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Qualification Studies of the Cleanroom for CSP Compounding

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There is increased interest in pharmacy cleanrooms with the recent changes in expectations for sterile compounding. While USP <797> contains a great deal of information on cleanrooms, this was not universally observed for the traditional pharmacist due to variations among the expectations and enforcement policies of different state Boards of Pharmacy. With the establishment of the 503B Outsourcing Facility under the review authority of the FDA the expectations for cleanrooms and their qualification rise to near pharma levels.

The pharmacy, whether a 503 (traditional pharmacy) or 503B (Outsourcing Facility), would be well advised to prepare a written protocol to assist in the cleanroom qualification. The qualification protocol should include a concise statement of the functional requirements for this facility to allow for each of the interested parties to confirm that the "User Requirements" are appropriate and achievable. In addition, the protocol will allow all interested parties to review the proposed evaluations, with their acceptance criteria, prior to initiation of work. As described in cGMP (Anon 2014) and in USP <1163> (USP 2014b), the Quality Assurance Unit should have a central role in this process.

The facility qualification protocol should include:

Facility Considerations

The protocol should have a series of accurate schematics of the cleanroom facility showing the intended uses of each of the rooms. Important aspects to be described in these diagrams also include:

1.A. Air Handling Considerations

It is useful to devote a set of schematics to the air handing system that ideally will include the air balance between different rooms in the cleanroom area, as well as the location of the HEPA filters and which rooms are serviced by which air handling unit (if appropriate).

1.B.Airflow Velocity

USP <797> recommends that airflow velocity of at least 40 ft per minute from the Class 7 areas into the Class 7/8 area set up to serve as a buffer region from the controlled to the uncontrolled environment. cGMP has different expectations for the 503B facilities. FDA has stated that a "... velocity of 0.45 meters/second (90 feet per minute) has generally been established, with a range of plus or minus 20 percent around the setpoint. Higher velocities may be appropriate in operations generating high levels of particulates." (FDA 2004 see Section IV.A.).

1.C. Smoke Studies

Smoke studies to confirm laminar air flow are required by USP <797> which states:

> "In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions."

In other words, part of qualifying the cleanroom is to demonstrate the ability of the cleanroom to maintain laminar flow while people are working in the direct compounding area (DCA). This has long been accepted practice in cGMP.

1.D. Ante-Area/Airlocks

USP <797> (2014) describes the use of an Ante-Area as an area were gowning, hand-washing and staging of components are accomplished. This area also "buffers" different pressure differentials. These functions in cGMP are normally handled by airlocks set up so that only one door can be opened at a time (Anon 2014, FDA 2014). The space within the airlock transitions between the two ISO levels.

1.E. Traffic Patterns

It is useful to include a schematic of the traffic flow patterns in this protocol as well. USP <797> has several requirements related to traffic including location of PEC, and traffic flow control. cGMP is even more stringent on expectations of controlled traffic flow, requiring that stringent controls be placed on the flow of both materials and personnel (FDA 2004; see Section IV.E).

1.F. Water System

Another useful facility schematic depicted the water system (if appropriate – many pharmacies purchase all USP Purified Water and USP Water for Injection). This diagram should indicate the water purification steps, the quality of water in the system and all water drops – both for sampling purposes only and point of use locations.

2. Process Considerations Sufficiency of Facility for Anticipated Workload

The "User Requirements" prepared in support of the cleanroom design should include an estimate of the workload that the cleanrooms will support. The qualification protocol should therefore include consideration of the activity going on in the cleanroom. In addition, the equipment required for various compounding activities must be part of the qualification.

The Microbiology NETWORK

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3. Confirmation of Cleaning Efficacy

Specific SOPs on cleaning of the facility should be prepared prior to the qualification of the cleanroom. These SOPs are required by both USP <797> and cGMP. The purpose of the SOPs should be to confirm that the facility is designed to be easily cleanable, that cleaning occurs at sufficient frequency and using appropriate methods to prepare the facility for sanitization.

The protocol should describe in detail the method of cleaning (perhaps by reference to the SOP) and the response in the event of a failure in the cleaning procedure.

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4. Confirmation of Sanitization Efficacy

Specific SOPs on sanitization of the facility should be prepared prior to the qualification of the cleanroom. These SOPs are required by both USP <797> and cGMP. The purpose of the SOPs should be to provide instruction on how to effectively decontaminate the cleanroom to acceptable levels.

4.A. Sanitization Qualification Study Design

The interested reader is referred to USP chapter <1072> "Disinfectants and Antiseptics" in this regard. While the process described in the informational chapter USP <1072> may not be expected of all 503A pharmacies, some evidence that the cleanrooms are effectively sanitized and are not contaminated is understood.

4.B. Environmental Sampling

This is a primary method to demonstrate the cleanroom is qualified for use and can maintain a state of control. Unfortunately, this is an area where many 503A and 503B facilities have issues. A common understanding is that environmental sampling is required only upon re-certification of hoods. This is erroneous. What <797> actually says in the section "Viable and Nonviable Environmental Sampling (ES) Testing" is

> "The ES program should provide information to staff and leadership to demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptably low viable and nonviable particle levels."

It is not possible to show that the PEC "consistently ensures" a state if only two samples are taken a year.

The cGMP is very clear on this topic for the 503B, and FDA cited issues of inadequate environmental monitoring (sampling) in over 80% of all 483 reports posted (Sutton 2014). Preventative Maintenance / Change Control

Summary

Cleanroom control is a complex undertaking involving multiple systems. Maintaining a state of control requires effective monitoring systems (for example perhaps gauges and alarms for air balance, sampling for water and environment) and appropriate responses when the system is trending out of control. The qualification of the cleanroom is essential to show the facility's ability to function under these expectations. The time taken to plan how the facility will meet the expectations of a modern pharmacy and to prepare a relevant qualification protocol will be well rewarded.

References

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