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Contamination Control In and Out of the Cleanroom: Contamination Control and CGMP

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Controlling the fabrication environment is not an end in itself. Manufacturers who process and assemble their product in controlled environments know that the clean-room or mini-environment must be appropriately designed and must also be maintained clean and contamination free. However, cleanliness of the product itself is the ultimate goal. This goal applies whether the application is from aerospace, military, medical device, pharmaceutical, or other disciplines.

Much can be modeled from those who process pharmaceuticals. High standards, many with the force of law, govern pharmaceutical and medical device production. The U.S. Food and Drug Administration (FDA) issues ever-increasing regulations to control the processes by which pharmaceuticals are manufactured and packaged. The regulations that appear in Title 21 of the Code of Federal Regulations, Section 210 (21CFR210) and in subsequent sections are referred to as Current Good Manufacturing Processes (cGMP). The word "current" emphasizes that knowledge of processes evolves and that a process that was "golden" 20 years ago may not be acceptable today. Similar medical device regulations are defined in other sections of 21CFR. Even those not governed by pharmaceutical or medical device requirements would profit by becoming familiar with the principles of cGMP practices.

CGMP HISTORY

The first GMP regulations from the FDA appeared back in 1963. A major revision in 1978 produced most of the regulatory language in use today. An axiom is that good manufacturing processes be documented and validated. Validation is defined as:

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." 1

In 2002, the FDA announced an initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulations. A key aspect of this initiative is to adopt risk management approaches in quality management systems. We have previously discussed the risk management approach for validating cleanliness of medical devices.2

Risk management inherently involves process understanding; so rather than being an expense, risk management can enhance productivity and profitability. In a report generated as a result of the initiative, the FDA states:

"Quality and productivity improvement share a common element — reduction in variability through process understanding (e.g., application of knowledge throughout the product lifecycle). Reducing variability provides a win-win opportunity from both public health and industry perspectives." 3

CROSS CONTAMINATION

The recall of a pharmaceutical product due to cross-contamination led to increased FDA awareness of the importance of validation and control of cleaning procedures.4 Drums containing recycled solvent used for pharmaceutical production had previously been used for solvent recycled from pesticide manufacturing. As a result of inadequate cleaning procedures for the drums, pesticide residues were inadvertently transferred to the pharmaceutical product. The example also illustrates

the need for well-documented acceptance and monitoring programs for process chemicals and storage containers.

SUPPLY CHAIN INTEGRATION

The incident involving cross contamination of drums brings to mind the need to control and monitor activities of the entire production supply chain. Manufacturers must be confident that raw materials, process chemicals, biologics, and components provided by suppliers are appropriately processed, packaged, and stored. Sub-vendor and supplier processes and certifications must be documented. Requirements, acceptance criteria, and audit policies and findings must be both available and supportable. As noted previously, if suppliers use commercial cleaners, formulations may change without notice or documentation. Such changes can compromise efficacy of cleaning 5 and adversely impact performance of the assembled product.

IQOQPQ

The concept of IQOQPQ (Installation Qualification, Operation Qualification, Performance Qualification) is often part of cGMP. IQOQPQ is employed to verify and validate process equipment. Installation Qualification (IQ) involves verifying that equipment is installed according to manufacturer specifications (i.e., the wiring is hooked up correctly). Operation Qualification (OQ) verifies that the equipment operates to manufacturer specifications (i.e., it does what the spec sheet says it should do). Maintaining equipment calibration is an aspect of OQ. However, correct installation and operation does not insure that the best or even suitable equipment has been selected for the task. Performance Qualification (PQ) verifies that not only is the equipment performing but that the process is working. Analytical testing may be required to verify that the product is sufficiently clean.

PROFITABLE CGMP

To achieve efficiency, quality, and profitability, cGMP should not be tacked on as a list of rules for assembler training; cGMP should not be implemented in a pro forma manner. Profitable cGMP involves understanding the process. Achieving profitable cGMP can require a paradigm shift. A developer of cGMP training programs in Ireland says,

“It is difficult to make workers aware of contamination issues. The hardest job is changing their attitudes and behaviors. A program that just presents ‘how to’ will not be as effective as one that also discusses ‘why.’ It is very important that all aspects of GMP are supported from the top management through to the workforce on the ground. It is a culture that should be planted and maintained throughout the business. A high standard of GMP should be not be an ‘extra’ part of the working day but should be part of the work ethic of all personnel.” 6

Quality management is a crucial part of the manufacturing process. The receiver of a manufactured item, your customer, performs their own version of IQ and OQ. As a manufacturer, it is your responsibility to insure that for your customer there will be no surprises either on incoming inspection or in subsequent utilization. By incorporating cGMP as part of the work ethic, you can minimize the occurrence of such surprises and quickly resolve any that happen.

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