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Guide to Inspections of Medical Device Manufacturers
December 1997

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7. **Process Validation - 21 CFR 820.75**
   The QS/GMP does not require the validation of all manufacturing processes. Before inspecting a manufacturing process for process validation, it is important to determine if the results of the process cannot be fully verified by subsequent inspection and test. The lack of a subsequent inspection and test should be stated in the EIR along with any process validation issues.

   Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

   Prospective process validation is validation conducted prior to the distribution of either a new product, or a product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

   Retrospective process validation is validation of a process for a product already in distribution based upon accumulated production, testing and control data.

   Generally, process validation is a pre-production activity. Prospective validation includes considerations made before a new product is introduced, or when there is a manufacturing process change which may affect the product's characteristics. The validation program must be planned and documented, and the validation results must be documented and maintained.

Installation qualification should be conducted for equipment used in a validated process to assure that the equipment has been properly installed, meets the device manufacturer's specifications and requirements for it, and is capable of operating in the range required for the process being validated.

During installation qualification, equipment maintenance and calibration schedules and procedures should be established. Equipment should be calibrated before and after process validation to determine whether the equipment remained in calibration during the entire process validation study.

If the equipment is found to be out of calibration at the end of the study, the validity of the results is called into question. Installation qualification does not have to be performed again if it was recently done for a previous validation. When equipment is moved, a new installation qualification should be performed.

The requirement for equipment qualification can be traced back to 820.70(g). Installation qualification is essential for successful process validation.

The process must be developed before it can be validated. From time to time we see manufacturers who try to validate processes before they have completely developed them and established process parameters. It is impossible to validate a process (i.e. show that it consistently operates within established parameters and produces results or products that meet specifications) until the process is fully developed, and appropriate parameters have been established. The requirement to develop the process can be traced back to 820.70(a). It is important to remember that validation is dynamic and specifications and parameters may be changed as a result of the validation efforts. These changes would need to be validated.

Finally, the product should be qualified. In other words, the product produced by the validated process should be checked to determine whether the process has had any adverse effect on the product or its performance.

For example, radiation sterilization may result in degradation of plastic devices which can lead to premature failure. Or, certain product specifications may have been changed to make the product easier or less expensive to manufacture, but these changes may adversely affect product performance. Product qualification for process validation may take place during design validation.

Retrospective process validation may be used, if adequate, for products which may have been on the market without sufficient pre-production process validation. Extensive review of manufacturing and assembly process data, along with product testing, may be used as a type of validation for devices manufactured individually or on a one time basis.

Validation should be performed (as applicable) for processes such as sterilization operations

(steam, dry heat, ETO, radiation, filtration, aseptic fill), manufacturing operations (lyophilization, molding, soldering, machining, blending/mixing, water purification systems), environmental control systems (clean rooms and laminar air flow units), test methodology, and packaging/labeling operations.

Determination should be made as to whether the firm's processes are or may be contributing to defective devices. There are several ways of making this assessment, for example;

a. Process validation information should be reviewed to identify defect characteristics and rate of expected defects of each characteristic for the finished product. If the rate of defects are found to be exceeded during in-process or finished device acceptance, the process(es) may be out-of-control or were not properly validated.
b. Review first and last article test results for continuous processes such as extrusion or injection molding, automated soldering, automated filling lines, automated testing, etc. which may show test failures of the last test article.

If a last article test was found out-of-specification and the firm accepted the products produced within the bracketed period, the firm may be accepting out-of-specification product for further manufacturing or distribution. Refer to the section of this guide on nonconforming product for guidance on inspecting product concessions.

The testing of the first and last article is to bracket a processing period to show the first and last article and all articles produced between the two tests met specification. If last article failures are found, the process may not be capable of operating in a steady state of control for the time period between the first and last article testing. Process validation, equipment control parameters, environmental (temperature and humidity) controls and condition of components (temperature and moisture content) should be questioned.

The inspection must determine whether adequate prospective or retrospective validation of the manufacturing process has been performed. Validation must ensure the quality of the product will be maintained if the process is controlled within established parameters and that the validation, either prospective or retrospective, has addressed the limits of these parameters.

The firm should be able to document they can control the process within their established limits, e.g. the high and low process parameters should be tested to determine whether the process can be controlled at these limits and whether the product will still meet specifications if the process is operated at these limits. Note: It is not necessary for the firm to run the process at the high and low limits for each of the validation runs. They do need to be able to show that operating the system within the established limits will produce acceptable product. Operating the process at established limits is a form of stress testing. Stressing the system does not require causing the system to fail.

Pay attention to the process parameters: temperature, humidity, tensile strength, viscosity; verify the manufacturer has included all the necessary parameters in the processing procedures. Validation, depending on the scope of the operation, can cover all aspects from the selection of components to various manufacturing processes to end-product testing.

There are special documentation requirements for validated processes. In particular, documentation is required to show what equipment what used in the process validation efforts to assure that equipment routinely used in production is the same as the equipment used in the process validation study for that process. Changes in equipment are cause for revalidating the process.

Operators of validated processes should be documented to facilitate checks to assure that operators are qualified to operate validated processes.

All operators should be qualified for their work, but because the results of validated processes need not be fully verified, the need for qualified operators is especially important to assure that validated processes are properly conducted and controlled and produce results or products that meet specifications.

Review and evaluation of process changes and deviations should be documented to show whether revalidation is necessary and if not, why not. It is important to remember that the manufacturer needs to maintain a validated state. Any change to the process, including changes in procedures, equipment, personnel, etc. needs to be evaluated to determine the extent of revalidation necessary to assure the manufacturer that they still have a validated process.

As noted above, QS/GMP regulations do not require all medical device manufacturing processes to be validated Per 21 CFR 820.75. However, where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated. Questions regarding whether a process needs to be validated can be directed to CDRH/Office of Compliance or via the ORA Banyan mailbox: validation@deio@fdaorahq.

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