Regulatory challenges in early access approaches—reflections from EMA/FDA workshop

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Content

- PRIME eligibility, quality challenges, regulatory aspects and case study
  (Veronika Jekerle)
- GMP & Comparability (Marcel Hoefnagel)
- Process control, validation and stability
  (Mats Welin)
PRIME eligibility

‘a major therapeutic advantage over existing treatments, or benefit patients without treatment options’

- medicine to show its potential to benefit patients with unmet medical needs based on early clinical data

SME 26 105
Other 27 67
Academia 3

data: April 2019


### PRIME eligibilities granted

**by product class - status April 2019**

<table>
<thead>
<tr>
<th>Product Class</th>
<th>Granted</th>
<th>Denied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td>16</td>
<td>72</td>
</tr>
<tr>
<td>Biological</td>
<td>11</td>
<td>32</td>
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<tr>
<td>ATMP</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>9</td>
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</tbody>
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**PRIority MEDicines scheme**

support the development of medicines with **major public health interest**

<table>
<thead>
<tr>
<th>Scientific &amp; regulatory advice</th>
<th>Robust data generation</th>
<th>Accelerated access</th>
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<tbody>
<tr>
<td>early interaction</td>
<td>focus the development</td>
<td>discuss filing strategies early on</td>
</tr>
<tr>
<td>raise awareness on regulatory &amp; scientific requirements as early as possible</td>
<td>promote robust &amp; high quality data</td>
<td>generate and leverage high quality data for MAA dossier</td>
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Challenges

- **Timelines** (e.g. commercial manufacturing sites/description, validation data, stability, control strategy)

- **Innovation & complexity** (e.g. product characterisation, potency, comparability)

- **Global development** (e.g. comparability, manufacturing sites, batch release testing)

→ **Module 3 data requirements** in line with scientific guidelines and technical requirements according to the EU legislation

*(Annex I of Dir. 2001/83/EC, Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances)*
Joint EMA-FDA workshop on quality support to PRIME & Breakthrough

26/11/2018 at EMA

• Problem statement & aims
• Process validation
• Control strategy
• GMP compliance
• Afternoon parallel sessions
  \emph{Biological} (Process validation & control strategy, \emph{comparability}, \emph{stability})
  \emph{Chemical} (Control strategy, stability)
• Regulatory tools
• Conclusions

Organising Committee (EMA & US FDA)

**EU ad-hoc expert group**
- Marcel Hoefnagel (NL), BWP member
- Mats Welin (SE), BWP member
- Sean Barry (IE), BWP member
- Jobst Limberg (DE), QWP member
- Kristofer Olofsson (SE), QWP member
- Tone Agasoster (NO), QWP member
- Giampiero Lorenti (IT), IWG member

**EMA**
- Dolores Hernan, Quality Office
- Kaidi Koiv, Quality Office
- Veronika Jekerle, Quality Office

**FDA**
- Andrew Byrnes, CBER
- Judith Arcidiacono, CBER
- Emanuela Lacana, OPQ, CDER
- Laurie Graham, OPQ, CDER
- Ramesh Sood, OPQ, CDER
- Scott Furness, OPQ, CDER
- Mahesh Ramanadham, OPQ, CDER
Outcome of the workshop

- Identify scientific elements/tools within existing guidance to help address the challenges (i.e. EU, US & ICH guidance)

- Identify gaps in the current guidance landscape

- Explore areas of common agreement & areas that would benefit from further harmonisation between EMA/FDA

*within the existing regulatory framework
Regulatory tools outcome

**Existing reg/proc tools**

**PRIME scheme** (support, frequent interactions, early Rapporteur appointment)

**Scientific advice** (including parallel scientific advice (FDA/HTA))

**Managing deferral of data** (recommendations, Annex II conditions, etc.)

**Change management** (PACMPs, life cycle strategy)

**Alternative data sources** (e.g. Prior knowledge)

**PACMP ‘with flexibility’**: level of detail, flexibility and possibility for adaptation/modification of the protocol

**Regulatory follow-up on comparability**: Tools to report comparability data from batches used to treat patients after licencing (i.e. variations/recommendations)

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CASSS – 2019 CMC strategy forum – Seville - PRIME and early access - Jekerle
Regulators conclusions

- PRIME is a **support scheme** for development with the aim to achieve product quality that is not compromised
- **Global alignment** to answer similar challenges (FDA-EMA joined follow-up actions)
- **Flexibility** can be considered in terms of **when** the quality data comes in (partly post-authorisation) (& managed Annex II conditions, recommendations)
- Alternative data sources (e.g. platform/pilot scale data) can help build the case (see EMA Prior knowledge workshop: [Meeting report - Prior knowledge workshop](#))
- **Risk-based thinking** to relate the available quality data vs. requirements
- Quality to be considered in the context of the **benefit/risk assessment**
Example (ATMP)
support to PRIME product during pre-authorisation & MAA (on Quality)

Comparability over process changes
- Starting materials control
- Potency/biological activity
- Process validation

CHMP/CAT Rapporteur & EMA team appointment & ad hoc interactions

Kick-off meeting

PRIME eligibility

Scientific advice (quality)

Scientific advice (quality)

Scientific advice (quality)

Month: -4             1            4             6

Application received

MAA start

List of Questions

CAT/CHMP pos. opinion

GCP inspection (s)

GMP inspection(s)

1 month clock-stop

CASSS – 2019 CMC strategy forum – Seville - PRIME and early access - Jekerle
Interaction between Regulators & Applicant

Quality support to a PRIME product

**PRIME eligibility orientation**
- Rapporteur & EMA team appointment
- Kick-off meeting
- Ad hoc interactions

**Advice on Applicant’s Quality package examination**
- Applicant & Regulators
  - Scientific advice & responses
  - Regulatory strategy

**Incorporation of outcomes into CTD preparation**
- Applicant & Regulators
  - Module 3 preparation
  - SA letters
  - Pre-submission Meetings
  - CoRapporteur

**MAA review & responses CHMP/CAT assessment**
- Regulators assessment of
  - Quality package
  - Benefit-risk
  - Product information
  - Inspections Recommendations/Annex II

**Post-authorisation phase commitments follow-up**
- Applicant
  - Fulfilment of commitments
    - PACMP(s)
    - Variations
    - Line extensions
  - Extended development

**MAA submission**

**MAA approval**
Next steps

• **Follow-up from the workshop**
  
  Presentations & Video Recordings:  

• **Meeting report:** organising committee finalised a first draft, comments by Industry Speakers & Panellists & priority on follow-up actions (by EMA / FDA & jointly)

• **Continued stakeholder dialogue/interaction:** monitoring of evolving experience

• **EMA/FDA & involved working parties:** to consider next steps for action
GMP and comparability
Marcel Hoefnagel
Challenges related to GMP

How to deal with specific GMP issues in development in line with a shortened development programme?

- Clinical trial data generated with products manufactured in a facility, like academic laboratory, that did not meet full GMP requirements
- Master Cell Bank (MCB) / Working Cell Bank (WCB) not manufactured under GMP
- Use of OOS material
- Batch release from lab based in a third country (importation testing)

- How can clinical GMP considerations be applied? (B/R)
- Harmonisation in inspections by different authorities
- Scientific Advice procedures to address GMP matters
GMP: Regulatory/Procedural tools

Existing reg/proc tools*:
- GMP for ATMP
- Concurrent validation
- Scientific advice (with Inspector/Assessor interaction)

Reg/proc tools* to be explored:
- Clinical trial material not manufactured under full GMP (e.g. academic lab)
- Comparability using non-GMP material
- Use of MCB/WCB not developed under GMP
- Batch release from a third country (Import)
- Administration of OOS cell/tissue based ATMP (in patient’s interest)
- Harmonising Approaches of Regulatory Authorities
How do you deal with demonstration of comparability (late) in development in line with a shortened development programme?
Challenges of Comparability

How do you deal with demonstration of comparability (late) in development in line with a shortened development programme?

- Moving from clinical site/process to commercial site/process
- Challenges of conducting comparability studies in a time-sensitive manner
- Challenging due to highly innovative and complex features (e.g. ATMP)
Comparability

**Issues raised during discussion**

- Risk-based approach (RBA) to assess extent of comparability exercise
- Multistep approach (impact of each change)
- Can analytical methods detect changes in CQAs?
- Understanding assay variability is critical to set appropriate comparability acceptance criteria.
- Supported by small-scale data / platform data / prior knowledge
Comparability

- Comparability protocols discussion with Authorities (FDA/EMA) prior to MAA
- Comparability with fewer pre- and post-change batches (<3)
- Launch from clinical site can shift comparability studies to post-authorisation
- Limit process changes based on RBA
Comparability (ATMP)

- Complex products that cannot be fully characterized
- Matrix of functional assays is valuable (Biological activity, phenotype, proliferation)
- Donor/Patient variability
- Higher risk for clinical comparability (analytical data might not suffice)
- Split batch manufacturing to deal with Donor/Patient variability
- Comparability with surrogate material (Difference patients-healthy donors)
- Concurrent validation: in case of strong benefit-risk ratio
Comparability: Regulatory/Procedural tools

- **ATMP:** Risk-based Approach

- Comparability using non-GMP material
- Concurrent validation based on preliminary specification
- Product launch from clinical manufacturing

Existing reg/proc tools*

Reg/proc tools* to be explored
Comparability: Scientific elements

- Prior knowledge/platform technology
- Risk-based identification of CQA (Critical Quality Attributes)
- Impact of separate changes on CQA
- Statistical tools

- Comparability using surrogate material
- Comparability using few and autologous batches
- Impact of manufacturing changes on ATMP (building knowledge database)
Process validation & control strategy
Mats Welin
Process validation

How do you speed up process validation activities in line with a shortened development programme?

**What are the solutions?**

- Innovative control strategies
- Prior knowledge
- Tailored process validation packages
- Use of models
- PACMPs

**Holistic approach**

Accelerated development programmes must balance regulatory flexibility with having an appropriate level of process validation data available at the time of approval.
Ongoing/continued process verification protocols

Protocols routinely used for e.g. full scale validation of resin lifetime and validation of re-filtration but in general are relatively under-utilised

- A more targeted use of protocols could facilitate deferral of certain process validation data to post-approval phase
- They could provide assurance to regulators that the appropriate data will be gathered and evaluated post-approval and could cover the entire manufacturing process or individual steps
- Where the license will need to be varied post-approval, a PACMP is more appropriate e.g. relaxing the control strategy after filling with additional controls and narrower ranges

What should be included in a protocol?
- What will be measured?
- How will it be evaluated?
- What are the acceptance criteria?
- Details of trending and statistical process control
- How will data be communicated
Process validation

There is no one-size-fits-all solution

- A combination of process validation approaches may be necessary to avoid delayed submission/approval for products on an accelerated path
- Be clear and transparent regarding deferred data and provide a plan to acquire data post-approval (with proposed timelines)
- Communication with regulators is critical!
- Consider a holistic approach by using protocols, concurrent validation, risk assessment, prior knowledge, process understanding and benefit/risk assessment to justify any deferral of process validation data
Issues for further discussion

• Commercializing clinical batches
• Decoupling of AS and FP process validation activities
• Deferral of process design studies/restricted control strategy
• Reinforce value of concurrent validation
• Mechanisms to submit delayed validation data
• Tailoring validation packages
• Widening control strategy post-approval through PACMPs (i.e. agreement on the principle of “relaxing” control strategy post-approval when supportive data is available)
Control strategy

- **Control strategy will differ...**
- Limited manufacturing and clinical experience
  - Too few batches to assess manufacturing consistency
  - Limited variability seen in clinical batches
- Commercial scale validation activities may be ongoing
- Understanding of criticality & interactions not fully mature

- ... but products are still expected to be safe and efficacious (and to have a positive benefit/risk ratio)
Control Strategy Expectations

- Increased knowledge of quality attributes and process can be used to support control strategy flexibility, including acceptance criteria and process parameter ranges outside of manufacturing and clinical experience.

- Applicant should address residual risks of control strategy and can include consideration for in-process testing, lot release, stability, comparability, monitoring, control of raw and starting materials, etc
  
  - Expedited development programs can, at the time of approval, lead to increased risks associated with element of the control strategy (e.g., uncertainty on the criticality of attributes, their control by the manufacturing process, and analytical capability) which will need to be addressed
Examples of Risk Mitigation for Control Strategies

• Potentially more attributes, process parameters, and assays in the application control strategy. The control strategy can be revised when more knowledge is gained.
  
  • e.g. consistent impurity removal by the manufacturing process, capacity of purification process to remove impurities as shown in validations or batch testing, updated criticality assessment showing less criticality for certain attributes
Topics raised in discussion

• Differences clinical justification small molecule- vs Biotech
  • For small molecules a lot of qualification of attribute levels can be performed in preclinical studies and main issue is consistency. For biotech only few such studies can be done as regards safety and clinical qualification would be the main issue.
• Using statistical process controls/ trending to set specifications
• International alignment of PACMPs
  • Specifications setting particularities
• References to PQS
  • Interaction Assessor- Inspector
Issues for further regulatory considerations

- Performance-based/intelligent control strategy/ New analytical strategies (e.g. multi attribute method)
  - Not unique for accelerated access products but more of a general issue allowing for more tailor-made controls.
- Front-loading of control strategy activities/ CMC development plan
  - Which areas may be less developed and how will the possible remaining non-mitigated risks will be compensated by other means also taking the benefit risk ratio of the product into account.
Stability

- Well recognised that stability will be a hurdle, in particular for biotech products following ICH Q5C- real time/ real condition data required. Need for discussion on use of accelerated data.

- Interesting presentation from industry- Stability model based on prior knowledge from similar products (MAbs)
  - Trend important, not actual levels.
  - Applied to new candidate to allow extrapolation beyond product specific stability data. End of shelf life acceptance criteria needs justification.
  - Important to understand when the model will fit- and when it will not.
  - Applicability to other types of biological products?
Acknowledgements

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Organising Committee: Sean Barry (IE), Jobst Limberg (DE), Kristofer Olofsson (SE), Tone Agasoster (NO), Giampiero Lorenti (IT), Andrew Byrnes, CBER, Judith Arcidiacono, CBER (FDA), Emanuela Lacana, Laurie Graham, Ramesh Sood, Scott Furnessn & Mahesh Ramanadham, OPQ, CDER (FDA), Kaidi Koiv, EMA Quality Office
Thank you for your attention

Further information

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