Process Validation of Macugen API:
An Exercise in Submission Preparation and Inspection Readiness

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Today’s Discussion

Process Validation of Macugen API: An Exercise in Submission Preparation and Inspection Readiness

This case study will examine the stages of Process Validation (Pre-Qualification, Manufacturing Qualification, and Life Cycle Qualification), and examine the relationship of each of these to the Submission Preparation and Pre-Approval Inspection Readiness.
Overview

- Process Validation
- Submission
- Inspection Readiness
Process Validation of Macugen API
Defining the Process to Validate

Phase 1
Define the Manufacturing Process

- Process Development
- Facility and Equipment Qualification
- Raw Materials Qualification
- Analytical Method Qualification/Validation

Final Manufacturing Instructions

Phase 2
Validate the Process

Process Validation (3 Stages)
List, References, and Reports

Phase 1
Define the Manufacturing Process

- Historical Development Reports
- Data Tables for In-process and Release Testing
- Support Validations
- Starting Materials
- Equipment
- Utilities
- Facility Layout and Flow
- In-process and Release Analytical methods
Phase 2

Process Validation

Pre-Qualification

- Identify Quality Characteristics
- Identify Parameters
- Perform Lab Experimentation to Evaluate Operating and Acceptable Ranges
- Determine Final Ranges and Critical Process Parameters
- Write Lab Pre-Qualification Report

Manufacturing Qualification

- Write Manufacturing Performance Qualification Protocol
- Execute Manufacturing Qualification
- Write Validation Report

Life Cycle Qualification

- Create Life Cycle Technology Validation Table
- Maintain Process Technology
- Update Information on Tables After Each Campaign
- Review and Evaluate Validation Package
- Documentation Validation Review
Stage 1 – Process Validation

- Identify Quality Characteristics
- Identify Parameters
  - Identify Process Parameters
  - Identify In-Process Controls
  - Identify Operating Ranges and Acceptable Ranges
  - Identify Potential Critical Process Parameters
- Perform Lab Experimentation to Evaluate Operating and Acceptable Ranges
- Determine Final Ranges and Critical Process Parameters
- Write Lab Pre-Qualification Report
  - Quality Characteristic and Process Parameter Tables
  - Discussion of Each Critical Process Parameter
  - Lab References
Critical Parameter Identification

Critical Process Parameters:

Identification of process parameters as critical is based on review of the current data for acceptable and operating ranges for these parameters. For the identified critical process parameters, the operating range is currently too close to the known acceptable range. Additional data can be generated to assess if a wider acceptable range can be justified, so that eventually these parameters may not be identified as critical.

Operating and Acceptable Ranges:

- Operating Range
- Acceptable Range
- Lower Failure Limit
- Upper Failure Limit
### Macugen API Pre-Qualification Report

**(Simulated Data)**

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Operating Range</th>
<th>Acceptable Range</th>
<th>Reference</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column packed volume</td>
<td>15 L ± 1 L</td>
<td>13 L – 17 L</td>
<td>Bed height study</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Load Equilibration at ambient temperature</td>
<td>4 - 6 hours</td>
<td>2 - 10 hours</td>
<td>Chromatography resin performance study</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Mobile Phase Column Inlet Temperature</td>
<td>45°C - 55°C</td>
<td>45°C - 55°C</td>
<td>Chromatography resin performance study</td>
<td>Critical</td>
</tr>
<tr>
<td>Eluent A Flush</td>
<td>71 L – 75 L</td>
<td>70 L – 100 L</td>
<td>Chromatography resin performance study</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Load Rinse #1</td>
<td>0.5 L – 1.5 L</td>
<td>0-20 L</td>
<td>Chromatography resin performance study</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Load Rinse #2</td>
<td>0.5 L – 1.5 L</td>
<td>0-20L</td>
<td>Chromatography resin performance study</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Fraction volume</td>
<td>5 L ± 100 mL</td>
<td>5 L ± 1 L</td>
<td>Production pooling strategy</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Fraction Cooling</td>
<td>≤ 30°C</td>
<td>≤ 45°C</td>
<td>Development Report</td>
<td>Not Critical</td>
</tr>
<tr>
<td>Solution Hold Temperature</td>
<td>2°C – 8°C</td>
<td>&lt; 8 hours at RT</td>
<td>Hold Time Study</td>
<td>Not Critical</td>
</tr>
</tbody>
</table>

### Justification

<table>
<thead>
<tr>
<th>In-Process Controls</th>
<th>Specification</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical Plates per meter</td>
<td>≥ 20,500</td>
<td>Chromatography resin performance study</td>
</tr>
<tr>
<td>Column Clean Hold</td>
<td>≤ 24 hours</td>
<td>Resin re-use – sanitization study</td>
</tr>
<tr>
<td>Endotoxin (Post-sanitization)</td>
<td>≤ 0.25 EU/mL</td>
<td>Resin re-use – sanitization study</td>
</tr>
<tr>
<td>Eluent A Flush pH</td>
<td>7.0 – 7.8</td>
<td>Chromatography resin performance study</td>
</tr>
<tr>
<td>Total Load Amount (OD&lt;sub&gt;260&lt;/sub&gt;)</td>
<td>≤ 5,000,000</td>
<td>Chromatography resin performance study</td>
</tr>
<tr>
<td>Chromatography Method</td>
<td>MACAX1</td>
<td>Custom program to run the first AEX Chromatography step</td>
</tr>
<tr>
<td>UV (Fractions)</td>
<td>≥ 10 OD/mL</td>
<td>Production pooling strategy</td>
</tr>
<tr>
<td>AEX-HLPC (Fractions)</td>
<td>≥ 65 % Full Length</td>
<td>Chromatography resin performance study</td>
</tr>
</tbody>
</table>

### In-Process Specification

<table>
<thead>
<tr>
<th>In-Process Specification</th>
<th>Acceptance Criteria</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEX-HPLC (Pool)</td>
<td>≥ 75 % Full Length</td>
<td>Chromatography resin performance study</td>
</tr>
<tr>
<td>OD&lt;sub&gt;260&lt;/sub&gt;</td>
<td>Report Value</td>
<td>Calculation of Yield</td>
</tr>
</tbody>
</table>
Stage 2 – Process Validation

- Write Manufacturing Performance Qualification Protocol
  - All Critical Process Parameters (CPPs)
  - All In-Process Controls
  - All In-Process Specifications
  - Release Specifications
  - Additional Consistency Testing (non-routine)

- Execute Manufacturing Qualification

- Write Validation Report
  - Complete Protocol Tables
  - Confirm No Unexplained Deviations and No Deviations of CPPs
  - Confirm Data Tables Meet Target Criteria
  - Complete Validation Report
Manufacturing Qualification Protocol

<table>
<thead>
<tr>
<th>Critical Process Parameter</th>
<th>Operating Range</th>
<th>Batch #1</th>
<th>Batch #2</th>
<th>Batch #3</th>
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<td>45°C - 55°C</td>
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<td>Specification</td>
<td>Batch #1</td>
<td>Batch #2</td>
<td>Batch #3</td>
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<tr>
<td>HETP</td>
<td>≥ 20,500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Column Clean Hold</td>
<td>≤ 24 hours</td>
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<td>7.0 – 7.8</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total Load Amount (OD$_{260}$)</td>
<td>≤ 5,000,000</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chromatography Method</td>
<td>MACAX1</td>
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<tr>
<td>OD$_{260}$</td>
<td>Report Value for Stage Yield</td>
<td></td>
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Stage 3 – Process Validation

- Create Life Cycle Technology Validation Table
  - Critical Quality Characteristics
  - Critical Process Parameters
  - Critical In-Process Controls
- Maintain Process Technology
  - Track Analytical Trends of Quality Characteristics
  - Track Performance of Critical Process Parameters
- Update Information on Tables After Each Campaign
- Review and Evaluate Validation Package
  - Compare to Commercial Validation
  - Compare to Lab Pre-Qualification
  - Evaluate Trending and Performance
- Documentation Validation Review
Phase 2
Validate the Process

- Process Description and Scale
- Critical Process Parameters
  - Critical Process Steps
  - In-Process Controls
  - In-Process Specifications
- Release Specifications
- Stability Methods and Specifications
Macugen API Validation Team Membership

- Process Validation (Technology and Manufacturing)
- Submission (Regulatory)
- Inspection Readiness (Quality Assurance)
IV. MANUFACTURE (S.2)

A. Manufacturers (S.2.1)

B. Description of Manufacturing Process and Process Controls (S.2.2)
   1. Flow Diagram
   2. Description of the Manufacturing Process and Process Controls
   3. Reprocessing, Reworking, Recycling, Regeneration, and Other Operations

C. Control of Materials (S.2.3)
   1. Starting Materials
   2. Reagents, Solvents, and Auxiliary Materials
   3. Diluents

D. Controls of Critical Steps and Intermediates (S.2.4)

E. Process Validation and/or Evaluation (S.2.5)

F. Manufacturing Process Development (S.2.6)
Macugen MAA Submission Preparation

MAA: Common Technical Document (CTD)
Module 3: Quality

3.2.S.2 Manufacture
  3.2.S.2.1 Manufacturer(s)
  3.2.S.2.2 Description of Manufacturing Process and Process Controls
  3.2.S.2.3 Control of Materials
  3.2.S.2.4 Controls of Critical Steps and Intermediates
  3.2.S.2.5 Process Validation and/or Evaluation
  3.2.S.2.6 Manufacturing Process Development

3.2.S.3 Characterization

3.2.S.4 Control of Drug Substance
Macugen Pre-Approval Inspection Readiness

Components of Readiness:

• Establish PAI readiness date
• Develop Site Approval Master Plan
• Evaluate and Rank Risks
• Mitigate Risks
• Allocate resources based on risk
• Manage time
Site Master Plan Categories

1. Product Description
2. Process
3. Analytical
4. Facility
5. Quality and Compliance
6. Supply Chain
7. Stability
Macugen API Site Approval Master Plan

1. Product Description
2. Process
   - Manufacturing Instructions
   - Historical Batch Performance
   - Process Development
   - Support Validations
   - Process Equipment
3. Analytical
   - Lab Practices
   - Analytical Equipment
   - Lab Investigations and Method Issues
   - Method Validation and Qualification: Site specific and Outsourced methods
4. Facility
   - Systems and Utilities
   - PM/Calibration
   - Change Over / Cleaning
   - Support Equipment (i.e., Freezers, stopper and glass washers etc)
   - Environmental Monitoring
5. Quality and Compliance
   - Quality Agreements
   - Investigations/Deviations Review/Remediation
   - CAPA closeouts
   - Training
   - Raw Material and Component Management
   - Storage and Warehousing
6. Supply Chain
   - Shipping Procedures
   - Shipping Validation
7. Stability
Coordinating Roles and Responsibilities

- Process Validation (Technology and Manufacturing)
- Inspection Readiness (Quality Assurance)
- Submission (Regulatory)

Lists and References

Data and Reports

Confidential
Summary

To maximize the benefit of the Process Validation exercise, the following is recommended based on this case study:

• Thoroughly map and define the Manufacturing Process prior to the start of Process Validation.

• Create a Validation Team which includes members from Technology, Manufacturing, Quality Assurance, and Regulatory.

• Perform multi-disciplinary reviews of protocols and reports that are generated to complete the three stages of Process Validation (Process Pre-Qualification, Manufacturing Qualification, Life Cycle Qualification).

• Modify and enhance validation documentation as needed to coordinate with the needs of Submission Preparation and Inspection Readiness.
BioTechLogic, Inc. is a team of manufacturing management professionals that serves the Biopharmaceutical industry by collaborating with companies which need to meet aggressive project timelines. Through our experience in production, validation, and third party management, we are able to define the path, focus the resources, and drive the process to meet every milestone.

www.biotechlogic.com

Eyetech Pharmaceuticals, Inc. is a biopharmaceutical company that specializes in the development and commercialization of novel therapeutics to treat diseases of the eye. Our initial focus is on diseases affecting the back of the eye, particularly the retina, because we believe that these diseases have the greatest unmet medical need and represent the largest potential market opportunities in ophthalmology.

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