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Deciphering The Regulations For Facility Design and Environmental Control

Wai Wong

With the FDA under fire in recent years regarding the quality of inspections, the effect on biotech, pharmaceutical, and medical device companies has been to err on the safe side of regulatory requirements by proving more evidence wherever they can. While this is a logical reaction, there is a risk that companies may be placing extra burdens on facilities, operations, and quality control departments. As companies seek to attain the high standards set by the FDA and associated agencies, how can they be sure they are solving the right problem?

What is the best way to decipher the guidelines from the FDA with respect to controlled environments, specifically 21 CFR Parts 210, 211, and 820? To assist with the thought process, I would like to explore that question through the example of real world facilities, taking a closer look at the requirements for design, monitoring, and control and how they relate to the product being manufactured or processed.

In some cases, facilities have been designed to a higher classification than required and facilities and operations departments are asked to operate and maintain their facilities according to strict ISO guidelines. Quality Assurance departments are asked to translate, impose, monitor, and enforce general guidelines provided by the FDA to ensure their companies have a speedy and 483-free inspection.

First, let's refer to the Code of Regulations (CFR) associated with controlled environments within the biotech, pharmaceutical, and medical device industries, in particular 21 CFR Parts 211.42, 211.46, and 820.130. 21 CFR Part 211.42 contains guidelines for the design and construction of the facility with respect to operations within the facility, while 21 CFR Part 211.46 focuses solely on the Heating, Ventilation, and Air Conditioning (HVAC) design. 21 CFR 820.130 pertains to the packaging of medical devices.

The key is to focus on the products and the processes that are being performed in the facility. This approach allows us to solve the issue of what is required for the facility and product rather than follow non-specific guidelines that may have no bearing.

Let's look deeper at this issue through the example of two different facilities. The first concerns the packaging area for a Class III drug-eluting stent that has already been sterilized and sealed; the second is a final assembly manufacturing area for a sterile drug product in pre-filled drug cartridges.

Determining the environmental conditions required for the packaging area of a drug-eluting stent can be done by first clarifying how the product will be handled. In this example, the stents are classified as a Class III medical device. As part of their

manufacturing process, the stents are sterilized and sealed in previous manufacturing steps in ISO Class 5 cleanrooms prior to being moved into other areas for final inspection and packaging. Class III Medical devices require this stringent environment for manufacturing as they are typically used for life-supporting or life-sustaining applications. Other examples of Class III devices are heart valves, pacemakers, and other implants. Ten percent of medical devices fall under the Class III category.

In many instances, one may think that the packaging area for these stents would be classified to ISO 8 standards at minimum, due to the strict environmental requirements for manufacturing. Or, companies may want to show their processes and products are under control by demonstrating a clean facility at a higher standard. However, when looking at 21 CFR 211.46 and 21 CFR 820.130, the regulations show that the manufacturer needs to ensure that the device is not damaged or altered from the packaging. In this case, the ventilation systems should be sufficient for manufacturing purposes only. The regulations do not specifically state that the packaging area for these stents needs to be controlled and classified at ISO 8. Yet if we take a risk-based approach, we see that as long as the stents are manufactured and coated in ISO Class 5 cleanrooms, they can be packaged in a controlled, unclassified area without affecting the product. Not only does this allow for a less stringent environment that costs less money and immobilizes fewer resources, it reduces the amount of monitoring and procedures surrounding the upkeep of the more rigorous requirements.

As a controlled unclassified facility, the company may choose to design their facility to meet ISO 8 standards with respect to layout, design, and “cleanability” as described in 21 CFR 211.42. However, to reduce cost, the company can choose not to purchase HEPA filters for use with their HVAC systems. Instead, terminal non-shedding bag filters can be purchased to reduce particulates in the environment. Since there are no particulate requirements, there are no acceptance criteria to meet. To prove to the FDA and other agencies that the company understands the environmental conditions, commissioning and/or validation of the HVAC systems should be performed to get baseline data. After the initial baseline data are collected, environmental monitoring should be performed periodically to ensure that conditions have not changed and to check on the overall performance of the equipment over time. With this approach, the company can assure the FDA and other agencies that their facility is in control and is kept under control by operational and preventive maintenance standard operating procedures (SOP).

The problem is different in the case of the company designing a final assembly manufacturing area for a sterile drug product. The drug, although sterile filtered, filled, and then sterilized, is completely enclosed and will not be manipulated other than as a step of the final assembly of the drug cartridge into the device. The device is categorized as Class II: 43% of medical devices fall under this classification. Examples of Class II devices are x-ray machines, surgical needles, and suture material, and the regulations are less restrictive with respect to the product. What should this company design this facility to conform to? Does the fact that the device is categorized as Class II affect the facility design and environmental conditions for the manufacturing area?

Again, we look at what processes are to take place in the room. In this case, final assembly of the drugdevice product will occur but no exposure of the sterile product will occur in the environment. If final assembly does not alter the drug in any way, we look to meeting the requirements of 21 CFR 211.46 and 21 CFR 820.130. As above, the main

focus of the company should be to design the facility to meet FDA requirements. If the company is able to prove that the drug will not be altered by the facility or the environment, then it can follow the same rationale that I described above to design, operate, and maintain its facility.

Companies should adopt a risk-based approach to the design, validation, operation, and maintenance of facilities based on the product and processes that occur there. Rather than taking the ultra conservative approach and guessing what the FDA will want when they inspect their facility, the companies themselves should demonstrate what their requirements are for the product they are manufacturing and prove that their processes are well defined and in control. A well-designed facility that is properly maintained and supported with sufficient data to prove the stability of the control and maintenance of the environment will result in an easily defendable regulatory position with no warning letters.

FOR REFERENCE:

21 CFR 211.42 – Design and construction features

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix ups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
(2) Holding rejected components, drug product containers, closures, and labeling before disposition;
(3) Storage of released components, drug product containers, closures, and labeling;
(4) Storage of in-process materials;
(5) Manufacturing and processing operations;
(6) Packaging and labeling operations;
(7) Quarantine storage before release of drug products;
(8) Storage of drug products after release;
(9) Control and laboratory operations;
(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
(ii) Temperature and humidity controls;
(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
(iv) A system for monitoring environmental conditions;
(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
(vi) A system for maintaining any equipment used to control the aseptic conditions.

21 CFR 211.46 – Ventilation, air filtration, air heating and cooling

(a) Adequate ventilation shall be provided.
(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.
(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

Subpart K – 21 CFR 820.130 – Device packaging
Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

Direct Links:

-21 CFR 211: Title 21 – Food and Drugs Chapter 1 – Food and Drug Administration Department of Health and Human Services Subchapter C – Drugs: General

-Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211 [1]

-21 CFR 211: Title 21 – Food and Drugs Chapter 1 – Food and Drug Administration Department of Health and Human Services Subchapter H – Medical Devices

-Part 820 Quality System Regulation
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820 [2]

Wai Wong *is the Vice President and General Manager of Pharmatech Associates, Inc. Mr. Wong has worked in the life sciences industry for over 15 years, starting with Genentech as an aseptic filling technician. He has held positions as project lead, validation manager, and West Coast regional manager. A Six Sigma Green Belt, he manages FMEA, Commissioning, Validation, and consulting projects at numerous client sites.*

Links:
[1] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
[2] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820