**Cleaning Validation Gap Assessment**

**Doc NO. #####**

**Generated by PSC Biotech for**

**Aphena Pharma Solutions – Easton, MD**

# APPROVALS

By affixing their signatures, the individuals below agree that they have reviewed and scope of the findings described in this Gap Assessment. The signatures below represent the approval for acknowledgement of the Gap Assessment and acceptance by Aphena’s authorized signatories on behalf of Aphena management and individual Aphena operating sites.

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| **Name / Title** | **Signature** | **Date** |
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| **Name / Title** | **Signature** | **Date** |
| Rafeh Raza  Manager, Technical Services |  |  |
| David Fidler  Vice President/General Manager of Easton, MD Site |  |  |
| Dan Bitler  Director of Quality and Regulatory Affairs |  |  |
| Matthew Prokopczyk  Vice President of Quality and Regulatory Affairs |  |  |

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# Executive Summary

Aphena’s Easton, MD site was visited on 17-Mar-2021 to observe and assess the current practices that are in place with respect to the cleaning of the various equipment lines, tooling, and ancillary equipment. The intent of this visit is to understand and recommend revisions/augmentations to critical processes related to the cleaning practices currently deployed at the Easton, MD site. During the visit, there was a tour of the production floor and various manufacturing and packaging suites/rooms that have direct product contact where representatives from the validation team.

Upon completion of the visit, a summary of recommendations (Section 4 of this document) was generated with details of the finding or deficiency and the recommendation to remediate or address these items.

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# PURPOSE

The purpose of this Gap Assessment of the cleaning validation systems at the Aphena’s Easton, MD is to describe the current deficiencies identified that are required to maintain compliance and adherence to current industry standards. The findings and deficiencies described in this document may serve as a guidance for remedial strategy.

# BACKGROUND

The cleaning validation system at Aphena’s Easton, MD has been identified as an area of enhancement based on various practices that have been implemented versus nature of the current cleaning CVP – Cleaning Validation Plan VP2011-03; Rev. 2; Effective Date 22-Aug-2018.

# Summary recommendations

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| **Risk Definition** | **GxP Impact** | **Effect** |
| High | Compromise ability to fulfill GxP requirements, likely resulting in a non-compliance observation. |
| Medium | Could potentially compromise ability to fulfill GxP requirements, possibly resulting in a non-compliance observation or major observation. |
| Low | Minimal effect on GxP compliance, possibly resulting in a minor observation or recommendation. |
| No Risk | No effect on GxP compliance. |

| # | Criticality | Gap Description | Recommendation |
| --- | --- | --- | --- |
| 1 | Medium to High | CVP speaks to recovery study, but there yet to have a study executed. | Recovery study must be executed in order to prove swabbing techniques for sampling are appropriate. |
| 2 | Medium | No logbooks in cleaning room. | Did not encounter any documentation regarding the activity of the cleaning room. A best practice would be to implement the use of a logbook or form that tracks the tooling that is going in and out of the room. Doing so would enhance the chain of custody from a compliance perspective. |
| 3 | Medium to High | Ancillary equipment is not product specific. As a result, using scoops across various products without evidence that the equipment can be cleaned poses a risk for cross contamination. | Scope ancillary equipment into validation by spiking it with worst-case API and subject to hold times via a supplemental validation or an addendum to the original validation protocol. |
| 4 | Medium | Numerous validated cleaning techniques | Harmonize one cleaning process across the plant. Assess current practices for cleaning product contact parts. |
| 5 | Low to Medium | CVP does not differentiate between Finished Product form (i.e., med device versus topical). | CVP must be updated to scope in different Finished product forms. This item can be omitted if there is one uniform cleaning process throughout the site as pointed out in Observation #4. |
| 6 | Low to Medium | CVP details monitoring of the cleaning validation process to ensure that the technique remains in a state of control during personnel shift changes and across personnel turnover – No monitoring has been executed. | To account for personnel shift changes and personnel turnover and validate the training of a manual cleaning process, an annual (or any prescribed interval) verification under a validation protocol must be completed. However, Aphena does sampling after every run (see Misc. Observation #1) which provides data that the process is in control, though this alone is not a preferred method for best practices. A retrospective validation (only for U.S. market) or a separate verification study could sufficient. |
| 7 | High | CVP does not have instructions for room cleanings after the completion of a production run. | Qualify procedure for cleaning room based on agency guidance (i.e., ISO 8). Develop SOP or Work Instruction for operators to clean rooms upon completion of qualification. |
| 8. | Low | CVP does not specify how to address long-running campaign productions. | Update CVP to add language in how to address or approach campaigned production runs. Typically, a customer request/requirement for long running campaigns that exceed dirty hold times. When/if required by a customer, generate a verification protocol for long-running campaigns based on total dosages/lots to determine the maximum run time a product can run before it gets cleaned. |
| 9. | Low | Mechanical tooling stored in cabinets of primary filling rooms. Risk for contamination. | Store mechanical tool cabinets outside of room or develop procedure to ensure tools are cleaned between product runs in order to minimize the presence of previous product residue is not present if tooling is used during production run of another product. |
| 10. | Medium | Logbooks in rooms such as K-2 were not closed out or reviewed going more than a year. | Logbooks across site must be reviewed and closed out with QA oversight. Need to revise SOP QA-004 Quality Documents and Records or implement procedure for issuance and control of logbooks since it is unclear how logbooks are issued and tracked. Could be remediated with the implementation of a GEMBA walk process. |
| 11 | Low to Medium | Pharmacy Room - Containers or drums containing product/raw materials can be in the room at the same time without any isolation/containment procedure in place. | Develop procedure or process flow map to ensure that raw materials for different products are isolated or contained to prevent cross-contamination. |
| 12 | Medium | CVP is silent to current practice of using Daily Exposure (ADE)/Permitted Daily Exposure (PDE) to determine worst-case product. | Update CVP to include ADE/PDE approach to determine worst case as per industry trends or update CVP to prescribe that Maximum Allowable Carryover calculations will be listed in the Approach/Methodology of the cleaning validation protocols. |
| 13 | Medium | No current logbooks or forms in place for monitoring the cleaning room to ensure various parameters and procedure remain in a state of control. | Implement logbook to track dedicated and ancillary equipment traveling in and out of the cleaning room to enhance compliance and traceability of equipment across all equipment trains. |
| 14 | Medium to High. | No approved, effective product matrix to identify worst-case product currently being manufactured in the plant. | Generate product matrix to identify worst case that will be entered into Aphena Quality Systems. Upon being approval to be effective, implement process and or procedure to track any incoming new product. |
| 15 | Medium | Validation of the PDE/ADE spreadsheet calculator. Using an unqualified instrument to generate critical data. | Qualify spreadsheet and upon completion of the qualification, spreadsheet shall be entered into Aphena Quality Systems document control to receive a form number. |
| 16 | Medium | CVP does not describe how the Decision Tree for Determining Need for Cleaning Validation in Appendix D is documented. | Generate form to document the outcome of the decision. Form should include assessment of MACO against the current worst-case product using qualified spreadsheet (See Observation #17). |

| Miscellaneous Observations | | | |
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| # | Criticality | Gap Description | Recommendation/Comments |
| 1 | N/A | Sampling after every run | Sampling after every run is conservative in nature and can be used as a defense for the absences of any monitoring but can be identified as a potential issue which shows that the organization does not have confidence in their validated process. Instead, follow the CVP to monitor at a lesser frequency such as doing a verification run quarterly, and then annually for example. This would improve product release lead times and double as a cost saving measure as well. |
| 2 | N/A | J1 packaging line has various rust throughout the equipment line near exposed product prior to final sealing. | Equipment Preventive Maintenance (PM) SOP(s) should be reviewed for needed updates to ensure equipment is maintained in the appropriate condition and working order per site requirements. In addition it should be determined if passivation is required. |