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DOCUMENT APPROVALS

This Risk and Impact Assessment and its attachments have been reviewed and approved by authorized representatives of Acme Biotech as indicated by the signatures below.

| | |
|---|---------------|
| _____ East Coast Validation Services, LLC. | _____ Date |
| _____ Facilities | _____ Date |
| _____ Analytical Chemistry | _____ Date |
| _____ Development | _____ Date |
| _____ Quality Assurance | _____ Date |

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1. PURPOSE

This Risk Assessment (RA) will serve to define the intended use of the Acme Biotech Thule Clinical Manufacturing Facility (TCMF) and will document potential risks to product Safety, Identity, Strength, Purity and Quality (SISPQ) as assessed by the signatories to this document.

2. SCOPE

This RA applies to the Acme Biotech TCMF located in Thule, Greenland. It addresses the facility, equipment and systems that will be used to perform Clinical Manufacturing operations in the TCMF.

While new product development activities will also be performed in the TCMF, the scope of this document will be restricted to define only Clinical Manufacturing risks and impacts.

3. RESPONSIBILITIES

3.1. East Coast Validation Services

- 3.1.1. Develop this RA, with input from Acme Biotech Facilities, Development and Quality Assurance.

3.2. Facilities

- 3.2.1. Provide input during the development of this RA to ensure that it is consistent with Acme Biotech Facilities practices, procedures and requirements.
- 3.2.2. Review and approve this RA.

3.3. Development

- 3.3.1. Provide input during the development of this RA to ensure that it is consistent with Acme Biotech Development practices, procedures and requirements.
- 3.3.2. Review and approve this RA.

Note: the Acme Biotech Development organization is responsible for Clinical Manufacturing at the TCMF.

3.4. Analytical Chemistry

- 3.4.1. Provide input during the development of this RA to ensure that it is consistent with Acme Biotech Development practices, procedures and requirements.
- 3.4.2. Review and approve this RA.

Note: the Acme Biotech Analytical Chemistry organization is responsible for Quality Control testing at the TCMF.

3.5. Quality Assurance

- 3.5.1. Provide input during the development and review of this RA to ensure that it is consistent with current Good Manufacturing Practices (cGMPs), Acme Biotech policies and requirements, and Regulatory expectations.
- 3.5.2. Review and approve this RA.

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4. DEFINITIONS

- 4.1 **Risk Assessment (RA):** Documentation of a review of a facility or process by responsible Acme Biotech personnel to assess potential risks to product SISPQ based on its design and intended use. This RA will be used to determine followup Validation activities and Acceptance Criteria for the identified equipment and systems.

5. FACILITY DESCRIPTION

5.1. General Process Description

Raw materials are stored in the Raw Materials Storage room (Room 512). They are classified as Quarantined or Released and are stored in the appropriate location. Quarantined Raw Materials are tested by Acme Biotech Analytical Chemistry personnel and Released. Quarantined and Released Raw Materials are stored in segregated, controlled areas.

Released Raw Materials are transported from the QC Lab into the Production Lab through a mechanically interlocked material passthrough. Personnel enter the Production Area Gowning Area from an uncontrolled corridor and don bouffant hair covers, beard covers (if required), lab coats and gloves. Personnel then proceed into the ISO Class 7 Production Lab.

Production activities include weighing out raw materials and initial formulation on bench space in the Production Lab. **Other Process Specific activities also occur.** The bulk product is then assayed for activity and is diluted as required. In-Process samples may be taken and submitted to the QC Lab for testing.

The Laminar Flow Hood (LAFH) is cleaned, and the bulk product is then transported into the LAFH along with Finished Product vials and disposable equipment for manual filling. A calibrated Particle Monitoring instrument is set up to monitor the environment inside the LAFH, and the vials are aseptically filled using a syringe and a sterile, pyrogen free stopcock. The product is filled through a sterilizing filter. This filter is Bubble Point tested for integrity (after the filling operation is complete) using high purity nitrogen.

The Finished Product vials are manually labeled and samples submitted to the QC Lab for Release Testing.

After the aseptic fill operation is complete, the interior surfaces of the LAFH are tested for viable activity using RODAC plates. In addition, operator fingertips are checked for bioburden using contact plates. The LAFH is then recleaned.

The Finished Product vials are packaged and labeled per the Batch Record and stored in Finished Product Quarantine until released for shipment by Acme Biotech Quality Assurance.

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5.2. Rooms and Equipment

The TCMF is located in the Glacier Building at 1228 Evergreen Road, Thule, Greenland. It houses areas for process development, clinical manufacturing, quality control, utility systems and administration. The Glacier Building is a multi-tenant building; Acme Biotech is the only tenant that is involved in FDA regulated activities.

The TCMF is designed and will be operated to isolate Clinical Manufacturing activities from contact with other interior building areas, utilities and activities. The intent is to minimize the possibility of cross-contamination between operations within the Clinical Manufacturing suite and activities in adjacent areas.

The functional areas and rooms associated with the manufacturing of Clinical materials include the Production Area (Lab 520), the Quality Control Laboratory (Lab 510) and a Raw Materials Storage area (Room 512).

5.2.1. Production Area

The Production Area is located in Lab 520 of the TCMF and will be used for the manufacture of Phase I/early Phase II Clinical materials. Operations that will take place in this room will include formulation, purification and final filling.

The Production Area consists of a gowning area and a Production Lab separated by a hanging softwall curtain. The gowning area is classified as ISO Class 8 (Class 100,000) and the Production Lab is classified as ISO Class 7 (Class 10,000). HEPA filtered air is supplied from ceiling mounted registers; return air is drawn from low mounted wall registers. The room finishes are smooth, hard, cleanable, water- and chemical resistant surfaces. The floors are constructed of chemical-resistant epoxy flooring and contiguous base, epoxy painted gypsum wall board and ceilings with sealed access panels and light fixtures. The wall mounted window is covered with flush mounted clear Plexiglas to facilitate cleaning.

Two wall mounted Magnehelic gauges are installed in the uncontrolled corridor at the entrance to the airlock. One gauge displays the differential pressure between the Production Area and the uncontrolled corridor; the other gauge displays the overall static pressure used to control the Air Handler serving the Production Area. The differential pressures and airflows are balanced to achieve containment and particulate control.

The door to the Production Area is of seamless hollow metal design with seals to the door jam. Door hardware consists of stainless steel pull handles and stainless steel butt hinges. The door is equipped with a mechanical lock. Access to the Production Area is controlled procedurally per Acme Biotech SOP 01-02-03, *Cleanroom Entry and Egress*.

The Production Area is equipped with laboratory bench areas, **process specific equipment** and a laminar flow hood for performing aseptic fill operations. In addition, nitrogen gas is supplied to the production hood to allow bubble point testing of product filters. Materials are passed into and out of a mechanically interlocked material passthrough that connects to the Quality Control Laboratory.

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5.2.2. Quality Control Laboratory

The Quality Control Laboratory will be used to perform Raw Material, In-Process and Final Release testing of Clinical Materials manufactured in the TCMF Production Area. It is located in Lab 510 of the TCMF, adjacent to the Production Area and is connected to it via a mechanically interlocked passthrough.

The Quality Control Laboratory environment is not classified and does not have temperature or relative humidity specifications. It is equipped with laboratory bench areas, a chemical fume hood, **process specific equipment** to measure product activity and several HPLC systems.

5.2.3. Raw Materials Storage

Raw materials are Received at the Acme Biotech Receiving Dock and are delivered to the TCMF Raw Materials Storage Area (Room 512) of the TCMF. The door to the Raw Materials Storage room is equipped with a mechanical lock and access is controlled procedurally.

The Raw Material Storage room is equipped with locked cabinets for storage of Quarantined and Released Raw Materials. It is also equipped with a 2°C – 8°C refrigerator and a -20°C freezer for storing temperature sensitive materials. The Raw Materials Storage Room is not classified and does not have temperature or relative humidity specifications.

5.3. Critical Utilities

5.3.1. HVAC system

The TCMF HVAC system is used to provide filtered air at a rate sufficient to maintain ISO Class 7 conditions in the Production Lab. It controls temperature via heating coils and chilled water lines, but has no active relative humidity control. Conditioned air passes through six ceiling mounted HEPA filters as it is delivered to the Production Area. The airflow and pressurization is balanced so that air leaves the Production Lab through the Exhaust Hood duct, through the low return ducting installed on the west wall, or under the hanging curtain between the Production Lab and the Gowning Area. Air is supplied to the Gowning Area from two ceiling mounted HEPA filters and from the adjacent Production Lab, and exits the Gowning Area through low return ducting installed on the west wall near the door, or underneath the door to the uncontrolled corridor. The airflow and pressurization is balanced to maintain a 0.03" – 0.07" WC differential pressure between the Production Lab and the uncontrolled corridor.

The HEPA filters are certified for airflow and integrity on a semiannual basis.

5.3.2. Nitrogen (N₂) system

High purity nitrogen is used to perform bubble point tests of the 0.2μ sterilizing filters. This nitrogen is supplied from a cylinder installed in the Gowning Area and is delivered to the Production Hood (where the Filter Integrity Test is performed) via 1/2" diameter PVC piping. The purity of the nitrogen is confirmed by reviewing a Certificate of Analysis that accompanies each cylinder, and the nitrogen delivered to the Production Hood is indicated by a calibrated pressure gauge.

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5.4. **Personnel, Material and Waste Flows**

The movement of personnel, materials and waste into and out of the TCMF during GMP production will be controlled procedurally to minimize the chances of contamination and/or material mixups.

5.4.1. Material Flow

Raw Materials will be taken from the Raw Materials Storage area per the Batch Record Bill of Materials and delivered to the QC Lab. The QC Lab will Release raw materials for production and transfer them to the Production Lab via a mechanically interlocked passthrough. Any In-Process samples will be submitted to the QC Lab via the passthrough. Finished Product will be labeled appropriately and also submitted to the QC Lab through the passthrough for Release Testing and final disposition.

5.4.2. Personnel Flow

Manufacturing personnel will enter the Production Gowning Area and gown per SOP 01-02-03, *Cleanroom Entry and Egress*. These Manufacturing personnel will take Released Raw Materials from the passthrough, stage them as required in the Production Lab, and manufacture Clinical Materials per the Batch Record. Upon conclusion of Production activities, Manufacturing personnel will degown per SOP 01-02-03 and exit the Production Gowning Area into the uncontrolled corridor.

5.4.3. Waste Flows

Waste materials generated during production activities are categorized as potentially biohazardous or nonbiohazardous. Potentially biohazardous waste materials are segregated, placed in clearly identified containers, and disposed of per applicable Acme Biotech SOPs and state and Federal regulations. Nonbiohazardous waste generated in either the Production Lab or QC lab is disposed of during normal cleaning activities.

There are no chemically hazardous wastes generated during GMP production at the TCMF

Refer to Section 9 for flow diagrams for Personnel, Materials and Waste.

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6. APPROACH

The focus of the product development process at the TCMF will be to develop initial product to support the initial phases of Clinical testing and to prepare for Technology Transfer to larger scale Contract Manufacturing facilities. In order to achieve this, the anticipated manufacturing processes will be reviewed and required equipment, instrumentation and utilities (process components) will be identified. The potential risks to product SISPQ by failure of each of these process components will be assessed.

6.1. Risk Assessment

Possible Failure Modes for each process component equipment, instrumentation and/or system will be identified and the following probabilities will be assessed as High (3), Medium (2) or Low (1) for each failure mode:

- Probability of Failure **P_F**
- Severity of the Failure mode (potential impact on product SISPQ) **P_S**
- Probability that the failure will be detected **P_D**

The risk (R_M) associated with each failure mode will be calculated as follows:

$$R_M = (P_F \times P_S) / P_D$$

Overall risk associated with each process component (R_{PC}) will be calculated as follows:

$$R_{PC} = \Sigma R_M$$

This Risk Assessment will be used to determine Validation activities and Acceptance Criteria to provide a high level of confidence that the TCMF meets the needs of Clinical Manufacturing operations.

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7. RISK IDENTIFICATION AND ASSESSMENT

| HVAC System | | | | | | |
|-------------------------------------|----------------------|----------------------|----------------------|-------------|---|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Insufficient Supply airflow | 2 | 1 | 1 | 2 | Particulate contamination from uncontrolled areas | Insufficient airflow will eventually be evidenced as loss of differential pressure |
| Insufficient Return airflow | 2 | 2 | 1 | 4 | Particulate contamination from uncontrolled areas or from production activities | Insufficient airflow will eventually be evidenced as loss of differential pressure |
| | | | | | | Severity of failure is judged to be greater for Return airflow as particles generated by operations will not be swept away |
| Loss of differential pressurization | 2 | 2 | 1 | 4 | Particulate contamination from uncontrolled areas or from production activities | Condition can be detected by visual check of room ΔP gauges, but there are no active ΔP alarms |
| Loss of temperature control | 2 | 3 | 2 | 3 | Product chemistry or particulate contamination from production activities | Low temperatures could affect solubility +/- or solution incubation |
| | | | | | | High temperatures could cause operator perspiration which could lead to potential viable contamination |
| HEPA failure | 1 | 3 | 3 | 1 | Particulate contamination from uncontrolled areas | Probability of detection is high as room particle levels are measured prior to each production run. |
| Overall Risk Assessment | | | | 14 | | |

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| Nitrogen System | | | | | | |
|---|----------------|----------------|----------------|------|---|---|
| Failure Mode | P _F | P _S | P _D | Risk | Potential SISPQ Impact | Comments |
| N ₂ Use Point pressure gauge calibration failure | 1 | 2 | 1 | 2 | Particulate contamination of drug product | Failed sterilizing filter could be accepted as good, would not be detected until recalibration or sterility testing during Release process. |
| Overall Risk Assessment | | | | 2 | | |

| Production Hood | | | | | | |
|----------------------------------|----------------|----------------|----------------|------|---|---|
| Failure Mode | P _F | P _S | P _D | Risk | Potential SISPQ Impact | Comments |
| Loss of airflow control (high) | 1 | 2 | 2 | 1 | Particulate contamination from uncontrolled areas | Higher airflow through hood will drop ΔP to uncontrolled corridor, will eventually be evidenced as loss of differential pressure |
| Loss of airflow control (low) | 2 | 3 | 2 | 3 | Potential biohazardous particulate contamination to production area | Operator safety concern is higher than potential product impact |
| Leaks in activated carbon filter | 1 | 1 | 3 | 0.3 | No significant impact | Potential biohazardous particulate contamination to environment (not to product). ΔP across carbon filter is monitored; airflow downstream of carbon filter is also monitored by calibrated flow element. |
| Overall Risk Assessment | | | | 4.3 | | |

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| Laminar Flow Hood | | | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|-------------|---|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Loss of airflow control (high) | 1 | 3 | 3 | 1 | Particulate contamination from Production area | ΔP is monitored by a calibrated differential pressure gauge; particle levels inside LAFH are continuously monitored during fill operations |
| Loss of airflow control (low) | 1 | 3 | 3 | 1 | Particulate contamination from Production area; potential biohazardous particulate contamination to production area | Operator safety concern is higher than potential product impact |
| Aseptic technique errors during fill | 2 | 3 | 1 | 6 | Particulate contamination from Production area or from operations | Product sterility is tested but results will not be known before product shipment |
| HEPA failure | 1 | 3 | 3 | 1 | Particulate contamination from Production area | ΔP is monitored by a calibrated differential pressure gauge; particle levels inside LAFH are continuously monitored during fill operations |
| Overall Risk Assessment | | | | 9.0 | | |

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| Manual Crimping/decrimping operations | | | | | | |
|--|----------------------|----------------------|----------------------|-------------|-----------------------------------|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Crimping/decrimping technique errors | 1 | 3 | 3 | 1 | Product seal integrity compromise | This is an operation that requires demonstrated proficiency; will be addressed as a Training activity and not as a Validation activity |
| Overall Risk Assessment | | | | 1.0 | | |

| Vortexers and Sonicators | | | | | | |
|--|----------------------|----------------------|----------------------|-------------|-------------------------------|---|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Mechanical failure - no operation | 1 | 1 | 3 | 0.33 | No significant impact | Batch Record instructions call for visual check of dissolution - problems will be identified during operations. |
| Mechanical failure - partial operation | 1 | 1 | 3 | 0.33 | No significant impact | |
| Overall Risk Assessment | | | | 0.67 | | |

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| HPLC Systems | | | | | | |
|---|----------------------|----------------------|----------------------|-------------|---|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Loss of flow control | 1 | 3 | 1 | 3 | Inaccurate In-Process +/-or Release Test data | Probability of failure is kept low as System Suitability runs are executed prior to testing |
| Loss of temperature control | 1 | 3 | 1 | 3 | | |
| Loss of detector accuracy +/-or precision | 1 | 3 | 1 | 3 | | |
| Loss of stored data integrity | 1 | 3 | 3 | 1 | | Primary failure mode is mechanical+/-or electrical failure which would result in nonfunctionality of the system. |
| Overall Risk Assessment | | | | 10.0 | | |

| pH Analyzer | | | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|-------------|-------------------------------|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Electrical or mechanical failure | 1 | 1 | 3 | 0.33 | No significant impact | Mechanical+/-or electrical failure would result in nonfunctionality of the system. |
| Loss of sensor accuracy or precision | 1 | 2 | 3 | 0.67 | No significant impact | Probes are standardized prior to use in testing |
| Overall Risk Assessment | | | | 1.00 | | |

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| LAL Analyzer | | | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|-------------|------------------------------------|---|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Electrical or mechanical failure | 1 | 1 | 3 | 0.33 | No significant impact | Mechanical+/or electrical failure would result in nonfunctionality of the system. |
| Loss of sensor accuracy or precision | 1 | 3 | 1 | 3 | Endotoxin contamination of product | |
| Overall Risk Assessment | | | | 3.33 | | |

| Osmometer | | | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|-------------|-------------------------------|---|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Electrical or mechanical failure | 1 | 1 | 3 | 0.33 | No significant impact | Mechanical+/or electrical failure would result in nonfunctionality of the system. |
| Loss of sensor accuracy or precision | 1 | 2 | 3 | 0.67 | No significant impact | Probes are standardized prior to use in testing |
| Overall Risk Assessment | | | | 1.00 | | |

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| Incubators | | | | | | |
|-----------------------------|----------------------|----------------------|----------------------|-------------|--|-----------------|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Loss of temperature control | 1 | 3 | 1 | 3 | False negative results | |
| Door seal failure | 2 | 3 | 1 | 6 | False positive results (particulate contamination from laboratory) | |
| Door seal failure | 2 | 3 | 1 | 6 | False negative results (loss of temperature control) | |
| HEPA failure | 1 | 3 | 3 | 1 | False positive results (particulate contamination from laboratory) | |
| Overall Risk Assessment | | | | 16.0 | | |

| RM Refrigerator | | | | | | |
|------------------------------------|----------------------|----------------------|----------------------|-------------|--|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Loss of temperature control (high) | 2 | 3 | 1 | 6 | Potential RM degradation | Critical Raw Materials are tested prior to use in production, but degradation within specification may not be detected |
| Loss of temperature control (low) | 2 | 3 | 1 | 6 | Potential RM degradation due to freezing | |
| Overall Risk Assessment | | | | 12.0 | | |

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| RM Freezer | | | | | | |
|------------------------------------|----------------------|----------------------|----------------------|-------------|-------------------------------|--|
| Failure Mode | P_F | P_S | P_D | Risk | Potential SISPQ Impact | Comments |
| Loss of temperature control (high) | 2 | 3 | 1 | 6 | Potential RM degradation | Critical Raw Materials are tested prior to use in production, but degradation within specification may not be detected |
| Loss of temperature control (low) | 2 | 1 | 1 | 2 | No known significant impact | |
| Overall Risk Assessment | | | | 8.0 | | |

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8. RISK SUMMARY

| Process Component | Assessed Risk |
|-----------------------------------|----------------------|
| Incubators | 16 |
| HVAC System | 14 |
| Raw Material Storage Refrigerator | 12 |
| HPLC systems | 10 |
| Laminar Flow Hood | 9 |
| Raw Material Storage Freezer | 8 |
| Radiation Exhaust Hood | 4 |
| LAL Analyzer | 3 |
| Nitrogen System | 2 |
| Manual Crimp Tools | 1 |
| pH Analyzer | 1 |
| Osmometer | 1 |
| Vortexers +/- or sonicators | 1 |

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9. TCMF PERSONNEL, MATERIAL AND WASTE FLOWS

Diagrams deleted for Confidentiality reasons.