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Points To Consider in the Application of Quality System Requirements to Medical Devices Intended for Use In Clinical Testing

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Introduction

Not all medical devices require clinical investigation in order to demonstrate their safety and efficacy. But, even for some class II medical devices that can be cleared by the Food and Drug Administration (FDA) through the 510(k) process, some degree of clinical testing may be required. Design validation is intended to demonstrate that the medical device design meets user needs, and sometimes the use of the product cannot be adequately simulated in a laboratory environment.

When testing in a laboratory environment cannot simulate actual clinical use of the product, design validation will include clinical investigation or some degree of clinical evaluation involving human subjects. In some cases, feasibility testing of a device on a limited number of human subjects may be necessary as part of fundamental research and development. This testing may not support design validation, but rather determines technical feasibility and becomes design input for establishing design requirements. Regardless of when testing with human subjects is performed, Good Clinical Practices (GCPs) must be applied and the manufacturer must comply with all relevant parts of the regulation (i.e., 21 Code of Federal Regulations (CFR) Parts 50, 52, 54, and 812.)

What Devices May Be Subject to Clinical Investigation?

Devices that may be subject to comprehensive clinical investigation or more limited clinical evaluations include:

- Devices for which FDA's Office of Device Evaluation requires clinical data to support a 510(k) or a Pre-Market Approval (PMA) submission prior to marketing.
- Those devices meeting the definition of "significant risk."
- Unapproved devices for which clinical comparisons between the unapproved device and an approved

device must be made for marketing purposes and where the comparison involves a human subject in a clinical environment.

The terms "*clinical investigation*," "*clinical trial*," and "*clinical evaluation*" are all commonly used by industry and appear throughout this article. FDA and international regulatory bodies generally apply the term "investigation," which is defined as "research involving one or more subjects," to determine the safety or effectiveness of a device. The term "*clinical trial*" implies a complex clinical investigation, such as one involving multiple sites, large numbers of subjects, or one for a product that requires an Investigational Device Exemption (IDE), in accordance with 21 CFR § 812.2. The term "*clinical evaluation*," for the purpose of this discussion, refers to a more limited test or evaluation done to verify or validate a specific device function that requires human testing. Evaluations may not involve the large numbers of patients or sites necessary to provide statistical significance or demographic variability that is necessary for a typical clinical trial.

Manufacturing Considerations for Devices to Support Clinical Testing

The following points should be considered when determining the type of control to be applied to the development, manufacture, and test of medical devices prior to their use in clinical testing. It is the responsibility of all manufacturers to apply the necessary controls to protect patients and users during the important design validation phase of product development. The FDA has established expectations regarding the use of devices in clinical trials.

The following excerpts from FDA regulations and FDA guidances provide a brief overview of the quality system requirements and design controls that manufacturers must consider when planning for device clinical trials. This is not intended to provide a description of the activities required to plan, perform, and monitor clinical trials, but rather provides an overview of expectations for the manufacturing and design controls that must be applied to devices that are used to perform these trials.

Investigational Device Exemption (IDE) and Design Control

IDE Regulations (21 CFR 812) require that medical device manufacturers comply with Design Control Regulation (21 CFR 820.30). The following is a quote from FDA's Medical Device Quality Systems Manual: A Small Entity Compliance Guide:

"Where [clinical evaluation] is needed, such as for complex substantially equivalent devices or new devices, clinical testing on humans should meet the applicable requirements in the Investigational Device Exemption (IDE) regulations (21 CFR Parts 812 and 813).

The general, IDE regulation (21 CFR Part 812) exempts a manufacturer during the "premarketing phase" from the following provisions of the Food, Drug, and Cosmetic (FD&C) Act [emphasis added]:

- *Misbranding*
- *Registration of the Establishment*
- *Pre-market Notification [510(k)]*
- *FDA Performance Standards*
- *Pre-market Approval*
- ***Production sections ONLY** of the Good Manufacturing Practices*
- *Color Additives*
- *Banned Devices*
- *Restricted Devices*

*Do not be misled by this list of exemptions -- being exempted from these provisions**does not mean that a manufacturer may develop a new device under uncontrolled conditions and then test it on humans** . Devices being clinically tested are not exempt from section 501(c) of the FD&C Act,**which states that a device is adulterated if it does not meet a manufacturer's quality claims**. Devices being manufactured for*

*use in clinical studies under an IDE are exempt ONLY from the production section of the Quality System (QS) regulation.**They are not exempt from design controls listed in 820.30. In addition, the IDE regulation has labeling requirements in 812.5 and quality assurance requirements in 812.20(b)(3) that shall be met.** Further, manufacturers should remember that human subjects are also protected through the courts via product liability laws and actions. In summation, protection of manufacturer interests, human test subjects, practitioners, and patients requires that all medical devices be developed, evaluated, and manufactured under a total quality system."*

In further support of this…the preamble 21 CFR 820 published in the Federal Register: October 7, 1996 (Volume 61, Number 195) states:

"FDA believes that it is reasonable to expect manufacturers who design medical devices to develop the designs in conformance with design control requirements and that adhering to such requirements is necessary to adequately protect the public from potentially harmful devices. The design control requirements are basic controls needed to ensure that the device being designed will perform as intended when produced for commercial distribution. **Clinical evaluation is an important aspect of the design verification and validation process during the design and development of the device. Because some of the device design occurs during the IDE stage, it is logical that manufacturers who intend to commercially produce the device follow design control procedures.** Were a manufacturer to wait until all the IDE studies were complete, it would be too late to take advantage of the design control process, and the manufacturer would not be able to fulfill the requirements of the quality system regulation for that device."

Investigational Device Exemption (IDE) and Production Controls

The IDE regulation exempts manufacturers from production sections of the Quality System Regulation; however, sufficient controls must be applied to ensure clinical devices are free from unacceptable risk. The IDE regulations require that the IDE application include a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device. Although there is an exemption from the production section, the manufacture must apply an adequate degree of control to ensure the quality of the device. Exemption from the "production section" of Good Manufacturing Practice (GMP) is not intended to give manufacturers freedom from considering and controlling those aspects of the production that would directly impact product safety.

What Are the Production Sections that a Manufacturer Must Meet?

To a great extent, the answer depends on the device itself and the controls that would be necessary to ensure the device is **reasonably safe**. For example, if the device is intended to be sterile, then contamination controls, environmental controls, and personnel controls (such as health, cleanliness, and proper gowning) would be applicable, because without them, product sterility may be compromised - which impacts product safety. The production control section includes requirements for contamination control, environmental control, and personnel cleanliness. These controls collectively contribute to preventing contamination of production equipment or product that could have an adverse effect on product quality. The 812 exemption is not intended to allow a manufacturer to disregard any specific controls that might be necessary to ensure the product is safe. The manufacturer will have to describe the controls that were employed in the IDE application to satisfy the FDA's concerns regarding product safety prior to initiating a clinical trial.

When considering the production and process controls that should be applied when producing clinical trial materials, it is important to consider that any testing data that is intended to release materials for clinical or other applications or is intended to support design verification or design validation must be obtained using inspection, measure, and test instruments that are calibrated and properly maintained. Any test methods or analytical methods used in testing must be validated prior to use, or the test data will have no integrity and cannot be trusted as being accurate and precise. Testing data collected via uncontrolled and un-validated

methods will not be accepted by FDA.

The degree and type of production controls applied during production of clinical trial materials should be commensurate with risk. Where the lack of a particular control increases the potential for a failure that is associated with a high degree of risk, that control should not be arbitrarily disregarded or overlooked based on the 812 exemption. Process risk analysis using methods such as Process Failure Modes Effects Analysis (FMEA) can be helpful in identifying and justifying those aspects of production that require control in order to minimize risk. This is one argument for executing process FMEAs early in the product development lifecycle as opposed to later. It is important to determine which aspects of production control may impact the safety of the clinical trial materials and to determine the extent of control necessary to reduce risk. The design plans developed as part of design control should specify what activities will be done prior to production of clinical trial materials to minimize risk of product defects that may render the device unsafe.

It is important to note that if the production sections only have exemption, then a firm conducting medical device clinical investigations under IDE must still comply with the following parts of the quality system regulation program:

- Quality System Requirements for Management Responsibility, Audits, and Personnel
- Design Control
- Document Controls (including Change Control)
- Purchasing Controls
- Identification and Traceability
- Acceptance Activities
- Nonconforming Product
- Corrective and Preventive Action
- Labeling and Packaging Control
- Handling Storage and Distribution
- Records
- Servicing
- Statistical Techniques

Process Validation Considerations when Manufacturing Devices for Clinical Testing

Producing devices for clinical testing does not require a validated manufacturing process, but it is reasonable to expect the equipment used in production to have been properly installed and capable of operating as intended. The exemption from the “production section” of the GMP stated in 21 CFR Part 812 would allow a manufacturer to develop devices to support clinical testing without necessarily having completed validation of the manufacturing processes. This is an important exemption for manufacturers, because it might be difficult to complete process validation studies using a statistically appropriate number of batches manufactured at full scale when only a small, limited number of devices are necessary to meet clinical trial supply demands.

Because process validation is resource intensive and costly, manufacturers may not have completed their process optimization studies and may not have completed performance or Process Qualification (PQ) runs at the time materials are needed for clinical trial. However, it would be expected that at the time the manufacturing equipment used to produce clinical trail materials was installed, it was subject to Installation Qualification (IQ) and some degree of Operational Qualification (OQ) to ensure proper installation and that basic functional requirements have been met. IQ activities in particular should be done AT THE TIME OF INSTALL ATION not later, regardless of the fact that full scale production runs may be many months down the road.

In some cases, the degree or extent of quality control testing for devices intended for clinical testing may need to be greater than what would be employed during commercial production to compensate for lack of process control provided via process validation. In other words, there is increased reliance on quality control

in the absence of quality assurance provided by having fully optimized and validated processes.

The Use of Actual Production Units vs. "Equivalent" Units

Clinical trials are performed in order to ensure that a device conforms to defined user needs and intended uses. Clinical trials for medical devices are considered by FDA to be an integral part of design validation (see quote above from Preamble 21 CFR 820, October 7, 1996).

“The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices” state:

*“Proper design validation cannot occur without following**all the requirements** set forth in the design control section of the regulation.*

The design control regulation requires that design validation (such as clinical trials and/or simulated use testing) be done using actual production units, lots, or batches, or their equivalents.

An “actual production unit” is one that is manufactured following all requirements of the Quality System Regulation (21 CFR 820), which describes Good Manufacturing Practices (GMPs). An “actual production unit” intended for use in design validation would be manufactured using the same methods, processes, materials, facilities, equipment and personnel that would be used to manufacture devices intended for commercial distribution. An actual production unit is, manufactured under GMP (since only GMP units can be commercially distributed.) Although there is no good published description of “actual production units,” industry generally accepts this description.

In some cases, it is necessary to produce “clinical batches” for use in clinical evaluation before completing all design transfer activities and before all the process validations are done. In other words, there is an option to use devices that are not “actual production units” for design validation; however, there are many requirements that must be met if this path is chosen. If actual production devices will not be used, then the manufacturer must later show that the devices used for clinical evaluation are “equivalent” to actual production units. This is more complicated than it sounds. In addition to providing a sound, risk-based rationale for this decision in design plans, validation, and clinical protocols, the manufacturer must later perform an “Equivalency Study” to demonstrate and provide documented evidence that the devices used in clinical studies are equivalent to the actual production units to be marketed post design transfer.

If the devices used in clinical testing were not **at a minimum:**

- manufactured under well-documented conditions (intentionally avoiding the term “GMP” here)
- manufactured with calibrated and controlled equipment and tested via validated test methods, using properly calibrated and qualified test instruments
- manufactured by properly trained personnel
- manufactured within a controlled environment

Then, it would be difficult to show equivalency. Without good documentation to demonstrate what specific controls were applied during production of the clinical materials, a manufacturer would not have documented evidence to facilitate comparison of the production conditions of the clinical materials to the conditions ultimately applied to the actual production units. For example, you could not compare functional testing and performance data of the clinical batches to the actual production batches if the data for the clinical batches was not obtained via calibrated instruments and validated test methods. Without calibration, the data obtained from the equipment and instruments has no integrity. The basic QC functional and performance data would be absolutely meaningless if they were not collected under controlled conditions.

Bibliography

- 21 CFR Part 812
- 21 CFR Part 820
- The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices," compiled by Kim Trautman. ASQ Press, 1996
- Medical Device Quality Systems Manual: A Small Entity Compliance Guide, First Edition, FDA/CDRH , 1996.
- Preamble to 21 CFR 820 published in the Federal Register: October 7, 1996 (Volume 61, Number 195).

Also See:

JVT: Validation of a Cleaning Process for Medical Devices
JVT: Verification and Validation for Use in the Medical Device Industry

Tags:
GMP - Medical Devices, GCP

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