Accelerated Development as the “New Normal”: Process Validation Considerations

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Agenda

• Accelerated Paradigm
• Regulatory Tool Challenges
• Acceleration: Validation Opportunities
• ADCX Case Study
  • ICH Q11: Enhanced vs. Traditional Validation
  • Validation Approach for ADCX
  • Risk/Benefit of Validation Approach
• Discussion Points and Opportunities
**Accelerated Paradigm**

- Acceleration is the "**new normal**", even when an accelerated pathway isn’t granted
- Divergent pathways: What to do when BTD granted, but not PRIME or SAKIGAKE?
- Not often practical to delay filings globally until data package “catches up”
- Risk/benefit profile may not support taking advantage of some regulatory tools
  - bar is often **very high**
  - often don’t have enough information for robust discussion with Health Authorities when decisions are needed
Challenges with Current Regulatory Tools

- **Concurrent Validation**: Is there too high a bar?
  - “in exceptional circumstances” (EMA, Annex 15, Qualification and Validation)
  - “to alleviate short supply” (FDA, Guidance, Process Validation)

- **Provide validation data during review**
  - May not have sufficient details for meaningful discussion with HA at the time a decision is needed
  - Some HAs may only accept a complete package at time of submission
  - May extend review period dependent on amount of data, thereby eliminating benefit of accelerated approach

- **Deferral of Validation Data**
  - Although Acceleration Pathway can give flexibility for when data is submitted (i.e. post-approval), this leads to a complex global post-approval setting

- **Post Approval Change Management Protocol (PACMP)**
  - Team focus is on generating a cohesive technical package for Marketing Application (lean resources); no time for a meaningful CP and/or may not have enough information to define CP AC
Acceleration: Validation Opportunities

- Simplify, while maintaining scientific rigor
- **Establish** robust quality development early on that will meet HA requirements *with or without* Accelerated pathway; avoids complex global post-approval landscape
- **Tailor validation package** to the program: Challenge which studies are critical; Risk based thinking and use of prior knowledge and scientific rationale
- **Communicate** with Health Authorities on:
  - Deferral activities; agreement on which are regulatory relevant
  - Which regulatory tools are acceptable for the program
  - Align on what is sufficient information in initial Marketing Application to potentially minimize post-approval complexity

A combination of approaches, unique to the program, will need to be defined and agreed upon with HA
ADCX Case Study

- Very promising clinical outcome observed for ADCX in the **Phase 1b/II Study**
  - Clinical results from this study were basis for PRIME & BTD
  - Orphan Drug Designation granted by EMA/FDA

- By the time of PRIME designation, pivotal material (process version 0.1) no longer being manufactured; significant manufacturing changes made to enable a process suitable for commercial use (process version 1.0)
  - Given compelling risk/benefit, the Phase 1b/II Study became pivotal

- To enable **global** fast-to-market scenario, accelerated validation strategy implemented
How fast can we be ready to launch a complex product like ADCX? *Compressed filing readiness from 3 years to 1.25 years*

**Diagram:**
- **Antibody Intermediate Site 1**
- **Linker-Drug Intermediate Site 2**
- **Drug substance Site 3**
- **Lyophilized Product Site 4**
- **Package + Label Site 5**
- **Distribution Center Site 6**

**Timeline:**
- **T0-5Q**
  - Q1
  - Q2
- **T0-4Q**
  - Q3
  - Q4
- **T0**
  - Q1
  - Q2
  - Q3
  - Q4
- **T0+3Q →**
  - Q1
  - Q2
  - Q3
  - Q4

**Key Activities:**
- **Promising Clinical Data**
- **PRIME**
- **BTD**
- **Mod 3 filing**
- **Marketing Application Authoring/Publishing**
- **Process validation studies feed into authoring**
- **HA Inspections**
- **FDA/EMA Approvals**

**2019 → 60+ Global MA Submissions**
### ICH Q11: Enhanced vs. Traditional Validation

<table>
<thead>
<tr>
<th>Enhanced Validation</th>
<th>Combination</th>
<th>“Target” Validation</th>
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<tbody>
<tr>
<td>High volume product</td>
<td>Medium volume product</td>
<td>Low volume product</td>
</tr>
<tr>
<td>More Time!</td>
<td>Accelerated</td>
<td>Extreme acceleration / Very high risk benefit profile</td>
</tr>
<tr>
<td>PV studies for all pCPPs → complete understanding of parameter impacts (no target validation)</td>
<td>PV studies for certain pCPPs → study parameters that are expected to have the highest impact or that are expected to require future flexibility</td>
<td>Target validation for the entire process → narrow acceptable ranges; all pCPPs become CPPs</td>
</tr>
<tr>
<td>Manufacturing flexibility fully enabled; Enables Design Space</td>
<td>Limited manufacturing flexibility to change targets, adjust the process</td>
<td>No flexibility to change targets, adjust the process within acceptable ranges</td>
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<tr>
<td>Process knowledge is generated that enables removing CQAs from the control system</td>
<td>Control system likely includes every CQA due to lack of process knowledge</td>
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**pCPP = potential CPPs; PV = Process Validation**
## Overall Validation Approach for ADCX

<table>
<thead>
<tr>
<th>Pre-Approval Activities</th>
<th>Post-Approval Activities</th>
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<tbody>
<tr>
<td>Development of <strong>product understanding</strong></td>
<td>Drug Substance process scale-up to ensure future supply/resilience for other potential indications</td>
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<tr>
<td>Validation of <strong>clinical</strong> manufacturing process at-target, at-scale</td>
<td>Additional studies to further increase process knowledge</td>
</tr>
<tr>
<td>Process Validation: Process Performance Qualification and <strong>safety related studies</strong> (e.g. virus clearance, impurity clearance, bioburden control, etc)</td>
<td>With increased process knowledge:</td>
</tr>
<tr>
<td><strong>Non-linear PPQ</strong>: Drug Substance and Drug Product campaigns using existing clinical Antibody Intermediate</td>
<td>- Potentially widen restrictive acceptable ranges and update CPPs → Post-approval submission, <strong>where needed</strong></td>
</tr>
<tr>
<td>Leverage <strong>Prior Knowledge</strong> and scientific rationale to define process parameter Acceptable Ranges</td>
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# Specific Examples

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial Marketing Application</th>
<th>Post-Approval Studies</th>
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</thead>
<tbody>
<tr>
<td>Reduction Reaction Time</td>
<td>• ±3-4% range around target Established based on manufacturing history</td>
<td>Study intended to support ±17-56% range around target; <strong>post-approval submission</strong></td>
</tr>
<tr>
<td>Chromatography step elution buffer</td>
<td>• Component amounts and pH very narrow • Established based on manufacturing history and equipment/weight tolerance</td>
<td>AR will not be widened; if exceed ARs, just discard buffer;</td>
</tr>
<tr>
<td>Chromatography process parameters</td>
<td>• ADCX has ~3 times as many CPPs as for other mAbs • CPPs identified using a risk- and science-based approach</td>
<td>Study intended to support widening Ars and potentially downgrade CPPs; <strong>post-approval submission</strong></td>
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## Risk/Benefit of Target Validation Approach

<table>
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<tr>
<th>Risks</th>
<th>Benefits</th>
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<tr>
<td>• Constrained manufacturing process</td>
<td>• <strong>Faster-to-Patient</strong>: Deferred Process Design Studies shortens time to submission</td>
</tr>
<tr>
<td>• Increased number of CPPs &amp; Narrow process ranges</td>
<td>• Complete validation at the time of the Initial Marketing Application, with focus on required process validation studies (i.e. safety related)</td>
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<td>• Limited process knowledge so can’t “validate out” some attribute testing (i.e. specific impurities test)</td>
<td>• Demonstration that Applicant can reproducibly make the product in the facility with a process that ensures consistent product quality, safety, and efficacy</td>
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<tr>
<td>• Narrow operating ranges and limits could lead to potential higher rate of deviations</td>
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<tr>
<td>• Higher risk of site transfer challenges</td>
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**Compromise**: Register a fully validated, but constrained manufacturing process, with intent to introduce additional process understanding post-approval to de-constrain the manufacturing process, *where needed*
**Discussion Points and Opportunities**

- Non-CPPs supported by Prior Knowledge
- In the case of limited number of batches: Use of pilot scale or other engineering runs to supplement data
- PACMPs
  - Where PACMP acceptance criteria not yet defined, describe the approach for setting AC and elements that will be assessed
  - Shortened review period for PACMPs
- Scenarios where concurrent validation is acceptable?
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