VALIDATION OF CLEANING FOR RESEARCH GLASSWARE

The U.S. Food and Drug Administration (FDA) states in its human drug current Good Manufacturing Practices (cGMP) notes for the second quarter of 2001 that it "expects firms to maintain lab equipment in a clean and sanitary manner to provide confidence in the results of analysis." One way to provide this confidence is through a validation program. This Technical Tip covers **validation of the cleaning of glassware used for research purposes** in a pharmaceutical or other regulated manufacturing environments.

It is understood that the term validation for this application carries the same definition as for process validation for any pharmaceutical application (documented evidence with a high degree of assurance that the process consistently makes product achieving its predetermined quality attributes). However, the details of what is required for this cleaning validation are not necessarily the same as those required for cleaning validation of process equipment in a manufacturing setting.

A cookie-cutter approach to cleaning validation, by trying to directly apply the specifics of process equipment cleaning validation to this case, can result in considerable frustration. For example, in establishing what is clean, it is inappropriate to establish limits based on pharmaceutical doses because the glassware is only used for research purposes. On the other hand, principles such as establishing (and justifying) a rugged Standard Operating Procedure (SOP), establishing limits based on sound scientific principles and selecting appropriate sampling methods should be considered for glassware validation.

Specific instructions for cleaning validation in a glassware washing operation are difficult because of different practices and because of different uses of glassware in individual facilities. These guidelines and comments are meant to be suggestive of what may be part of a program to validate glassware washing. These suggestions should only be utilized where it makes good scientific sense based on proper control of critical steps and parameters, and based on the need to appropriately document the process.

The following are key steps to establish a validated glassware washing process for glassware used for research purposes:

1. **Developing a rugged, controlled glassware washing SOP:** This includes selection of the equipment, selection of cycle conditions (such as times, temperatures, detergent, detergent concentration and water quality for wash and rinse), determination of any limitations on loading pattern and drying conditions.
2. **Developing acceptance criteria for what is clean:** This has to be done on a case-by-case basis, and should be based on possible interferences of soils and cleaning agents with the subsequent use of the cleaned glassware.
3. **Developing suitable handling and storage procedures for cleaned glassware:** The key is to have procedures that do not allow recontamination of the glassware before use.

Each of these purposes is presented in more detail below.

Washing Procedure

There are two basic options:

- either clean glassware manually
- clean glassware in an automated glassware washer

It is important to develop a SOP which adequately controls critical washing parameters so that the glassware is consistently clean. For this reason, cleaning in an appropriately controlled automated glassware washer is preferred. For illustration purposes, we use an automated system (although the principles can be applied to manual washing).

Once the automated vs. manual decision is made, a second option involves whether there is one cycle for all glassware or different cycles for different types of glassware (types can refer either to the glassware configuration or to the soil on the glassware). The SOP should include any precleaning, presoaking or prerinsing requirements before loading into the automated glassware washer.

The first step in validation of an automated washer is the Installation Qualification (IQ) and the Operational Qualification (OQ) of the washer itself. Manufacturers of such equipment can assist in the IQ/OQ process. Parameters that then need to be established to operate an automated washer consistently might include:

- loading configuration
- water temperature(s)
- wash water quality
- rinse water quality
- detergent
- detergent concentration
- cycle times (prerinse, wash, rinse)

The **loading configuration** should be defined, with designated racks for specific pieces of glassware. For the validation protocol, the worst-case loading configurations should be addressed.

The **water temperature** used for the wash cycle will affect the cleaning performance. The water temperature used for the rinse cycle may affect rinsing characteristics as well as drying time. Water temperature should be controlled, generally within a ±5°C (±9°F) range. **Water quality** for the wash cycle is typically either:

- tap (potable) water
- softened water
- deionized water

If tap water is used for the washing cycle, care in detergent selection is necessary to verify the cleaning agent has additives to handle the hard water salts that may be present (thus preventing deposition of calcium carbonate, for example). A more pure water, preferably Water for Injection (WFI), is preferred for the final rinse because of the possibility of leaving mineral deposits behind with tap or softened water. It is also preferable that the final rinse be once-through-to-drain (nonrecirculating) to maximize the rinsing performance. For glassware washers, a recirculating rinse is generally less efficient in removing residues dissolved, suspended or emulsified in the cleaning solution.

The **detergent** used should be adequate to effectively clean the soils present under specific washing conditions. It is important that the detergent be selected from a supplier that assures formula integrity. A change in a detergent composition, even one which is an improvement, can call into question the validity of a validated process. The **detergent concentration** should be specified and controlled by the dispensing system within the automated washer. Optionally, different detergent concentrations can be used for different cycles (provided that a mechanism is in place to control selection of cycle parameters so that the wrong concentration is not used).

The most important **cycle parameter** to control is the length of time of the various cycle steps. This includes the time of prerinse, time of washing and time of rinsing. As with detergent concentration, these can vary for different cycles. Other items that should be checked on a regular basis for consistency could include spray pattern variation due to spray nozzle blockage. A system to verify that detergent supply has not been depleted is also helpful.

Cycle development (or the process for arriving at a rugged cleaning process that can be taken forward for validation) can be done in a number of ways. If there is an existing cleaning process that is adequately controlled, it may be possible to write a tentative SOP and proceed to the validation stage. If a new process has to be established, this can best be done by selecting worst-case soil conditions and worst-case load configurations, and then varying cycle parameters to arrive at glassware that is at least consistently visually clean. If there is a representative worst-case soil, such as bovine serum albumin (BSA) to simulate proteinaceous soils, this can be used during the cycle development process. Otherwise, real-life soils should be employed.

Visual cleanliness may not be the ultimate acceptance criteria that is chosen; however, it is probably acceptable as a standard to use during the early stages of cycle development work. During the final phases of cycle development work, the sampling and analytical methods to be used in the validation protocol should be employed to verify acceptable cleaning performance.

Acceptance Criteria

The acceptance criteria for glassware to be used for research purposes should be based on levels of contaminants that could **potentially interfere** with those research purposes. In a research environment, this may be very hard to define, particularly with a central glassware washing operation serving many laboratories. The most practical approach is to establish an acceptance criteria of visual cleanliness ($4\ \mu g/cm^2$ is a generally accepted value for visual cleanliness) for the cleaned glassware processed in the central glassware washing operation. If there are any special requirements for ultraclean glassware for a particular research project, then those requirements can best be handled on an individual basis using special cleaning processes (over and above the routine glassware washing procedure) to meet those special objectives.

Handling and Storage

Once the glassware is cleaned, it is necessary to verify that handling and storage is appropriate to prevent recontamination. This may mean handling with gloved hands only. It also may mean defined shelving, storage containers and/or wraps. This must be specified based on individual circumstances. It is preferable to define the time that cleaned glassware is still clean for use purposes. This may be supported by analytical data (perhaps using the same methods for the validation protocol) after a specified storage time under defined conditions.

General Considerations

The testing which is utilized in the validation protocol generally is not part of the routine monitoring that is done on a regular basis to monitor washing performance. It generally would only be repeated in case of required revalidation and/ or specific troubleshooting because of washing process problems.

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