SOP Title: **Pre-Production Clearance**
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1. PURPOSE

This procedure describes the steps necessary to ensure that areas, rooms, equipment, and materials assembled to produce clinical grade intermediates, bulk, and final product comply with CGMP requirements.

2. SCOPE

This procedure is to be followed by Production personnel and QA staff involved in performing pre-production clearances to produce clinical grade materials. This procedure does not apply to the production of pre-clinical (toxicology or GLP) material, or to the movement and staging of cleaned and released equipment in preparation for clearance.

3. RESPONSIBILITIES

3.1 Director, Regulatory Compliance

- Defines this procedure.

3.2 Quality Assurance (QA)

- Manages the Pre-Production Clearance Request and performs the area clearance inspection.
- Initiates and completes the Clearance Audit in eQMS

- Dispositions the GMP area(s) (as appropriate) prior to the initiation of production campaigns, filling operations, and labeling operations of clinical grade product.
- Notifies the responsible person regarding the status of the pre-production clearance.
- Maintains files of original documentation (Pre-production Clearance Request Form and QA Pre-Production Clearance Qualification Checklist and Release Form/Report) in eQMS.

3.3 Responsible Person (Area Owner)

- Notifies QA of process schedules and requests pre-production clearance at least one week prior to the expected clearance date for any production campaign, filling, or labeling operation.
- Ensures that equipment calibration, maintenance, and cleaning are performed and documented as required during the clearance period.
- Immediately provides updated information to QA regarding changes to SOPs, equipment, personnel, and any conditions that may impact an issued Process Area Clearance.
- Addresses any QA observations and action items in eQMS for remedial action in a timely manner prior to the clearance approval.
- Informs QA as soon as possible of any activity that would void the clearance approval.

3.4 Appropriate Project Team members

- Provides information and support to QA so that the pre-production clearance may be accomplished in a timely manner.

3.5 QA Quality Engineering Team

- Communicates the ATRF GMP area compliance status to QA Auditing and the Area Owner per **SOP 21554 - GMP Area Status Management.**

4. TYPES OF CLEARENCE

Clearances are grouped into one of the following categories.

- **Campaign Clearance:** The clearance of a specified area or areas that will be used to perform an uninterrupted process or series of processes applicable to one or more lots of the same product. A campaign clearance may be used prior to and/or after the manufacture of a single lot or a series of lots of the same product.

- **Process Clearance:** The clearance of a specified area or areas that will be used to perform a process applicable to a specific set of MPRs for a specific lot of product.
- **Filling Clearance: T**he clearance of a specified area(s) for the fill/finish of a specified lot of product.
- **Labeling Clearance:** The clearance of a specific area(s) or areas for the labeling of a specific lot of product.
- **Extension:** A clearance that requires additional manufacturing time for the same type of processes the original clearance was issued for.

5. OVERVIEW OF THE CLEARENCE PROCESS

5.1 The requesting department's Responsible Person requests a clearance by submitting **Form 21104-01, Pre-Production Clearance Request Form.** This form captures information about the proposed clearance (type of clearance being requested, estimated start and end dates, MPR(s) to be used, product lots applicable, location of scheduled activities, equipment to be used, raw materials to be used, SOPs applicable, personnel involved, and a schedule of events, including PA/QC testing schedule, if available).

5.2 QA reviews and evaluates this request (including an inspection of the area), creates any observations in eQMS that require a response from the Responsible Person. The department or Responsible Person must address any QA concerns about the readiness of the area for clearance before clearance can be approved. Clearance is given by QA for the specified operation(s) after issues have been satisfactorily resolved.

5.3 A copy of the completed report, QA Pre-Production Clearance Status is posted in a visible location to the area cleared. This report is provided by QA to grant clearance or conditional clearance. During the time-period of the clearance, scheduled area cleaning, calibration, preventive maintenance, employee training, etc., is conducted and documented according to approved procedures.

5.4 In the event that the area experiences a situation that would void the area clearance (introduction of equipment, employees, procedures/processes that are not listed on the initial request for clearance, or any changes that would affect the environmental/utilities status of the area, etc.), and if no harm will result to product, production should stop and another area clearance is completed in the QMS. If harm to product would result from stopping production, a deviation must be written to address issues and QA is notified as soon as possible.

6. PROCEDURE

6.1 Pre-Production Clearance Request (**Form 21104-01**)

6.1.1 The Area Owner or designee requests an area clearance, prior to the start of any processing. This request will be documented on **Form 21104-01, Pre-Production Clearance Request,** and submitted by email to QA at least one week prior to the start of any processing.

6.1.2 A Pre-Production Clearance Request Form includes the information listed below. Alternatively, acceptable lists may be copies of pages from an MPR, Excel spreadsheets, Word documents or equivalent that cover the requested information.

6.1.2.1 **Header:** Date requested, Responsible Person, Project Number, Process/Project Name and Lot Number(s).

6.1.2.2 **Section I:** Type of clearance being requested (Campaign, Process Filling, Labeling, Extension, or Other). If an other type of clearance is required. Please include a description of that other clearance type.

6.1.2.3 **Section II:** List the rooms that are to be used during the project, including a description of activity that will occur in each area. Document the date of the last cleaning, and type of cleaning (routine, interproduct, etc.) or the future scheduled date of cleaning. Include a summary of activities that occurred since the last production activity.

6.1.2.4 **Section III:** List equipment to be used during the project, including the MEF numbers and the equipment calibration due dates. Alternately, if a list is attached, check the box and attach the list.

6.1.2.5 **Section IV:** List raw materials, buffers, product-contact consumables, etc., to be used in the production. Alternately, if a list is attached, check the box and attach the list.

6.1.2.6 **Section V:** List Standard Operating Procedures (SOPs) and Master Production Records (MPRs) to be used, include their document numbers and titles. Alternately, if a list is attached, check the box and attach the list.

6.1.2.7 **Section VI:** A list of the personnel along with their responsibilities, who will be involved with the work in the area for the clearance period. Include personnel assisting from other groups, personnel who will be in the area as observers of the manufacturing operations (if known), and include personnel scheduled to perform vial inspection process (if known). QA may also add QA observers and inspectors in this section (as needed).

6.1.2.8 **Section VII**: A tentative manufacturing schedule and PA\QC testing schedule for the project (if available).

6.1.2.9 **Section VIII:** Manufacturing Certification & Approval Signature. The manufacturing supervisor or Responsible Person for the request approves the completed form prior to being submitted to QA. This approval signature includes a confirmation statement that each raw material used will be appropriately cleared, stored properly, and used within its defined expiration date. It also includes a confirmation that equipment usage, calibration, and cleaning logs and other applicable documentation are complete, current, and demonstrate compliance to established schedules and specifications and will continue to be maintained according to established schedules and specifications.

6.1.3 QA is responsible for the following actions and for completing the Area Clearance Audit Checklist Report in eQMS

6.1.3.1 Review training records, based on the identified personnel and their responsibilities listed on the Pre-Production Clearance Request Form. Confirm that the appropriate training has occurred for the appropriate SOPs listed in the production MPRs. Confirm that personnel identified for Filling/Stoppering functions are within current validation status (gowning and aseptic fill authorized). Confirm that personnel identified as vial inspectors are qualified as vial inspectors.

NOTE: Observers must be trained on applicable SOPs (gowning and egress) to allow access to manufacturing areas.

6.1.3.2 Confirm that QA Validation Engineering has released the Area for CGMP operations as per **SOP 21554 - GMP Area Status Management.**

6.1.3.3 Confirm that prior product and/or prior product labeling materials have been removed from the area.

6.1.3.4 Confirm that documentation of interproduct wash down cleaning (campaign cleaning) (applicable between projects and with recommissioning) of the area has been completed.

6.1.3.5 Review cleaning logs, equipment usage logs, and other applicable documentation to ensure they are complete and correct.

6.1.3.6 Confirm that documentation of interproduct cleaning (where appropriate) of equipment has been completed.

6.1.3.7 Confirm that the calibration will not expire for the critical equipment listed in the MPR or Clearance Request during the intended manufacturing period.

6.1.3.8 Confirm that project Master Production Records are approved. Confirm that the Master Specifications (as applicable) are approved. If the Master Specifications are not approved, a planned deviation is required to grant clearance.

6.1.3.9 Confirm that critical materials have release stickers, will not expire prior to the anticipated use of the material, and are stored appropriately. For Process Area Clearances, verify that the confirmation statement for use of appropriately cleared, properly stored, and in-date materials and supplies has been signed on the Pre-Production Clearance Request Form.

6.1.3.10 QA may issue a Conditional Clearance that applies only to a specific portion of a process or operation (i.e., preparation of materials to be sterilized, etc.) in order to expedite production. A Conditional Clearance may also exclude an area or process, etc., from being used. Once the conditions that lead to the exclusion are resolved, these areas/processes may be added to the clearance. The QA Pre Production Clearance Status may be amended to 'Released' status should the issues be resolved and the status is no longer conditional. A change from the conditional status to the release status requires a new report and audit module in the eQMS.

6.2 QA Inspection of the Area

6.2.1 The Responsible Person, identified on **Form 21104-01** ensures that the area(s) identified in the clearance request is ready for a walk thru by QA, at least 3 working days prior to the start of any processing (when possible).

6.2.2 It is preferred that the raw materials, buffers, and equipment for a Campaign either be staged in the rooms that the manufacturing operations will occur or, if possible, in rolling racks that are locked and properly identified with product name, project number, and lot number. They should be staged in one holding area (when possible) if not in the room where manufacturing will occur.

6.2.3 The logbooks associated with equipment listed in the MPR are made available for review if they are not located with the equipment.

6.2.4 QA inspects the Production Area(s) to verify that prior product labeling and product have been removed from areas.

6.2.5 Additional requirements, deviations and engineering events that may affect the clearance are listed on the clearance report.

6.2.6 QA notifies the responsible person of any recommendations for remedial action within 24 hours of inspecting the production areas.

6.3 QA Recommendations and Observations

6.3.1 QA documents observations and required action items in eQMS and assigns the Responsible Person an action item through the eQMS.

6.3.2 The Responsible Person, or designee, corrects any deficiencies noted by QA and makes arrangements for final review by QA of the documents or areas, prior to QA granting Clearance.

6.3.3 Observations are categoriezed as:

- **Minor** - a deficiency that would not obviously cause a product failure (e.g. training on a previous revision of an SOP, equipment logbook deficiencies, incorrect material lot numbers identified)
- **Major** - a deficiency that could cause a product failure. This level of deficience would require approval from the QA Manager. A deviation would be required to proceed with granting clearance.
- **Critical** - a deficency that would cause a product failure. (e.g. a process failure). This would preclude clearance from being granted.

6.4 Completion of the Pre-Production Clearance Status and Checklist Report

6.4.1 Upon satisfactory completion of QA review, generates the Pre-Production Clearance Status and Checklist Report and provides it to the Responsible person to post in a visible location to the cleared area (usually at the entrance to the cleared area(s), or is posted by the auditor.

6.4.2 Clearance is approved for the time period listed on the QA Pre-Production Clearance Status and Checklist Report or until an event occurs that would void the clearance approval or a time extension is requested/granted.

7. CLEARANCE EXTENSION

7.1 When needed, an approved Clearance may need to be extended past the time period listed on the Pre-Production Clearance Status and Checklist Report.

7.2 An extension to an existing clearance should be considered when the same processes will be performed in the same area one after the other.

7.3 The Area Owner or designee requires another clearance with the extended timeframe utilizing the **Pre-Production Clearance Request (Form 21104-01)**. The request will be completed as described in the aforementioned section.

7.4 QA is responsible for the same actions listed above when initially granting clearance.

7.4.1 It is not required to re-verify the equipment listed on the master production record if it does not change between lots.

7.4.1.1 The calibration dates should still be valid through the manufacturing time period.

7.4.1.2 Any interproduct cleanings should be verified, if applicable. The information regarding the interproduct cleanings should be added to the QA Pre-Production Clearance Qualification Checklist and Release Report. This becomes a second report.

7.4.1.3 The TOC for the SOP manual should be reviewed for any updates.

7.5 QA Inspection of the Pre-Production Clearance Status and Checklist Report is completed as previously described.

QA notifies the responsible person of any recommendations for remedial action within 24 hours of inspecting the production areas. Observations and action items are sent by QA through eQMS.

7.6 Follow-up on QA Recommendations

7.6.1 Completion of the QA Pre-Production Clearance Qualification Checklist and Release Report with the new extended period requested.

7.6.2 The start date on the original Clearance Request should remain on the checklist and the end date should be updated to the end date of the extension.

8. EVENTS THAT VOID CLEARANCE APPROVALS

8.1 The following events, occurring prior to or during the time interval approved by the clearance, VOIDs the clearance and requires that QA re-establish that the area is acceptable for use again by completing a new area clearance. If no harm would occur to product, production must stop until QA Area Clearance approval is re-obtained.

8.1.1 Use of the area for an activity/process not documented in the Pre-Production Clearance Request Form and not routinely performed that may compromise the integrity of the area for its intended use, as determined by QA.

8.1.2 Equipment introduced into the area that is not listed on the approved request for clearance.

NOTE: Replacement of equipment with cleaned and released equipment on a "like-for-like" basis must be documented in the batch record but will not void the clearance. Equipment located in area and identified as not being used for the current production does not void the clearance.

8.1.3 Employees that are not listed in the approved request for clearance and that are expected to perform any of the activities documented in the Pre-Production Clearance Request Form.

8.1.4 New procedures or processes affecting the activities documented in the clearance request without an approved deviation.

8.1.5 Any changes (planned or unplanned) that would affect the environment/utilities status of the area.

8.1.6 Introduction of non-product related biologic materials or highly toxic materials into an area unless specified on the Pre-Production Clearance Request Form.

8.1.7 Failure to maintain scheduled equipment maintenance or calibration requirements, unless covered under a deviation.

8.1.8 Failure to maintain scheduled area cleaning requirements (unless scheduled cleaning would jeopardize production).

9. DOCUMENTATION AND RECORDS

9.1 Pre-Production Clearance Requests are documented on **Form 21104-01**. Originals of completed forms are maintained in the Clearance Audit file in eQMS. Copies may be made as required.

9.2 Disposition of the Pre-Production Clearance Requests are documented in the Pre-Production Clearance Status and Checklist Report. This report is maintained in eQMS. Copies may be made as required.

9.3 A copy of the completed report is provided to the Responsible Party originating the Pre-Production Clearance Request for posting, and inclusion in batch records.

9.4 Records are retained as per **SOP 21407 - Records Retention.**

10. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
21407	Records Retention
21554	GMP Area Status Management
21104-01	Pre-Production Clearance Request