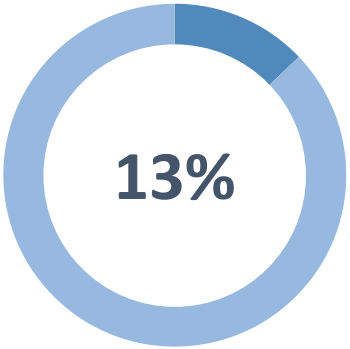


Quality MO

Covering very different areas on quality & manufacturing:
Comparability and validation

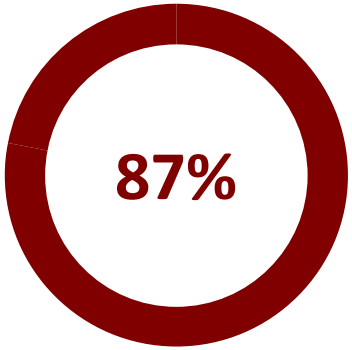


Non-clinical MO



Safety MO

Limited data set
Lack of long term data



Efficacy MO

Indication (vs study population)
Magnitude of effect
Insufficient evidence
Appropriateness of conditional MA

Key findings

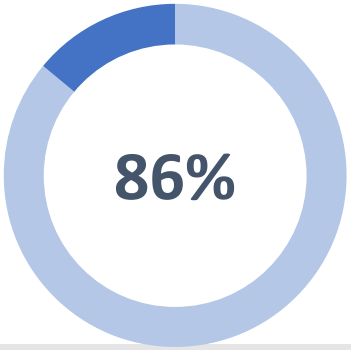
- The majority of these applications targeting an unmet medical need had a positive opinion.
- Most applications presented a comprehensive development package obtaining full marketing authorisations (20% were conditional).
- 61% of these medicines finalised their assessment under accelerated timeframe (including some applications in 120 days).
- Most PRIME products maintained their AA (5/6).
- Even when reverting to standard time table, the total assessment time is, on average, faster than never having started it.
- Majority of AA in oncology area; followed by antivirals and neurology.
- 64% orphan medicines. 3 medicines approved under Article 58

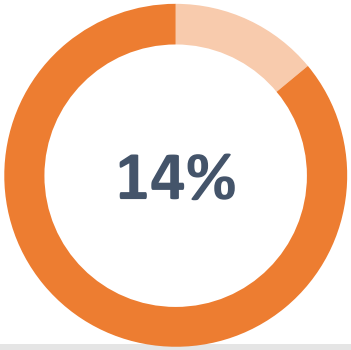
Key findings

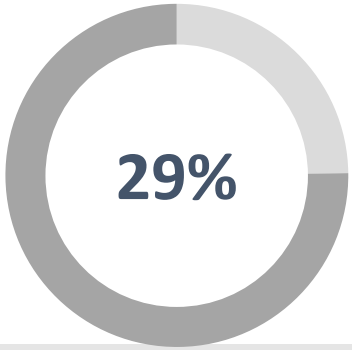
- Overall there were more critical questions raised on the applied indication than on any other aspect of drug development.
- A more robust discussion is needed to support the **applied indication** (population for which the risk-benefit balance is positive **vs the studied population**) as this seems to be one of the biggest bottlenecks.

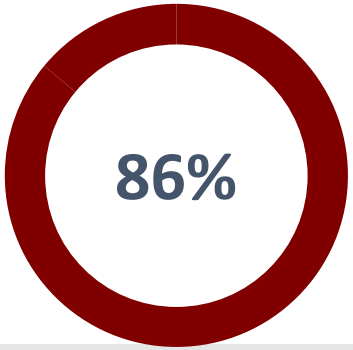
MAJOR OBJECTIONS RAISED DURING ASSESSMENT

FOR ATMP









Quality MO

Comparability
Potency testing & consistency

Non-clinical MO

Extrapolation findings

Safety MO

Limited data set

Efficacy MO

Identification population,
Clinical data with commercial manufacturing process

Key findings for ATMPs under AA applications :

- To date, CAT has finalised 7 AA and 4 applications are ongoing
- Only one application has managed to finalise its assessment within 150 days
- 3 ATMPs finalised its assessment within 180 days
- All ongoing and granted MA are **orphan** medicinal products.
- From the 7 orphan medicines authorised, 3 are conditional and 4 full MA (none MA under exceptional circumstances).
- All applications had a very high number of Major objections and other concerns.

Key findings from ATMPs AA applications:

- 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**, and **potency** testing can lead to serious delay in approval.
- On the clinical side, again, the **identification of the population that will benefit the most** for which the risk-benefit balance is positive (vs the studied population) seems to be the biggest bottleneck in the assessment.

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

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.
- Refer to the Guide on the Wording of the therapeutic indication
- Refer to BWP/QWP/IWG toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications.

Remember that timelines are very challenging for applicants and for regulators, so a **robust data package** is key to maintain AA.

Thank you

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