5.0 VALIDATION POLICY

5.1. Equipment changeover cleaning procedures must be validated for all major and minor product contact equipment used for multi-product production, subdivision and sampling of drug products and in process materials.

5.2. Equipment cleaning validation shall be based on a worst-case product with the minimum calculated acceptable carryover limit using the calculation model for Residue Acceptability Limit. For Non-Therapeutic materials the Residue Acceptability Limit for Non-Therapeutic materials based on toxicity applies. The minimum calculated acceptable carryover will be used as the cleaning validation criteria for all products manufactured in the specified equipment.

5.3. Three consecutive successful applications of the cleaning procedure are required to demonstrate that the procedure is validated. Batches of another product cleaned by a different cleaning procedure may intervene the three applications of the procedure undergoing validation trials shall be executed using one or more of the following options:

- Cleaning validation trials performed at the end of a regularly scheduled campaign; and/or
- Cleaning validation trials conducted at campaign lengths less than the maximum campaign length, so long as at least one trial is at full campaign length. Additional cleaning validation trials, using the next most difficult to clean product, may be conducted prior to completion of the three validation trials of the most difficult to clean product. For retrospective cleaning validation studies, a second worst case product should be considered if the worst case product is manufactured infrequently. Failure of a validation trial for the next most difficult to clean product is equivalent to a failure of the validation trial for the most difficult to clean product

5.4. When there is a deviation from the planned cleaning procedure on one of the replicate runs, it may be removed from the sequence if an assignable cause can be determined and the deviation is unrelated to the cleaning procedure. e.g., power loss, cleaning utility malfunction. In situations where an assignable cause can not be determined a review of the procedure should be conducted, followed by three successful cleanings.

5.5. Where acceptance criteria has not been met, a complete review of the cleaning procedure should be conducted, followed by three successful cleanings. In this situation the cleaning run cannot be removed from the sequence.

5.6. The effectiveness of the cleaning procedure must be evaluated by visual inspection and if required, testing for drug residue, cleaning agent residue and microbial bioburden. Where evaluation demonstrates that routine cleaning procedures are not acceptable, cleaning SOPs and equipment will be reviewed and revised or modified as necessary.

5.7. A product grouping or equipment bracketing strategy can be used to avoid the need to validate all combinations of equipment, processes and products in the program. A

systems and pre-defined parts of automated cleaning systems. Special attention should be paid to areas that are difficult to clean, observe or reach and where residue may accumulate.

Swab analysis may be used to quantitatively determine the presence of worst case products or cleaning agents on the surface of the equipment. Appropriate methods will be developed and validated for each target residue prior to the validation of the equipment cleaning procedures.

Rinsing volume analysis is used to assess the cleanliness of surfaces which cannot be reasonably accessed for accurate assessment via swabbing. Rinse methods must be validated.

Microbial Acceptability Limits for Equipment Cleaning shall be established and validated, when required.

5.15. For many OTC products the residue carryover limit will be above the visual limit of detection per standard surface area. Under these circumstances full swab and rinsate testing may not be justified and visual inspection is acceptable. In order to utilise visual inspection only, limits of detection for visual inspection should be established and validated.

5.16. Dirty Holding Time is defined as the interval between use and cleaning and must be specified in the protocol and validated using at least one cycle. If the validated Dirty Holding Time is exceeded a risk assessment must be performed and if necessary the equipment must be assessed for product and microbial contamination following cleaning.

5.17. Clean Holding Time is defined as the interval between cleaning and use and must be specified in the protocol and validated. If the Clean Holding Time is exceeded the equipment shall be cleaned again prior to use and verified as clean

5.18. Validation of the removal of cleaning agent and/or sanitizing agent residue is required for dedicated equipment campaign cleaning or interval cleaning whenever major cleaning is performed. Full cleaning validation is not required for product dedicated equipment if cleaning/sanitizing agents are not utilized; visual examination and microbial testing only will apply. Dedicated equipment includes:

- Equipment used to manufacture one or more strengths of the same product
- Different products or dosage forms with the same active ingredient and excipients

5.19. Contract manufacturers that produce and/or control site products are to use practices that are validated to standards equivalent to those specified in this guideline.

5.20. Prior to introduction of any new cleaning agent an assessment report must address the probable impact on the current equipment cleaning validation plan

8.0 SUPPORT AND CONTROL ACTIVITIES

8.1 Maintaining the Validated State

All cleaning procedures once validated will be maintained in a validated state. Maintaining the validated state will be achieved by change control, re-qualification, training, SOPs, calibration and engineering maintenance programs. Revalidation of the cleaning procedure will be required if any of the following occur:

- Change in cleaning instructions and/or cleaning agent
- Introduction of a new product (if it reduces the worst case limit) or changes to a production process
- Changes to the equipment being cleaned
- Sampling, analytical or microbiological methods
- Number of batches in a campaign
- Maximum time interval between use and cleaning

8.2 New Product Introduction

When a new product is introduced to equipment an assessment is made to determine if cleaning validation is required. If the new product carry over limit is above the previously determined residue carry over limit AND the new product is more soluble than the target component of the previous product then cleaning validation is usually not required. This will be documented in the cleaning validation plan.

8.3 Periodic Evaluation – Cleaning Verification Programs

Each cleaning program should be reviewed on a two yearly basis or in the case of a failure of a critical parameter to assure the procedure remains in a validated state. The review should at minimum include change control documentation and deviation reports. The review should be documented in a report.

Cleaning effectiveness after each cleaning episode will be verified as a minimum via visual inspection of the cleaned equipment and or review of automated cycle printouts. Results must be recorded in batch records

8.4 Training

Training and Qualification in the use of validation sampling (swabbing and rinsate techniques) and analytical methods shall be part of the training record for personnel performing these functions.

Swab recovery must be validated at ≥50% . The recovery value must be used as a correction factor in the calculation of results.

Trained operators will be used for performing a cleaning procedure during the validation program. Their records should document that their training is complete and up to date.

The facility requires a cleaning SOP for each item of manufacturing equipment. These will form the basis of the cleaning procedure for cleaning validation.