TOPRA Annual Human Medicines Symposium 2017

Accelerated Pathways
CMC considerations

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Director Global CMC, Pfizer
Learning Outcomes

The key learning objectives for this session are:

- Accelerated pathways options
  - EU, US, Global

- Challenges and Considerations
  - CMC specific issues
  - Opportunities

- Case study
EU: Accelerated access Tools and Initiatives

**PRIME:**
- Major public health need, unmet medical need
- Dedicated and reinforced support
- Enable accelerated assessment
- Better use of existing regulatory and 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 Marketing Authorisation:**
- Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in an emergency situations
- Early approval of a medicine on the basis of less complete clinical data

Timely Access to Medicines in the EU
### Fast Track:
- Potential to address unmet medical need
- Nonclinical or clinical data
- Frequent FDA interaction, rolling review, possible priority review

### Breakthrough therapy:
- Substantial improvement over available therapy
- Preliminary clinical data
- All fast track features, intensive FDA guidance, cross-disciplinary team leader, Senior managers, experienced reviewers

### Accelerated approval
- Surrogate / intermediate clinical endpoint
  “reasonably likely” to predict benefit. Meaningful advantage over available therapy
- Data from NDA/BLA submission
- Subject to conducting post marketing trials to describe/confirm benefit

### Priority review
- Significant improvement in safety or effectiveness over available therapy
- Data from NDA/BLA submission
- Decreases goal for completion of NDA/BLA review by 4 months
# Other global expedited pathways

<table>
<thead>
<tr>
<th>Country</th>
<th>Pathway / Designation</th>
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| **Japan** | **Priority review**: Target serious/life-threatening condition, exhibit improved clinical usefulness over existing therapies. PMDA commits to 9, rather than 12 months review.  
**Sakigake**: Qualifying criteria:  
• Target serious/life-threatening condition  
• Demonstrates improvement over existing therapies (safety or efficacy)  
• Has different mechanism of action than existing therapies  
• Sponsor intends to conduct early clinical dev & submit drug in Japan (initial filing). In exchange, prioritized PMDA consultations, designated liaison contact between the sponsor /review team, rolling review of application & accelerated review of 6 months.  
**Conditional and time-limited approval scheme** targeted at regenerative therapies. |
| **Canada** | **Priority review**: To qualify intended to treat a serious, life-threatening, or severely debilitating disease or condition, and substantial evidence of  
• an “effective treatment, prevention, or diagnosis of a disease or condition that does not have an approved drug in anada”-or  
• Demonstrates improvement in the risk-benefit profile over existing therapies  
Approval decision within 180 days, rather than the standard 300 days. |
CMC development: Non accelerated

Informational and Strategy Activities

DS commercial route selection
DP comm formulation process
Material risk assessment
Bioequivalence (BE) strategy

ICH/Registration Stability Batches

Further optimizations required

MA Module 3

Registration submission(s) & associated query responses

Amendments may be required; CTAs to support new studies (increased content)

CTA Amendments Module 3

Bridging studies

Health Authority Meetings

Product knowledge and understanding increase

Initial Ph 3 Submission

CTA Module 3

Commercial manufacturing validation and launch supplies

Amendments

Module 3

Registration submission(s) & associated query responses

Health Authority Meetings

Bridging studies

MA Module 3

Further optimizations required

ICH/Registration Stability Batches

CTA

Module 3

Initial Ph 3 Submission

Product knowledge and understanding increase

Post-Approval Changes

Product approval and launch

Amendments may be required; CTAs to support new studies (increased content)
Acceleration, how does it feel?
Acceleration – CMC Challenges

- Availability of Data
- Establishing meaningful and practical specifications
- Manufacturing and launch site considerations
- Inspection readiness
- Product lifecycle planning
- Agency Interaction
CMC Challenges – Availability of data

Process & formulation development

- Shorter clinical development programs can impact on product and process development timelines
- Necessitates risk-based approaches to development,
  - Focus on process reliability over cost/yield
- Process optimization prioritized based on risk
- May end up with narrow process descriptions and higher level of regulatory commitments
- Dosage Form/Formulation Optimization may be post launch

Opportunity - Leverage Comparability Protocols/post approval change management plans
Stability data

- Consider how to deal with (lack of) stability data.
  - Lead to reduced shelf life which can impact launch / continuous supply
  - Agree an overall shelf life strategy for effective approval and launch
- Creative strategies can be considered where possible to provide latest stability data to extend shelf life.
- Some markets require site specific data
- Challenge when primary stability studies originate from development sites and stability data on batches made in the full commercial supply chain is limited.

Opportunity: Discuss mechanisms to extend shelf life and maximise such opportunities during regulatory review
Experience to establish meaningful and practical specifications

- Specifications are traditionally set based on the batch data
- Limited data may mean tighter specs
- Opportunity to consider wider specs based on overall risk
- Utilize the flexibility provided in ICH S9 when setting specifications

Opportunity – Safety based specifications
Strategy for site selection

- Focus on a reliable supply of quality product available to meet and sustain market demand
- Possible for accelerated projects timing of first approval may occur before completion of process validation.
- Alternative approaches for launch site maybe required and should be discussed with regulators prior to submission

**Options:** Launch from development site or launch with clinical material

**Opportunity:** Use comparability protocol / post approval change management plan to implement key changes
CMC Challenges – Inspection readiness

- Regulatory authority maybe interested in pre approval inspection as soon as possible
- Planning for an inspection can be challenging while also planning for launch
- **Opportunity**: Waive the PAI based on site inspection history
Lifecycle Planning

- Likely to have list of process improvements that require post-approval
- Need to define post-approval strategies to secure supply required much earlier,
  - may include addition of manufacturing sites, scale-up, or process optimisations to increase yields
- Plan for supply chain strategy for individual market launches
- Challenge to manage these while other markets are being filed
- Potential for sites to have to manage numerous forms of the same product
- **Inventory planning very challenging**
CMC Challenges – Regulatory authority interaction

Communication

➢ Open and timely communication with reviewers desired

➢ Adherence to procedural timelines prohibits timely discussion

➢ Some development decisions can’t wait

➢ During review, regulatory authorities willing to interact more frequently as queries are issued

➢ Prepare, Prepare, Prepare for short timelines for queries

➢ Opportunity: Direct and real time communication possible
Gaining concurrence on final market image (color, shape, size, and package for tablets) prior to formal stability batches or develop a bridging plan (i.e., color change)

Evaluation of genotoxic impurities

Impurities, impurity controls, and the establishment of Regulatory Starting Materials (RSMs)

Accelerated development & validation of analytical methods

Options:

• Defer some aspects of development work until post-approval
• Defer optimisation, this has the potential to make the post-approval regulatory strategy more complex
## Summary: CMC Challenges & Opportunities

<table>
<thead>
<tr>
<th>CHALLENGE</th>
<th>OPPORTUNITY</th>
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<tbody>
<tr>
<td>Set <strong>specifications</strong> with limited experience</td>
<td><strong>Safety</strong>-based specifications, not based on limited batch data</td>
</tr>
<tr>
<td><strong>Process</strong> not optimized at launch</td>
<td>Comparability Protocol (US) <strong>Post Approval</strong> Change Management Plan (EU)</td>
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<tr>
<td>Process <strong>validation</strong> - delay to launch, lots may never be used</td>
<td>Concurrent or Continuous Process Verification, Market Image vs unmarked</td>
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<tr>
<td>Pre-Approval Inspection (<strong>PAI</strong>) Readiness</td>
<td>PAI <strong>Waived or Post Approval</strong> PAI</td>
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<tr>
<td><strong>Global</strong> market registration demands</td>
<td>Dedicated CMC <strong>resources</strong> establish country specific strategies. Market by market.</td>
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<tr>
<td>Numerous registration <strong>configurations</strong></td>
<td>Accelerate some market registrations to enable <strong>consistent supply chain</strong></td>
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<td><strong>Health authority interactions</strong></td>
<td>Strong relationship opportunities</td>
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Case Study

- **Breakthrough Therapy Designation**
- Indication: Oncology
- Immediate Release Solid Oral Dosage form
- NDA filing accelerated by approximately 2 years
## Case Study: Breakthrough Therapy Drug

### Challenge

- Pivotal Phase 2 data generated with prototype formulation
- Drug substance form, drug product formulation and manufacturing process may not be commercializable
- Scale up of the drug product formulation. Identified a change in the dissolution profile across the production batch
- Stability data requirements for the NDA
- Post-approval formulation, process and/or specification improvements

### Remediation

- Rapidly select and optimize formulation to ensure product launch
- Perform bridging studies to link commercial form to pivotal clinical studies. Identified food effect – more BA/BE studies, label impact
- Temporary clinical batch cut-off in place while developing solution. Redesign encapsulator hopper and agitator to enhance product flow and eliminate tail effect
- Negotiate early and continue dialogue through submission process
- Leverage Comparability Protocols (2), careful inventory management
# Case Study: Communication

<table>
<thead>
<tr>
<th>CMC Related Mtgs Pre-NDA</th>
<th>CDER – NCE NDA</th>
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<tbody>
<tr>
<td>NDA Filing</td>
<td>Procedural timelines</td>
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<tr>
<td>Day 60/74 Letter</td>
<td>Rolling</td>
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<tr>
<td>Mid-Cycle Review Mtg</td>
<td>Priority Review, PDUFA date</td>
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<tr>
<td>Facility Inspections</td>
<td>Telecon</td>
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<tr>
<td>Queries</td>
<td>Waived PAI for DS and DP</td>
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<tr>
<td>Telecons/Mtgs during review</td>
<td>5 rounds</td>
</tr>
<tr>
<td>Late Cycle Review Mtg</td>
<td>3 x Telecons</td>
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<tr>
<td>Approval Timing</td>
<td>Label review</td>
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<td></td>
<td>5 ½ months</td>
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Prepare for accelerated GLOBAL filings

Expect bumps on the road ahead!
The key learning outcomes from this session are:

- Accelerated pathways options: **EU, US, Global**
- Challenges and Considerations
- **CMC expectations are not reduced**
- Ability to meet expectations facilitated by opportunities
  - Open and timely communication with reviewers
  - Accepting of additional information during review
  - Comparability protocols, post approval change management plans, post marketing commitments
- Commitment of resources
- Prepare for accelerated GLOBAL filings
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TOPRA CMC SPIN

Thank you
PRIME Designations

Applications and eligibility decisions

Type of applicant

- SME: 7
- Other: 7
- Total: 14

Therapeutic areas

- Oncology: 5
- Haematology-haemostaseology: 2
- Infectious diseases: 5
- Gastroenterology-Hepatology: 3
- Pneumology-allergology: 4
- Neurology: 3
- Vaccines: 2
- Immunology-haematology-transplantation: 2
- Ophthalmology: 3
- Cardiovascular diseases: 3
- Psychiatry: 2
- Diagnostic: 1
- Musculo-skeletal system: 1
- Endocrinology-Gynaecology-Fertility-Metabolism: 1
- Dermatology: 1

Breakthrough Designations

Period: 7 March - 21 September 2016

* Out of scope applications are not included in the detailed charts.
Current Status

One year of PRIME

108 requests received
> 90 eligibility requests assessed
> 50% from SMEs
20 granted*

22% success rate

*+
Publication of report and list of products on EMA website