Introduction to CMC Challenges and Opportunities for MAPPs/Accelerated Pathways

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Regulatory pathway for accelerated approval of medicines in Europe

Early access tools: Overview

**PRIME**
- Major public health interest, unmet medical need.
- Dedicated and reinforced support.
- Enable accelerated assessment.
- Better use of existing regulatory & procedural tools.

**Adaptive Pathways**
- Scientific concept of development and data generation.
- Iterative development with use of real-life data.
- Engagement with other healthcare-decision makers.

**Accelerated Assessment**
- Major public health interest, unmet medical need.
- Reduce assessment time to 150 days.

**Conditional MA**
- Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.
- Early approval of a medicine on the basis of less complete clinical data.
Where are we with ‘Prime’ and ‘accelerated’ approvals?

From pure facts to wild guessing..!
Where are we with ‘adaptive licensing’?

Some Statements*

• CMC may become the critical path / time-limiting factor for patients’ access to new medicines approved under Adaptive Pathway
• The current CHMP Scientific Advice framework might not be flexible enough.
• Limited CMC package at the time of initial MAA submission. Need for rolling review

In June 2012 the European Federation of Pharmaceutical Industries and Associations (EFPIA) Board adopted the R&D and Regulatory Pathways Strategy with the objective of adapting the regulatory and development models to scientific progress and rationalizing them to improve R&D productivity and probability of success. A key component of this strategy is the Medicines Adaptive Pathways to Patients (MAPPs) initiative, which is aligned with the EMA Adaptive Pathways (AP) project.

MAPPs refer to an overall framework which describes proposals for addressing all aspects of adaptive approaches from early development to patient access and for the life-cycle of the therapy. It aims at faster translation of scientific breakthroughs to new, high quality medicines benefitting patients and society, improving dialogue between industry, patients, regulators, Health Technology Assessment (HTA) bodies and payers during the development process. Ultimately, it will reduce uncertainty for innovators and increase predictability for patients.
EFPIA INITIATIVE TO ACCELERATE ACCESS TO NEW MEDICINS: MAPPs


- As a next step, EFPIA/EBE MAPPs CMC sub-team has developed a white paper that elaborates on the CMC challenges and opportunities that will be encountered as part of an expedited development approach.

- This white paper now forms the basis for further discussions with BWP/QWP.
Problem Statement

An accelerated clinical development programme will usually be a prerequisite for acceptance onto an Adaptive Pathway project. This will decrease the amount of time available for the development and understanding of the drug substance, the drug product and their associated processes; therefore, there must be a strategy to ensure that the critical aspects of Chemistry, Manufacturing and Controls (CMC) provide assurance that safety and quality will not be compromised. This strategy must also assure the flexibility needed to deliver consistent and reliable supplies of product to patients in a less predictable environment, with potential controlled distribution to patients.
Guiding principles:

- The MAPPs CMC approach must always ensure product quality and patient safety whilst enabling the earliest access as possible for patients;

- Regulator(s) will enter into early discussion with the sponsor to agree on a viable expedited development programme;

- Consideration of the MAPPs CMC approach is comprised of three essential elements:
  - aspects associated with commercializing a new product more typical of a late stage Investigational Medicinal Product than Commercial Product;
  - commitment, timescale and assessment of an ongoing rolling submission of data, if required;
  - potential adoption of new working practices, predictive models and technologies that reduce uncertainty, provide greater verification and may help offset some of the traditional CMC data required at the time of filing;
Examples of CMC approaches for development and manufacturing to enable early access

<table>
<thead>
<tr>
<th>Topic</th>
<th>Traditional approach</th>
<th>MAPPs aligned approach</th>
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<tbody>
<tr>
<td>Process development</td>
<td>Complete package at filing. Process supported by extensive development studies</td>
<td>Partly based on <strong>platform knowledge</strong>, to be refined as more batches/materials are investigated. Process accepted on normal operating ranges based on limited stretching.</td>
</tr>
<tr>
<td>Viral Clearance Validation</td>
<td>Validated in small scale.</td>
<td>If appropriate <strong>platform data</strong> are available: include such data in dossier, validate in small scale prior to launch, and agree mechanism for provision of data to Competent Authorities.</td>
</tr>
<tr>
<td>Specification</td>
<td>Established and documented. Supported by extensive dataset.</td>
<td>Established and documented; possibly broader specifications as little data is available. May include some parameters where the data will be reported but acceptance criteria not defined. Commitment to update (rationalise) after x time or y batches, based on pre-defined criteria and to reassess the control strategy.</td>
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<tr>
<td>Process validation</td>
<td>Prospective or Continued Process Verification.</td>
<td>Concurrent validation approach, including extended monitoring.</td>
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**Note:** The table format is used to present the information in a structured manner, allowing for easy comparison between traditional and MAPPs aligned approaches.
Use of platform/prior knowledge and platform/prior data in a Marketing Authorization Application are a prerequisite to facilitate early access of medicines. It is a topic of high interest for regulators and industry.

The topic will be addressed in more detail in the next 4 presentations:

- Mats Welin: Use of prior Knowledge: A Regulatory Agency Perspective
- Earl Dye: Prior Knowledge in Drug Substance Process Validation
- Alistair Kippen: Prior Knowledge in Establishing Control Strategy / Critical Quality Attributes
- Ciro Cottini: Drug Product Modeling in Scale-up and Transfer of Lyophilization Processes
THANK YOU!