Use of Microfluidic Capillary Gel Electrophoresis for Release and Stability Testing of Monoclonal Antibodies

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Presentation agenda

• Development of CGE Platform Method
• Current status and lessons learned
• Case study: use of CGE method in a GMP contract lab
• BAS is a non-GMP department responsible for all biopharmaceutical analytical method development (post-CS)

• Primary responsibilities
  – New method development
  – Analytical support for process and formulation development
  – Assist in method transfers and troubleshooting

• Analytical methods are transferred for multiple CMC purposes
Identification and Implementation of CGE Technology to Replace SDS-PAGE Analysis

- CGE technology was implemented beginning in 2010 due to the limitations of SDS-PAGE analysis
- The PerkinElmer LabChip GXII System offers substantial improvements over SDS-PAGE
  - Accuracy, precision, and linear range
  - Robustness
  - Automation
  - Assay throughput
  - Instrument ruggedness
- Implementation strategy
  - Replace SDS-PAGE methods for late-phase projects
  - Develop and qualify new methods for early-phase projects
  - Develop and implement CGE platform method
Function of Platform Methods within the Analytical Method Lifecycle

• Platform Methods facilitate the efficient development, qualification, and transfer of early-phase (post-CS – pre-PhIII) analytical methods for a class of biopharmaceutical (mAbs)

• Platform Method features
  – Statistically mapped analytical design space using ≥ 2 examples
  – Validated using ≥ 2 examples
  – Efficient implementation for new products through lean Sample Verification experiment

• Terminology
  – Master Platform Method
  – Sample Verification Procedure
  – Derivative Method
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<table>
<thead>
<tr>
<th>DOE Factor</th>
<th>Significant?</th>
<th>Center point</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating time</td>
<td>Yes</td>
<td>12 minutes</td>
<td>± 2 min</td>
</tr>
<tr>
<td>Heating temp</td>
<td>Yes</td>
<td>70ºC</td>
<td>± 2ºC</td>
</tr>
<tr>
<td>Sample buffer volume</td>
<td>Yes</td>
<td>11 µL</td>
<td>± 20%</td>
</tr>
<tr>
<td>Protein conc.</td>
<td>Yes</td>
<td>1.0 mg/mL</td>
<td>± 10%</td>
</tr>
<tr>
<td>Reducing agent conc.</td>
<td>Yes</td>
<td>33 mM</td>
<td>± 25%</td>
</tr>
<tr>
<td>Dye volume</td>
<td>Yes</td>
<td>19 µL</td>
<td>± 10%</td>
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Design Space Mapping

- Identification of relevant experimental conditions for optimization
- Design statistical experimentation (DOE) to identify acceptable ranges
- Perform DOE experiments on two examples

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CGE Platform Method Development

Output: a robust Design Space and Platform Method that has efficiently produced Derivative Methods for > 10 products
Sample Verification and Development of Derivative Methods

Sample Verification
- Method conditions may be optimized within the Platform Method Design Space as needed
- Sample Verification is documented in lab notebook

Derivative Method
- Populate template method instructions with specific assay conditions
- Method instructions and criteria aligned for all derivative methods

Product-specific method validation occurs as a product progresses to late-phase development
• Robust design space, with options for improvement as needed
• Transferred to multiple GMP labs for validation and release and stability testing
• Primary challenge in GMP labs – high invalid rate
• Training and knowledge transfer are processes, not events
• OE GEMBA (go and see) approach to method troubleshooting
  – Observe the analyst
  – Identify gaps
  – Address gaps through procedures and training
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10

Case Study: GEMBA Approach to Method Troubleshooting at CRO

Mean pass rate: 58%
Case Study: GEMBA Approach to Method Troubleshooting at CRO

GEMBA input: establish potential gaps that could cause failures, document “expected” process flow

Input Fishbone Diagram

Input Process Map

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Output: updated Fishbones and Process Maps to identify/prioritize gaps, align process flow between labs

Primary gaps/root causes:
- Software settings
- Standard work not embedded within the procedure
- Reagent storage and handling

Output Fishbone Diagram

Output Process Map
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Stability Testing of Monoclonal Antibodies

Case Study: GEMBA Approach to Method Troubleshooting at CRO

History of Method Improvements and Impact to Method Performance

CGE Assay Performance

System repair
GEMBA workshop
Reagent investigation
Reagent issue resolved, GEMBA changes implemented
Analyst boo-boo

% Pass rate
0 20 40 60 80 100 120 140 160 180 200
No. of test samples

Mar-12 April-12 May-12 Jun-12 Jul-12 Aug-12 Sep-12 Oct-12 Nov-12 Dec-12 Jan-13 Feb-13 Mar-13 Apr-13 May-13 Jun-13 Jul-13 Aug-13

% Pass Rate

Mean %Pass rate

GEMBA Assay Performance

No. of test samples
% Pass Rate
Mean %Pass rate

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Stability Testing of Monoclonal Antibodies
Conclusions

- CGE Platform Method facilitates the efficient development and transfer of analytical methods for the analysis of monoclonal antibodies
- CGE Methods have been transferred and validated for GMP release and stability testing
- Progress has been made in reducing invalid rate in GMP environment
- CGE improves GSK’s analytical testing capabilities, and these benefits will be passed on to patients in the form of better medicines
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