

# **Analytical testing of Advanced Therapy Medicinal Products: The European Experience So Far**

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Analytical Technologies Europe (AT Europe 2020)

3-6 November 2020

# Disclaimer

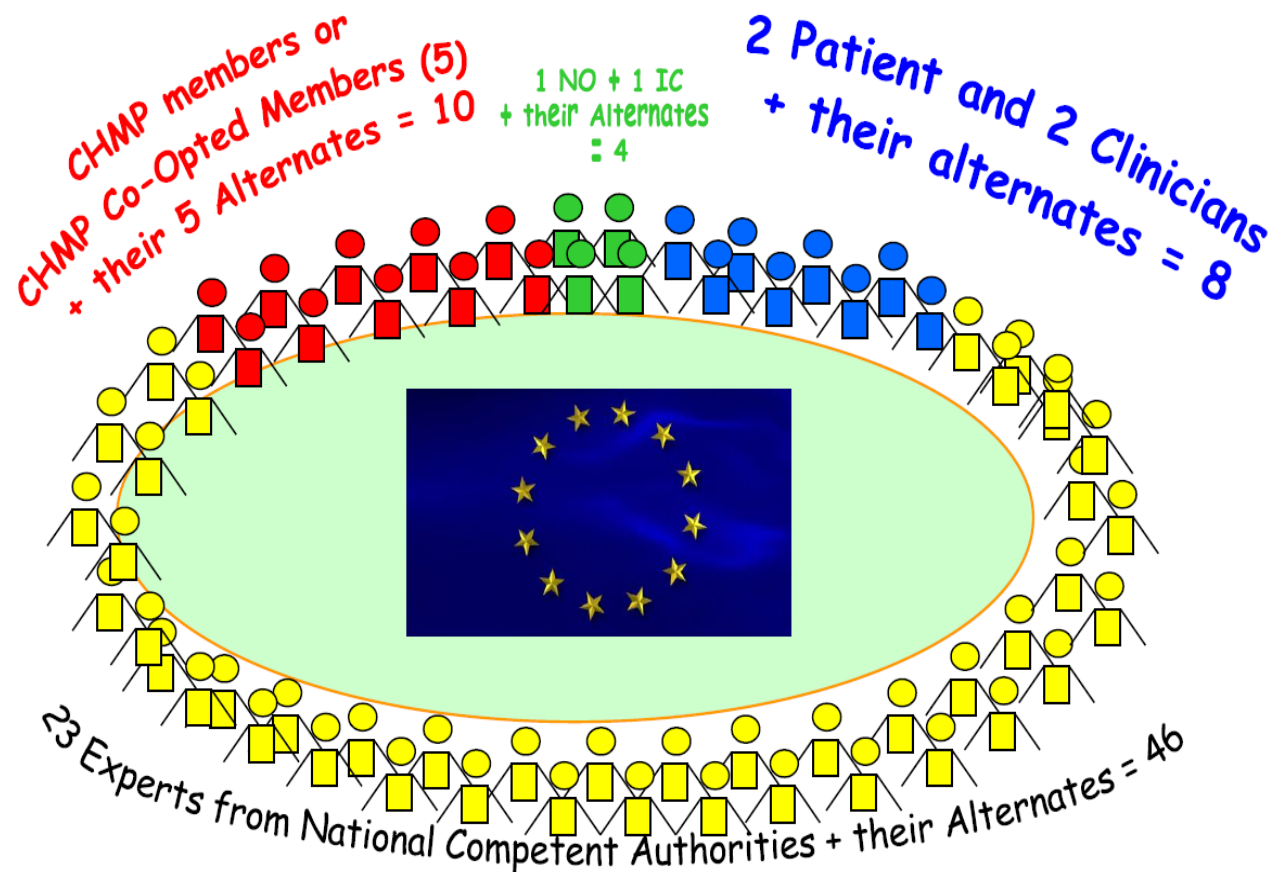
The views expressed in this presentation are those of the speaker, and may not be understood or quoted as being the official opinion of AIFA, EMA or any of its committees or the WHO.

# Overview



- The Committee for Advanced Therapies (CAT)
- The PRIority Medicines (PRIME) scheme
- ATMP analytical testing challenges
- Comparability & Potency
- Examples

# Committee for Advanced Therapies (CAT)



Paolo Gasparini, MD  
IT CAT member

Giulio Pompilio, MD  
IT CAT alternate

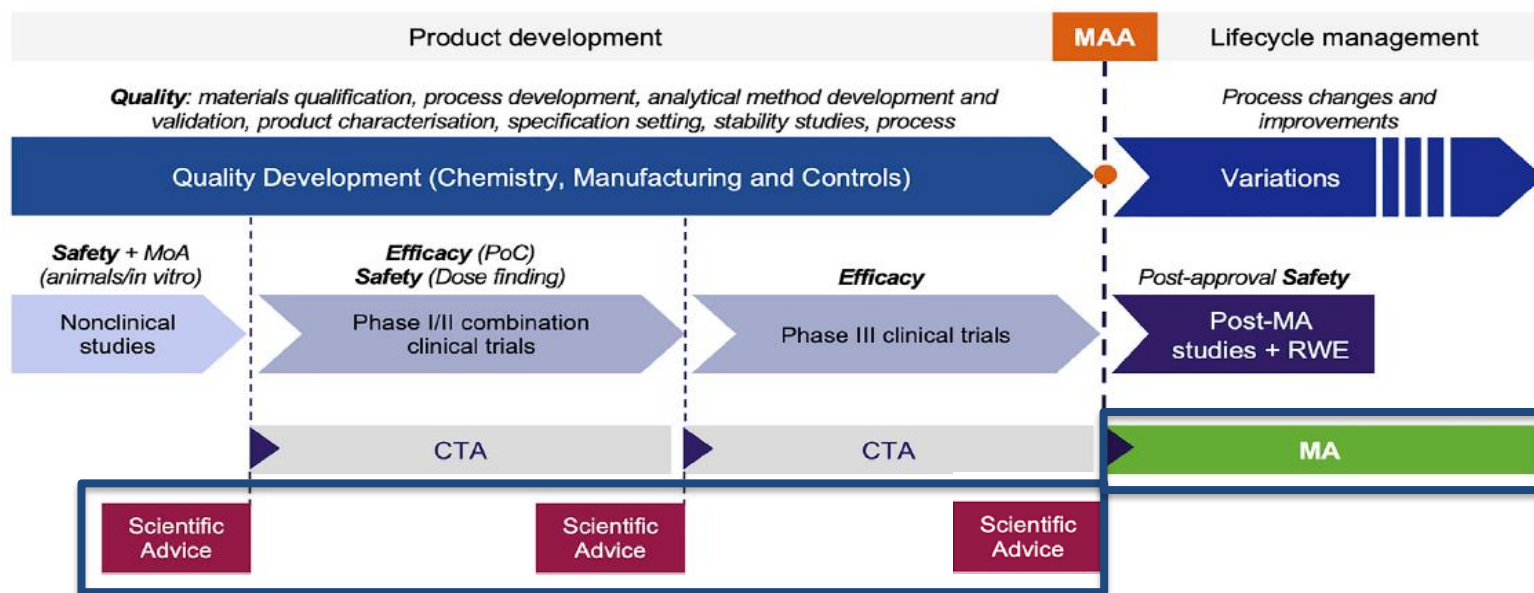
# CAT main responsibilities

- Evaluation of marketing authorization **(MA) applications for ATMPs**: centralised MA (one license valid in the entire EU/EEA, 150/210-day procedure, CAT draft opinion, CHMP final opinion, EC decision, granting of the MA).
- **Certification procedure** (pre-evaluation of Q and NC data, any stage of the ATMP development, development on track for a future MA application).
- **Classification procedure** (confirmation of compliance with ATMP definitions)
- **Scientific advice** (SA)/protocol assistance (PA) (questions on Q, NC and C development + post-marketing issues)
- Involvement in any **scientific or regulatory matter/context** requiring expertise in ATMPs including early dialogue platforms fostering innovation (*e.g.*, innovation task force (ITF) meetings).



# More recent CAT responsibilities

The CAT reviews the PRIME scheme eligibility requests and provide recommendation to CHMP, for ATMPs.



# EU expedited access: Designations and Regulatory Procedures

PRIME Scheme	Accelerated Assessment	Adaptive Pathways	Conditional MA
<ul style="list-style-type: none"><li>• Unmet medical need</li><li>• Major therapeutic advantage to patients</li><li>• Support <b>early</b> development</li><li>• Reinforced Agency support throughout development.</li><li>• Improve use of Regulatory and procedural tools</li><li>• <b>Multidisciplinary</b></li><li>• <b>SA free of charges</b></li><li>• <b>Enable accelerated assessment for MA</b></li></ul>	<ul style="list-style-type: none"><li>• Product is of major interest for public health and therapeutic innovation</li><li>• 150 evaluation days of MAA, rather than 210</li></ul>	<ul style="list-style-type: none"><li>• High Medical need</li><li>• Iterative development</li><li>• Approval in stages (from restricted patient population to wider pop)</li><li>• Approval based on early surrogates to be confirmed by real life data</li></ul>	<ul style="list-style-type: none"><li>• Approval of a medicine that address <b>unmet medical needs</b> with <b>less comprehensive clinical data</b> than normally required</li><li>• Benefit of immediate availability &gt;&gt; risks of having less data</li><li>• Applicant should be able to provide the comprehensive clinical data in the future.</li></ul>

'All we have to decide is what to do with the time that is given us.' J.R.R. Tolkien



# The PRIME scheme – an early access tool



## PRIME: in brief

Medicines eligible for PRIME must address an unmet medical need.

Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.

EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients' access.



**EARLY & ENHANCED DIALOGUE. HOW?**



# The PRIME as a journey



**MAA accelerated assessment (potential)**

**SA at key development milestones**

**EMA dedicated contact point**

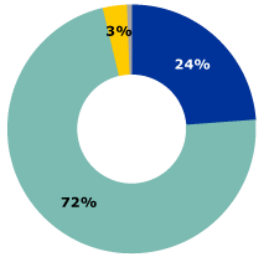
**Kick-off meeting**

**Early appointment of a CHMP/CAT rapporteur**

**PRIME eligibility (SAWP/CAT/CHMP)**

# ATMPs and the PRIME – more than a fairy tale

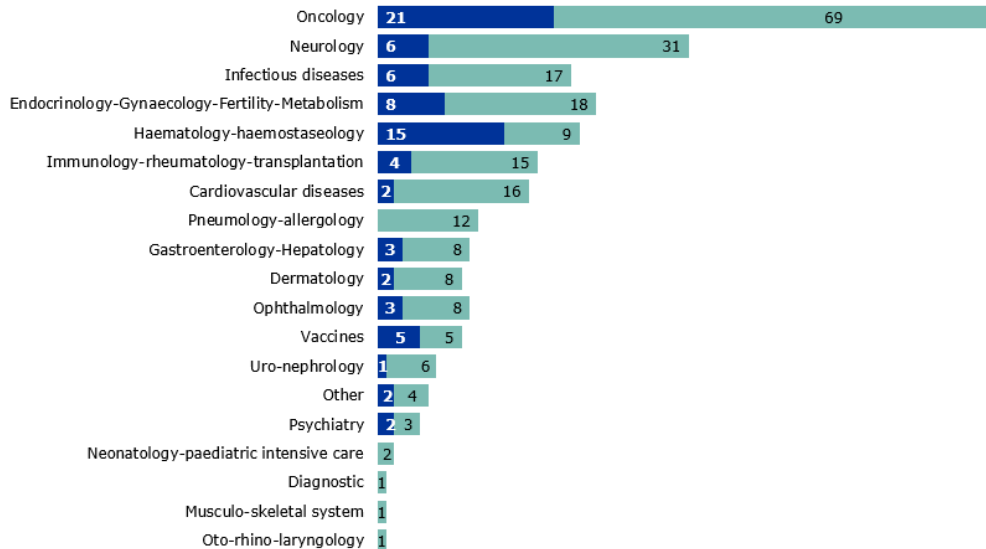
Applications and eligibility decisions



Type of applicant



Therapeutic areas



Recommendations adopted by 15 October 2020

\* Out of scope applications are not included in the breakdown by type of applicant or by therapeutic area

■ Granted ■ Denied ■ Out of scope\* ■ Withdrawn

EMA updates the list of all products granted access to the PRIME scheme on a **monthly basis**.



23 out of 58 PRIME products are **ATMPs**.



**~ 40%**  
(last update 22/10/2020)

# List of ATMPs currently in the PRIME scheme

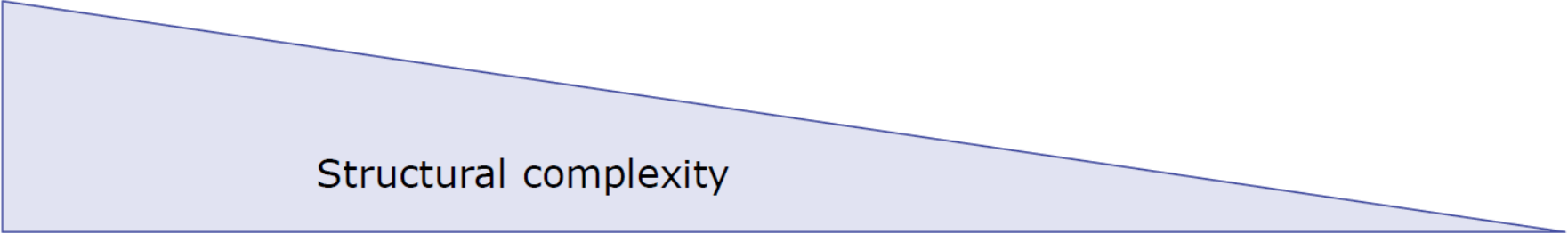
Adeno-associated viral vector serotype 8 containing the human MTM1 gene (AT132)	Adenovirus associated viral vector serotype 5 containing the human RPGR gene	Adenovirus associated viral vector serotype 8 containing the human CNGB3 gene (AAV2/8-hCARp.hCNGB3)	ADP-A2M4 (transduced CD4+ and CD8+ cells)	Allogeneic EBV-specific Cytotoxic T Lymphocytes	Allogeneic multi-virus specific T lymphocytes targeting BK Virus, cytomegalovirus, human herpes virus-6, Epstein Barr virus, and adenovirus (ALVR-105)
Autologous anti-CD19/CD20 CAR T transduced cells (MB-CART2019.1)	Autologous CD34+ cells transduced with lentiviral vector encoding the human beta globin gene (OTL-300)	Autologous CD34+ enriched cells transduced ex vivo with lentiviral vector carrying the FANCA gene, PGK-FANCA-WPRE (RP-L102)	Autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptor to target the cancer-testis tumour antigen NY-ESO-1 (NY-ESO-1c259T)	Autologous CD4+ and CD8+ T-cell populations transduced with a genetically-engineered replication-incompetent, self-inactivating lentiviral vector to express a BCMA-specific CAR (JCART125)	Autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human ATP-binding cassette, sub-family D (ALD), member 1 (ABCD1) from cDNA
Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor (CAR) for B-cell maturation antigen (BCMA) (JNJ-68284528)	Etranacogene dezaparvovec (AMT-060, AMT-061)	Fidanacogene elaparvovec (PF-06838435/SPK-9001)	Fully human anti-BCMA autologous CAR T Cell (CT053)	Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII (KB103)	Lisocabtagene maraleucel (JCART17)
Rebisufilogene etisparvovec	Recombinant adeno-associated viral vector serotype S3 containing codon-optimised expression cassette encoding human coagulation factor IX variant (FLT180a)	Recombinant adeno-associated virus vector based on the AAV serotype hu37 containing a single stranded DNA genome encoding a form of human FVIII (BAY2599023)	Tabelecleucel (Allogeneic Epstein-Barr virus-specific cytotoxic T lymphocytes, ATA129)	Tasadenoturev (Adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain, DNX-2401)	

# ATMPs & the PRIME – why?

~ 40 % of currently designated PRIME products are GMCs

## Product complexity

Genetically modified cells	Cell/Tissue engineered products	Viral vectors GTMPs	Viral & other vaccines	Recombinant proteins	Synthetic peptides / oligos	Chemically derived small molecules
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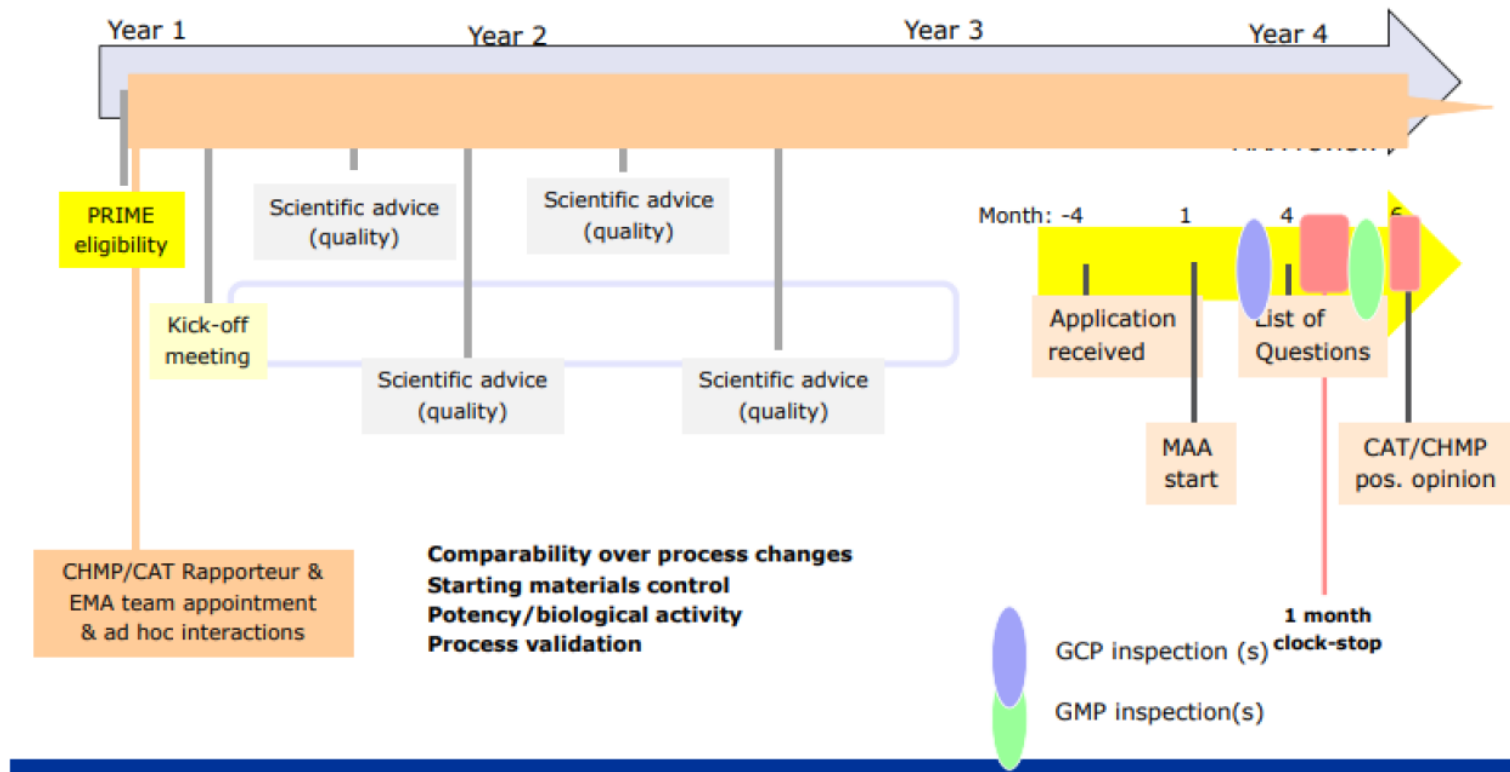
Structural complexity

# Looking to the next 5 to 10 years...?

New innovative medicines, manufacturing processes and regulatory challenges!



# Support to PRIME product during pre-authorization & MAA on quality



# Scientific advice: Q scientific challenges of PRIME candidates

areas - scientific advice requests (data up to July 2018)

API/ Substance	Areas	Raw materials	Orphan similarity	Cell banks	<b>Starting materials</b>	GMP/site	<div>Critical areas</div> <div>Number of question &gt; 7</div>
	# Q	2	2	4	8	6	
Process	Areas	Process development	<b>Comparability</b>	Change management	<b>Validation</b>		
	# Q	4	22	2	8		
Control	Areas	Potency assay	<b>Analytical control strategy</b>	<b>Specifications</b>	Adventitious agents	<b>Stability</b>	Product-rel. impurities
	# Q	6	14	7	3	9	5

(Source: Presentation – Perspective from the EU - Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies – V. Jekerle)

# Use of analytical tests

All testing results should be considered in the context of ensuring **product quality**, which combines process control and appropriate testing:

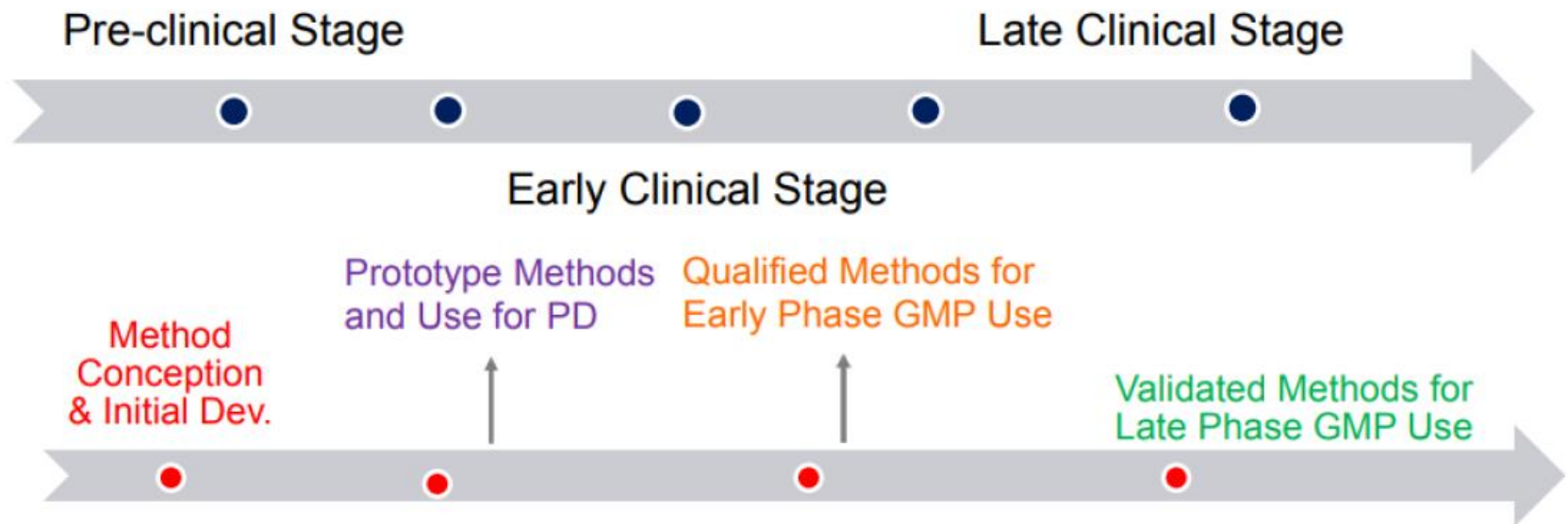
- Product **characterization** data to be collected throughout development (elucidation of structure and other characteristics, impurities)
- Manufacturing **consistency** (in-process testing, lot-to-lot consistency, process validation)
- Product **release**
- Product **stability**
- Product and process **comparability** (process improvement, global development and multiple site manufacture)



# Lifecycle analytical method development

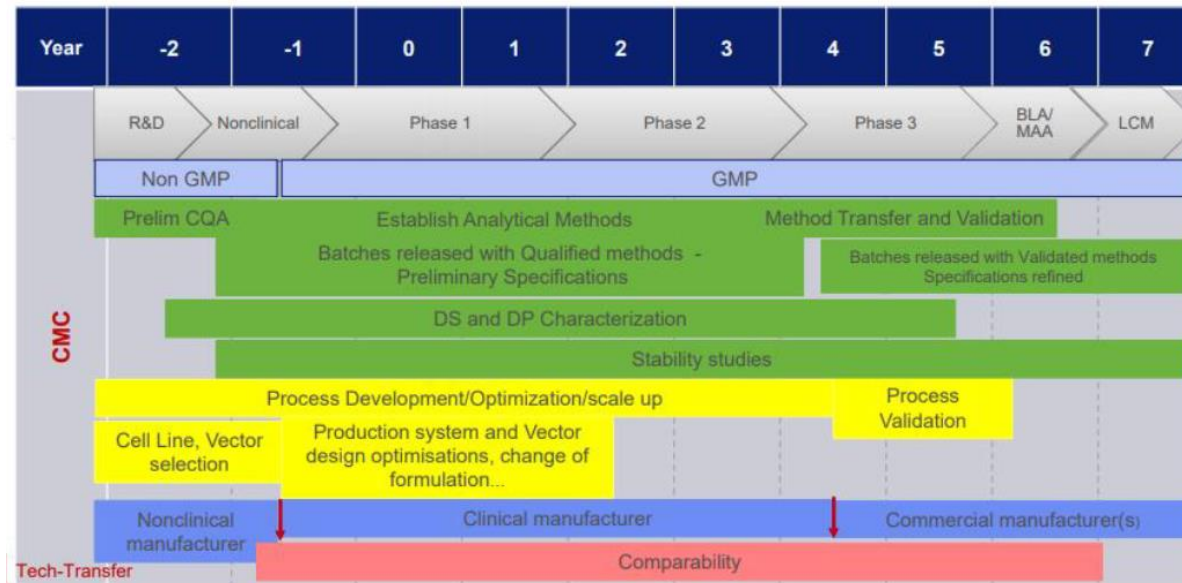
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Good analytics is a key enabler to product development and advancement to marketing of any therapeutic

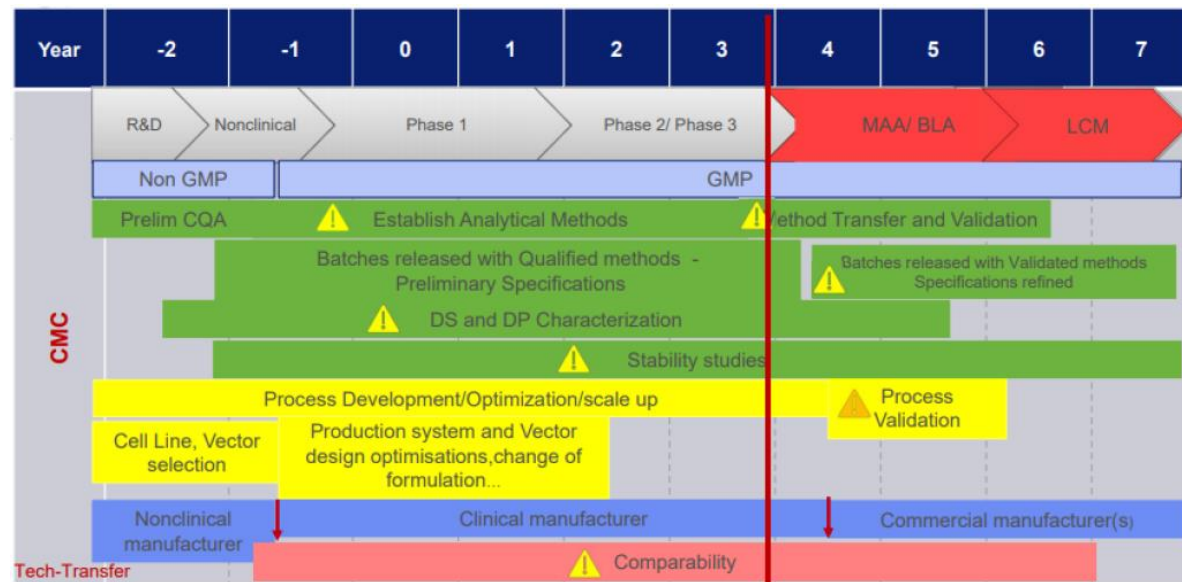


# CMC Development Roadmap/Timeline

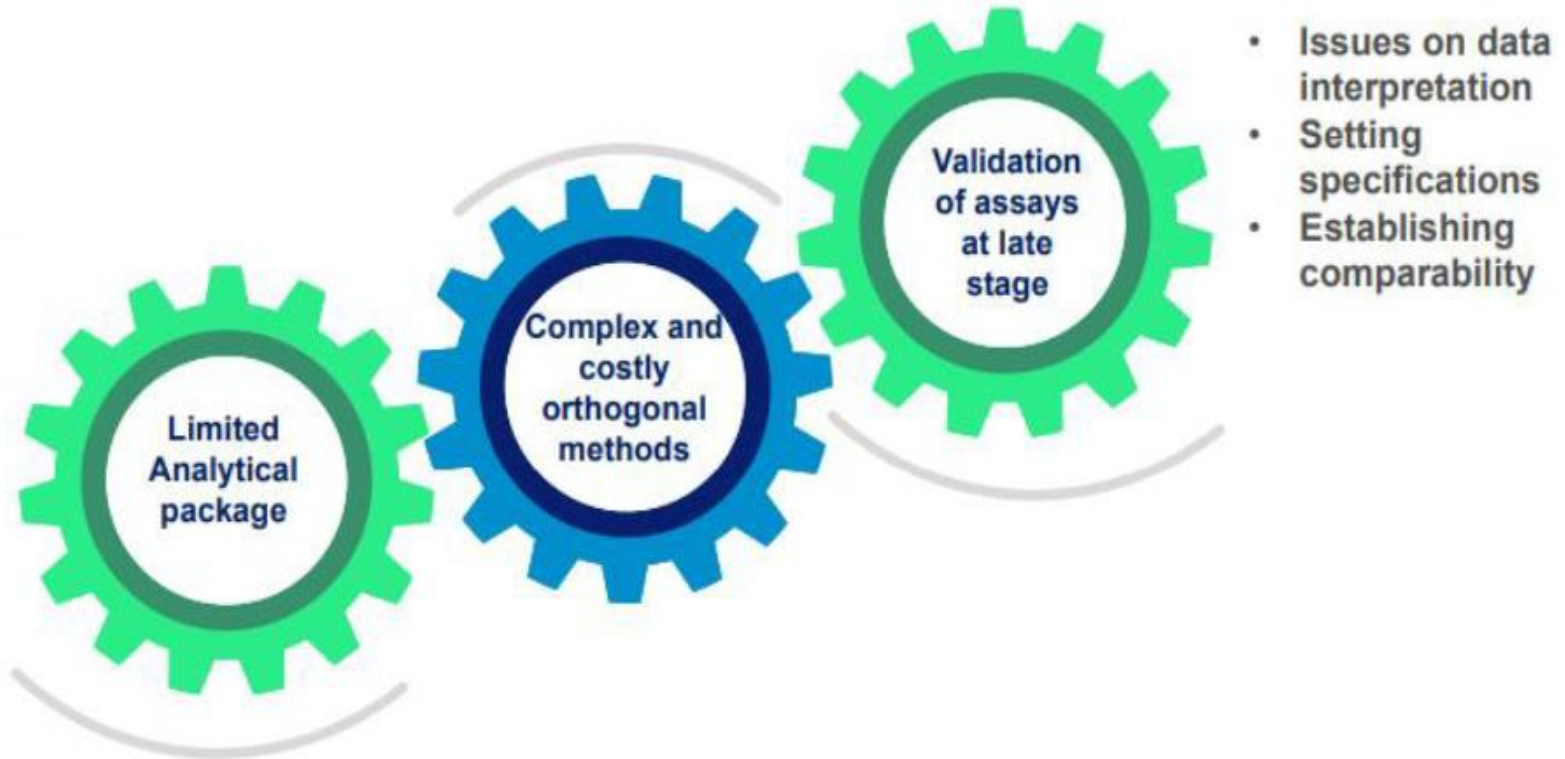
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# CMC challenge & ATMP: analytical development



# Analytical challenge for ATMP

- New analytical techniques required to monitor CQAs
- Complex testing requirements - specific characterisation, purity, potency and identity assays for each product
- Rapid methods to account for short shelf-life (endotoxins, mycoplasma, sterility)
- Potency assay – to correlate with clinical efficacy, mode of action
- Characterisation NB especially for comparability studies to support process changes during development. Next-gen techniques include proteomics, transcriptomics.
- Limited batch sizes– method adaptation to deal with small sample volumes
- Validation of non-compendial methods? Reference standards?

# Recurrent hurdle - 1: comparability (1)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

6 December 2019  
EMA/CAT/499821/2019  
Committee for Advanced Therapies (CAT)

## Questions and answers

Comparability considerations for Advanced Therapy Medicinal Products  
(ATMP)

# Recurrent hurdle - 1: comparability (2)

## **Q6: What are the analytical tools to consider in a comparability exercise?**

**A:** For a comparability study of pre- and post-change materials, analytical methods used for release testing are the starting point. Extended characterization tests are needed to demonstrate the comparability of these types of materials at a quality level. Methods related to the functional and biological characteristics of the drug product are of particular interest and should therefore be developed for characterization/comparability purposes early in the development.

The analytical methods should be qualified for the analyte and sufficiently specific, robust, and sensitive. See also Question 2.

In the undesirable and complex situation when pre-change material is no longer available and side-by-side testing is not possible, the emphasis should be on the used analytical methods. Insufficient information on the analytical methods will cause doubts on reliability of the recorded data. If, in addition, the used analytical methods differ, it will be difficult to establish a link between the pre- and post-change material on the basis of quality. Therefore, bridging of methods used during development needs to be considered to support the comparability claim.

- Orthogonal methods to be used to measure a CQA
- Current technology-based methods to be included



# Recurrent hurdle - 1: comparability (3)

**Q10: Is there a minimum number of batches that should be included in a comparability exercise?**

**A:** There is no 'one size fits all'. For considering the required level of comparability demonstration, the intrinsic variability of the product needs to be evaluated and taken into account.

Depending on the type of change introduced, while a small number of batches can serve to demonstrate comparability for a given analytical method where intrinsic variability is minimal and precision and sensitivity is high, other methods such as biological characterisation methods may require more extensive testing of significant numbers of samples as the inherent variability is high. The number of batches included in the comparability exercise needs to be evaluated case by case, and the approach taken requires careful consideration and justification based on the type of change, product and manufacturing process understanding, overall control strategy, sensitivity of the methods and the level of risk.

The higher the variability between batches, the higher the number of batches required to conclude the comparability exercise.

# Recurrent hurdle - 1: comparability (4)

Measuring something that changes with something that changes as well...

Variations the the terms of the original MA must be submitted to support analytical assay changes as part of product life-cycle management to address scientific advancement, assay suitability over time and/or reagent replacement:

- Replacement to assay methods
- Changes to existing methods

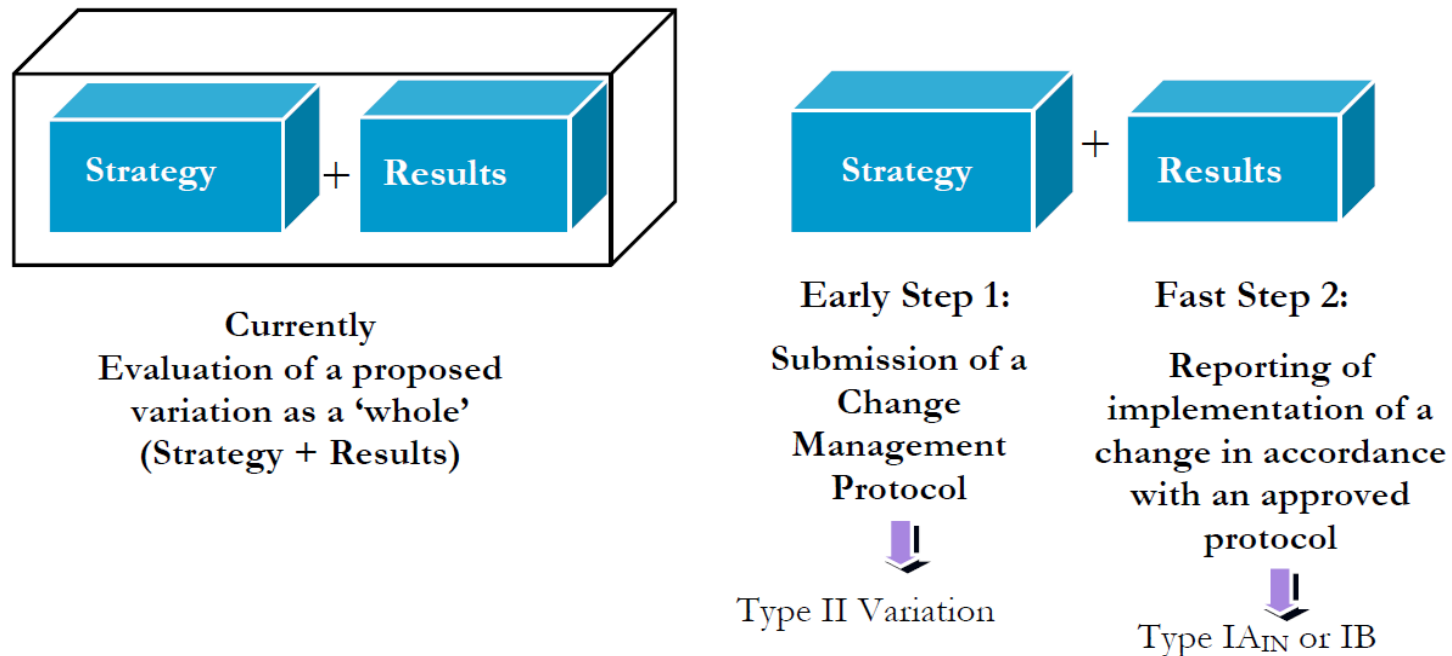
New or modified methods must have equal or better performance as compared to the approved ones and assure that lots are comparable to those shown to be safe and effective.



# Recurrent hurdle - 1: comparability (5)

## Post-Approval Change Management Protocols

**Figure 1: Post Approval Change Management Protocols**



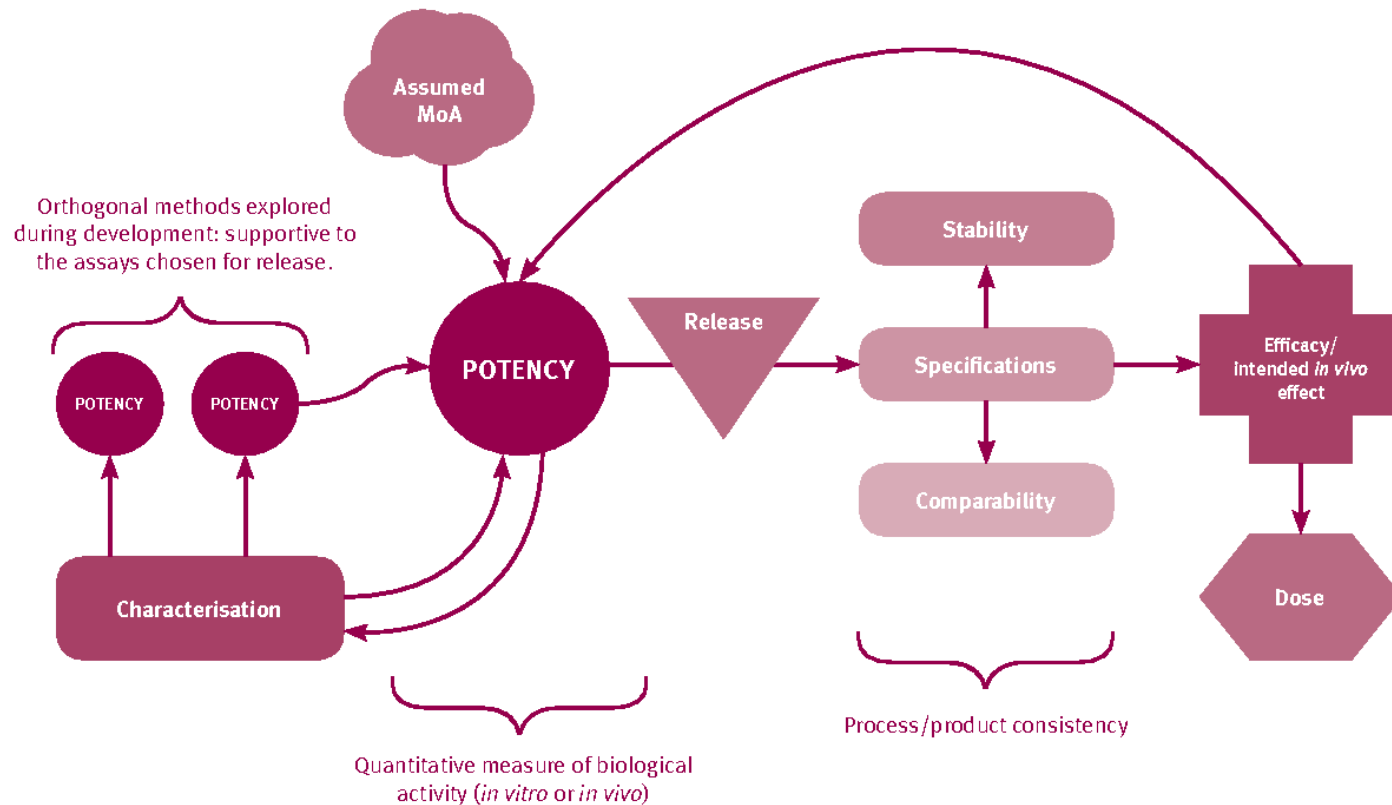
# Recurrent hardle - 2: potency (1)

Potency testing is at the corner stone to a solid product development and relevant quality control strategy:

- To be established early during development (phase I),
- To be designed based on anticipated MoA and/or anticipated functional activity of the product and sensitive enough to detect clinically meaningful changes,
- Intrinsic challeges, e.g., complexity of the products, impossible to fully recapitulate the expected overall clinical response in an assay, MoA not fully known and  $\geq 1$ ,
- Operational challenges, e.g., limited shelf-life, limited volume (autologous products), no reference standard, mutiple methods,
- Surrogacy and matrix approach might be an option, in this case the choice of the assay should consider complementarity regarding MoA coverage and/or correlations.

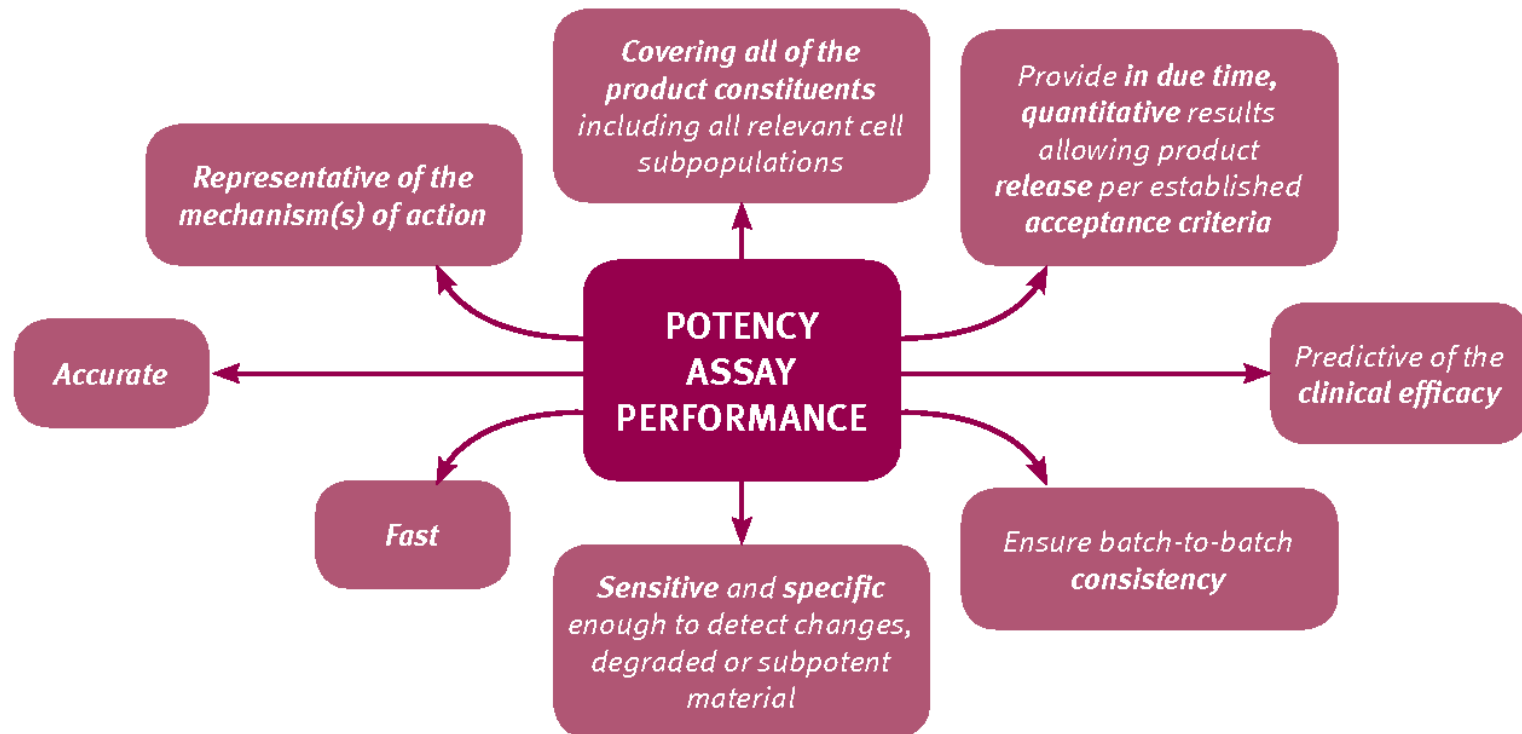
# Recurrent hardle - 2: potency (2)

Figure 1: Potency at the core of product development.



## Recurrent hardle - 2: potency (3)

Figure 2: Desired characteristics of potency assays.



# Early access scheme and the management of deferral of Q data

- Full regulatory compliance is required!
- Flexibility can be considered in terms of **WHEN** the quality data comes in and **not IF**,
- Post-authorisation measures: recommendation (not binding) & annex II conditions (binding).

# KYMRIAH – European Public Assessment Report

(<https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah>)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

28 June 2018

EMA/485563/2018

Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Kymriah

International non-proprietary name: tisagenlecleucel

Procedure No. EMEA/H/C/004090/0000

### 2.2.5. Recommendations for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CAT recommends several points for investigation including **completing the characterisation and testing of the viral vector**, the leukapheresis starting material and the finished product.

The CHMP endorses the CAT assessment regarding the recommendations for future quality development as described above.

# YESCARTA – European Public Assessment Report

(<https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta>)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

22 June 2018

EMA/481168/2018

Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### YESCARTA

International non-proprietary name: axicabtagene ciloleucel

Procedure No. EMEA/H/C/004480/0000

#### 2.2.6. Recommendations for future quality development

In the context of the obligation of the applicant to take due account of technical and scientific progress, several points for investigation, including the manufacturing process and **control of the product**, were recommended.

The CHMP endorsed the CAT assessment regarding the recommendations for future quality development.

# LUXTURNA – European Public Assessment Report

(<https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna>)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

20 September 2018  
EMA/CHMP/700911/2018  
Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Luxturna

International non-proprietary name: voretigene neparvovec

Procedure No. EMEA/H/C/004451/0000

### 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation: 10 recommendations aimed at providing **further data on viral testing**, effect of cell passage on CQAs, monitor performance of transfection solutions, ability to adequately discriminate between empty and full capsids, **additional characterisation and release test**, **refine analytical methods and re-valuation of specification** once additional batch data becomes available.



# Zynteglo – European Public Assessment Report

(<https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo>)



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

26 April 2019  
EMA/56140/2020/Corr.<sup>1</sup>  
Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Zynteglo

International non-proprietary name: betibeglogene autotemcel

Procedure No. EMEA/H/C/003691/0000

#### 2.2.6. Recommendations for future quality development

14 recommendations aimed at improving control of raw materials, providing additional stability data for starting materials, installing in process controls and/or limits for LVV and active substance manufacture, **completing characterisation of LVV particles, providing further data on LVV and finished product test methods**, revising acceptance criteria as warranted, re-evaluation of specifications after manufacture of additional batches of LVV and finished product, **implementing additional test methods and acceptance criteria**, respectively.

# Zynteglo – Summary of Product Characteristics

([https://www.ema.europa.eu/en/documents/product-information/zynteglo-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/zynteglo-epar-product-information_en.pdf))

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further confirm the appropriateness of the acceptance criteria, the MAH should re-evaluate the acceptance criteria for attributes related to potency tests using batch release data and clinical results after 6 months follow-up of 20 patients treated with commercial batches.	Interim report: at each annual renewal  When 20 patients have been treated with 6 months follow-up

# Zolgensma – European Public Assessment Report

([https://www.ema.europa.eu/en/documents/assessment-report/zolgensma-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf))

26 March 2020  
EMA/200482/2020  
Committee for Medicinal Products for Human Use (CHMP)  
Committee for Advanced Therapies (CAT)

## Assessment report

### Zolgensma

International non-proprietary name: onasemnogene abeparvovec

Procedure No. EMEA/H/C/004750/0000

#### 2.2.4. Recommendation(s) for future quality development

1. Control of vector genome integrity: The applicant should develop and **implement a release test** and define scientifically justified acceptance criteria. 4. The applicant will **develop a more sensitive and precise method** for analysis of protein impurity 6. The applicant will **validate an aggregation assay** and, once validated, submit a variation 8. The applicant commits to **revalidate the sterility test method**. 10. The applicant commits to **establish an independent assay control for the potency assay** by August 2020 to monitor assay performance as well as reference standard stability.

# Zolgensma – Summary of Product Characteristics

([https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf))

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
<p>Non-interventional post-authorisation efficacy study (PAES):</p> <p>In order to further characterise and contextualise the outcomes of patients with a diagnosis of SMA, including long-term safety and efficacy of Zolgensma, the MAH should conduct and submit the results of a prospective observational registry AVXS-101-RG-001 according to an agreed protocol.</p>	<p>Interim results:</p> <ul style="list-style-type: none"><li>- Safety with PSUR,</li><li>-Efficacy and safety with annual renewal</li></ul> <p>Final results:</p> <p>2038</p>
<p>The applicant should perform a further evaluation of the finished product specifications when primary and key secondary endpoint data from additional patients with 2 copies of SMN2 are available (i.e. completion of CL-302 and CL-304 cohort 1). Based on this evaluation, it should be determined whether tightening of the release specification limits is needed to improve consistency of the batches and ensure optimal clinical outcome.</p>	<p>Dec 2021 with completion of Study CL-302 and Cohort 1 in Study CL-304</p>

**Thank you for your attention!**

спасибо 谢谢  
**GRACIAS**

**THANK YOU**

ありがとうございました **MERCI**

**DANKE** धन्यवाद

شُكراً **OBRIGADO**

