Efficient Analytical Development Strategies to support Accelerated CMC Development

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The need for acceleration of CMC development

- Better understanding of disease pathways have increased the number of potential targets
- Improved ability to generate specific mAbs against new targets has resulted in more compounds
- Translational science based on disease models is not fully predictive of efficacy in humans
- Increase the success rate by allowing more compounds to enter the clinic in a cost-effective way
- Streamline CMC activities to minimize the time from compound elevation to clinic
Outline

- Approaches for streamlining CMC development
  - CMC development and timelines
- Streamlined approach to analytical method development and qualification
  - Begin with the end in mind (Analytical Target Profile)
  - Prioritization of development activities (Risk assessments)
  - Method alignment
- Data integrity and Documentation
Organizing the CMC development process

- CMC Development is complex and involves stakeholders from various disciplines
- Transparent communication between stakeholders is critical for efficiency
- Use of standardized development paradigm
  - QTPP provides a definition of the requirements for the final product and guides the development activities
  - Prospectively agree on approaches for establishing testing paradigm, stability program, reference standard program etc. and consistently apply that across programs
  - Simplify document generation by using platform protocols or templates
To allow us to accelerate we need to understand what slows us down

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Technical challenges</td>
<td>• Use platform approaches for common modalities</td>
</tr>
<tr>
<td>• Methods not available or not sufficiently sensitive or precise</td>
<td>• Maintain transparency through robust knowledge management</td>
</tr>
<tr>
<td>• Duplication of work due to lack of information or knowledge</td>
<td>• Maintain visibility regarding activities and responsibilities between different groups</td>
</tr>
<tr>
<td>• information exists but is not readily available</td>
<td>• Establish common formats to capture decisions (QTPP, Testing paradigm, Analytical Target Profile)</td>
</tr>
<tr>
<td>• Rework due to miscommunication,</td>
<td>• Harmonize methods and maintain alignment across all groups involved in analytical testing</td>
</tr>
<tr>
<td>• Decisions are changed or not properly captured or understood</td>
<td>• Defined and efficient documentation and review processes</td>
</tr>
<tr>
<td>• Different interpretation of terms</td>
<td>• Establish well-defined review and approval matrix</td>
</tr>
<tr>
<td>• Analytical alignment across groups</td>
<td></td>
</tr>
<tr>
<td>• Documentation</td>
<td></td>
</tr>
<tr>
<td>• Transcription of information</td>
<td></td>
</tr>
<tr>
<td>• Redundancy in documents</td>
<td></td>
</tr>
<tr>
<td>• Multiple review cycles</td>
<td></td>
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</tbody>
</table>

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Analytical Deliverables Must Align with Project Timeline

**Early Dev**
- Platform method POC
- Initiate analytical support for process and product development
- Research reference standard, product specific reagents

**Preclin Tox**
- Product-specific method development and qualification for GLP tox supply
- Release GLP tox supply
- Emphasis on safety

**Phase 1**
- Testing paradigm focused on safety. Release P1 supplies, file IND/IMPD
- Initiate development of product-specific cell-based potency assay
- Reference standard program. Characterize P1 supplies

**Phase 2**
- Implement product specific potency assay
- Update and refine analytical test methods (risk assessments)
- CQA refinement, Control strategy established, Method transfer to P3 site

**Phase 3**
- Finalize control strategy
- Method validation before PPQ or registration stability batches
- Perform structure function studies and forced degradation studies

**Approval**
- Submit BLA/MAA
- Product launch

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12-18 months

3-4 years

4-5 years
During early development ensure alignment between high throughput in-process methods and QC methods is established/maintained.

- Analytical data is generated in many different parts of the organization and used to make development decisions.
- It is important to understand the connectivity of results obtained during initial screening experiments, process/product development activities and release testing.
- Harmonize methods where possible, maintain flexibility during development but understand impact of changes.
  - Comparative testing
  - Common controls or standards
- Document information so it can be shared across all interfaces.
- Methods need to be suitable for their intended use independent if it involves GMP or non-GMP testing.

All methods used throughout development must be suitable and fit for use.
Lifecycle approach to analytical method development and qualification/validation

Elevation
- CQA V1
  - Method qualification/confirmation
  - Control Strategy (Platform)

P1
- CQA V2
  - Establish/Update ATP
  - Method establishment/update (platform/custom)

P2
- CQA V3
  - Finalize Control Strategy
  - Update ATP
  - Method optimization, Robustness, Method control strategy
  - Method validation

P3
- Approval
  - Continued Performance Verification

CQA: Critical Quality Attribute
ATP: Analytical Target Profile
Method development with the end in mind: Analytical strategy and requirements captured in the analytical target profile (ATP)

<table>
<thead>
<tr>
<th>Product attribute (CQA)</th>
<th>Platform Method</th>
<th>Target Accuracy (%)</th>
<th>Intermediate Precision (%)</th>
<th>Range</th>
<th>QL/DL</th>
<th>Proposed criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein Content</td>
<td>A280</td>
<td>95 – 105</td>
<td>≤ 5</td>
<td>70% -130% of Target conc.</td>
<td>N/A</td>
<td>+/- 10% of Target</td>
</tr>
<tr>
<td>Aggregation</td>
<td>SE-HPLC</td>
<td>80 – 120</td>
<td>≤ 20</td>
<td>LOQ to 6%</td>
<td>≤ 0.5 %</td>
<td></td>
</tr>
<tr>
<td>Charge Variants</td>
<td>cIEF</td>
<td>70 – 130</td>
<td>≤ 20</td>
<td>70 – 130 % of Target conc.</td>
<td>≤ 5 %</td>
<td></td>
</tr>
<tr>
<td>Glycosylation</td>
<td>HPLC-FLD</td>
<td>70 – 130</td>
<td>≤ 20</td>
<td>N/A</td>
<td>≤ 1 %</td>
<td></td>
</tr>
<tr>
<td>Identity</td>
<td>Peptide Map</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>CQA 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CQA x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATP can also capture business needs, operational needs, and technique preferences or constraints
1. Design platform and product specific methods that can be used end to end (i.e. Pre-candidate selection to commercial)

2. Make robustness central to platform and early development (Risk assessments, Job Aids)

3. Use risk-based approaches to assess work required to perform method development and method qualification/validation
### Challenges
- Development experience and approaches vary significantly between people involved in method development.
- Job aids work well with platform methods but may not be as effective for new development.
- Development reports often capture what was evaluated but typically do not capture why certain factors were not evaluated.
- Input from other SMEs occurs when problems are encountered (reactive).

### Solutions
- Establish a systematic approach to evaluate methods with input from multiple SMEs (proactive).
- Establish a consistent and transparent way to capture the decision making process regarding which factors to evaluate and why (method assessment).
- Include method assessments in the development reports.
An analytical method consists of multiple distinct unit operations

**Input**
- Buffer salts / solvents
- Reduction/derivatization reagents
- Critical reagents (antibodies/ cell lines)
- Retrieve/thaw sample
- Reduce/ Derivatize/ Digest
- Sample cleanup/ filtration
- Reference standards
- Assay controls
- Autosampler temperature
- Equipment type, Column age
- Flow rate, focusing time, separation conditions
- Integration
- Suitability controls
- Standard and sample comparison

**Unit Operation**
- Reagent preparation
- Sample preparation
- Standards and controls
- Instrument Set Up
- Sample analysis
- Data Analysis

**Output**
- Mobile phase
- Critical phase solutions
- Sample preparation solutions
- Sample ready for analysis
- Standards and controls ready for analysis
- Robust conditions for sample analysis
- Analysis results obtained for samples, standards, and controls
- Accurate and precise result
Risk assessment template evaluates the steps within each unit operation

- Complete proof of concept experiments
- Establish outline of proposed procedure
- Transfer each activity performed in the method (method step) and the associated “unit operation” to the risk assessment
- Identify potential failure modes (one step can have multiple failure modes)
- Identify the analytical quality attribute impacted by the failure mode

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**List Method Steps Sequentially**

<table>
<thead>
<tr>
<th>Method Unit Operation (Parent)</th>
<th>Method step (Child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample preparation</td>
<td>Predilution of samples and control to 3 mg/mL in HPLC water</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Samples and control further diluted to 0.3 mg/mL in final prep</td>
</tr>
<tr>
<td>Standards and controls</td>
<td></td>
</tr>
<tr>
<td>Instrument set up</td>
<td></td>
</tr>
</tbody>
</table>

**List Potential Failure Modes and Analytical Quality Attributes**

<table>
<thead>
<tr>
<th>Potential failure mode</th>
<th>Analytical Quality Attribute</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample concentration after predilution incorrect</td>
<td>Ab concentration</td>
</tr>
<tr>
<td>sample concentration incorrect in final prep</td>
<td>Ab concentration</td>
</tr>
</tbody>
</table>
Definition of potential failure mode and analytical quality attribute

- Potential failure mode describes differences from the intended state when this step is performed
  - Temperature set points, incubation times volumes transferred, impact of different lot, buffer concentration differences
- Analytical quality attribute is the parameter or action associated with the failure mode
  - Temperature, incubation time, reagent lot (input in robustness studies)
  - Pipetting, mixing (method control and training)

<table>
<thead>
<tr>
<th>Potential failure mode</th>
<th>Analytical Quality Attribute</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample concentration incorrect</td>
<td>Ab concentration</td>
</tr>
<tr>
<td>sample concentration incorrect in final prep</td>
<td>Ab concentration</td>
</tr>
<tr>
<td>incorrect concentration of ampholyte</td>
<td>Ampholyte concentration</td>
</tr>
<tr>
<td>Different ampholyte lots</td>
<td>Ampholyte lot</td>
</tr>
<tr>
<td>incorrect pl marker</td>
<td>Calibration standard</td>
</tr>
<tr>
<td>wrong peak assigned as pl marker</td>
<td>Calibration standard</td>
</tr>
</tbody>
</table>

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Risk assessment scoring and ranking

<table>
<thead>
<tr>
<th>Impact of changes in the attribute on accuracy or LOQ (H=5, M=3, L=1)</th>
<th>Impact of changes in the attribute on intermediate precision (H=5, M=3, L=1)</th>
<th>Probability H, L</th>
<th>RPN</th>
<th>Tier</th>
<th>Current experience (setpoints/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
<td>linear range established, example of calculation included in SOP</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
<td>volumes to use shown in SOP</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>H</td>
<td>125</td>
<td>Tier 1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
<td></td>
</tr>
</tbody>
</table>

- Does the failure mode have an impact on accuracy (i.e. bias) or LOQ
  - Carry-over in HPLC methods
  - Incorrect baseline correction in a UV measurement

- Does the failure mode have an impact on variability
  - Non-robust incubation conditions (time, temperature)
  - Sample stability
## Example of a risk assessment for an analytical method

<table>
<thead>
<tr>
<th>Method Unit Operation (Parent)</th>
<th>Method step (Child)</th>
<th>Potential failure mode</th>
<th>Attribute</th>
<th>Impact of changes in the attribute on accuracy or LOQ (H=5, M=3, L=1)</th>
<th>Impact of changes in the attribute on intermediate precision (H=5, M=3, L=1)</th>
<th>Probability H, L</th>
<th>RPN</th>
<th>Tier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent preparation</td>
<td>Add 1% MC to mastermix</td>
<td>incorrect concentration of methyl cellulose</td>
<td>MC concentration</td>
<td>5</td>
<td>5</td>
<td>L</td>
<td>63</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Reagent preparation</td>
<td>Add 1% MC to mastermix</td>
<td>MC lot to lot variability</td>
<td>lot to lot variability</td>
<td>5</td>
<td>5</td>
<td>L</td>
<td>63</td>
<td>Tier 2</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>add 180 uL mastermix to tube</td>
<td>wrong volume added</td>
<td>pipetting</td>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>add 20 uL sample, control or water (blank) to tube</td>
<td>wrong volume added</td>
<td>pipetting</td>
<td>1</td>
<td>1</td>
<td>L</td>
<td>1</td>
<td>Tier 3</td>
</tr>
<tr>
<td>Instrument setup</td>
<td>Add anolyte, catholyte to tanks</td>
<td>Insufficient amount of anolyte and catolyte present</td>
<td>NA/Setup</td>
<td>3</td>
<td>3</td>
<td>L</td>
<td>14</td>
<td>Tier 3</td>
</tr>
<tr>
<td>Reagent preparation</td>
<td>Add Pharmolyte to mastermix</td>
<td>Different ampholyte lots</td>
<td>Ampholyte lot</td>
<td>5</td>
<td>5</td>
<td>H</td>
<td>125</td>
<td>Tier 1</td>
</tr>
</tbody>
</table>
Risk assessment presented as a fishbone diagram

Tier levels listed for illustration only
Benefits of using a risk assessment approach during method development

- Creates a forum where SMEs can provide input and share expertise and where junior personnel can learn about the criticality of key method steps
- A risk assessment ensures a systematic evaluation of all factors influencing the method is performed
- Helps elucidate whether factors are expected to interact and should be included in an experimental design or if factors can be studied “one at a time”
- Transparently captures thought process and prioritization decisions
- Connects available information (literature, prior reports) to optimization and development activities (traceability matrix)
- Ensure development activities are focused on areas of greatest concern

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Data integrity and Documentation

Traceability of samples and information is essential for knowledge management, compliance and dossier compilation.
Conclusions

Accelerated CMC development requires

- Teamwork and transparent communication
- Well established and transparently communicated development paradigms
- Close alignment of testing activities across different functions or groups (characterization, process/product development support, release)
- A systematic approach to method development
- Robust systems and processes for documentation and knowledge management
Acknowledgements

- Members of Sanofi Biologics Development
- Claire Davies
- Rebecca Sendak
- Organizing committee
Questions?