Q&A Session with the FDA

This document summarizes the Ask the FDA / Q&A Session from the FDA Validation Workshop held on October 6, 2011 at the Crystal Gateway Marriott in Arlington, Virginia.

What is Process Validation?

Process Validation means establishing by objective evidence that a process consistently produces a result or HCT/P meeting its predetermined specifications (§1271.3(kk)). Validation is performed before a process is used to manufacture HCT/Ps.

In validating a process, the process must be performed according to the protocol and containing all the steps of the protocol even if some steps are not required on all occasions, (i.e., iris removal). For the FDA, the importance of the validation is to determine the steps of the process do not lead to opportunities for contamination or cross contamination.

Is validation of refrigerator storage conditions required? (Follow up to discussion regarding temperature control inside the refrigerator, as required by 1271.260.)

No – Storage is not part of processing. It is good to qualify the equipment to ensure proper functioning (e.g., routine temperature monitoring with alarm recommended), but not validation. Also, check your policies and EBAA standards.

Under 1271.200(c), manufacturers must routinely calibrate an instrument used to monitor the temperature of an HCT/P storage unit.

Is monitoring pH changes of preservation media part of validation?

Monitoring pH changes is not necessarily part of validation processing per se, but a best practice for receipt of media and its subsequent use. Media should be checked for pH changes as part of the acceptance criteria for storage media and tissue in storage media should not be accepted if the pH change falls outside the acceptable parameters. Checking the pH by examination for color changes is a safeguard for bacterial contamination.

Monitoring pH change or assuring a certain pH range is a manufacturer’s responsibility in processing. Eye Banks should only have such responsibility if they produce their own storage media and pH is a storage factor.
What steps is the FDA taking to standardize inspections?

New investigators receive initial training, shadow senior inspectors, and take classroom courses according to the compliance program. The FDA is aware of inconsistencies and welcomes feedback. They cannot fix the situation if they are unaware. If a bank has information about inequality in inspections, they could provide this information (with any appropriate supporting documentation), to the district office of the district in which they are located, at minimum. Additionally, the bank could copy the district's regional office and/or CBER/Office of Compliance and Biologics Quality/Division of Inspections and Surveillance.

If a district decides a compliance action may be appropriate, additional review by the Compliance Branch will likely occur. If additional review by the district’s compliance branch results in a recommendation for a compliance action, the recommendation will receive multiple layers of review by CBER prior to any action being taken."

Is FDA going to require all processing facilities to perform bacteriostasis & fungistasis (B&F) testing?

B&F testing is not performed as a validation of processes, but is done to validate the microbiological method used. Bacteriostasis and fungistasis is a form of microbiologic testing that assures the culture methods used are adequate to recover microorganisms under the conditions which may be present in a sample which could inhibit growth, (i.e., antibiotics in storage media). Unlike sterility testing which determines log reduction of organisms by disinfection or removal techniques, B & F testing is often a component of sterility testing but sterility testing of processing in eye banking may not necessarily be required. Bacteriostasis and fungistasis establishes a method/dilution or neutralization procedure for the effective recovery of organisms from a given source.

Once a registered testing laboratory has done B&F testing on Optisol GS, they may provide that documentation to you. However, the bank must still perform their own process validation, to prove that their own equipment, environment, and personnel do not contribute to contamination and cross-contamination of the tissue.

Does the cleaning of durable instruments and equipment need to be validated?

There are no specific requirements for cleaning validation. There are requirements under 1271.200 for cleaning equipment /sterilizing instruments which need to be documented and followed, according to the manufacturer’s recommendations for the products/equipment used.

Do we need to validate sterilization?

The bank will need to document sterilization of instrumentation where sterility is necessary. You must provide documentation of how sterility is assured. This may require validation or require documentation of how the sterilizing agency has validated the sterility.
Do computer programs need to be validated?

You must validate any computer program that is used to make suitability decisions, but not if it only stores information.

The bank only needs to verify the performance of the commercial computer software used to make donor eligibility determinations if used off-the-shelf, without customization or modification.

Do we need to validate the aliquoting of reagents?

Yes, the bank must validate the aliquoting of reagents if the reagent is used in processing. Aliquoting of reagents must assure the sterility of the reagent if sterility is required. Using pre-made solutions simplifies this question especially where povidone iodine is involved, as a neutralization step would be necessary as part of validation.

Please discuss temperature and humidity controls for LFHs and clean rooms.

Humidity is not required to be controlled in a clean room setting except for personnel comfort and to decrease static electricity and minimize shedding and mold. Most HVAC systems will control humidity.

LFHs provide their own controlled environment, and do not require temperature & humidity controls. Banks may choose to investigate this if they have a contamination issue.

Is culturing of tissue a necessary part of process validation, since we know that there is no correlation between eye bank and surgical cultures?

The FDA recognizes that corneas are not sterile, but there is no other way to validate, unless the bank cultures before and after processing for the validation study. The bank can use this information to identify problems in the processing steps and address the appropriate corrections.

The requirement for validation has been in place since 1993. However, the culturing of tissue is only required for process validation, not for retrieval and storage, and not as a routine practice.

Could corneas be irradiated and then inoculated with bacteria and fungi as part of the validation methodology?

This would not conform to actual practice, unless you provide irradiated corneas. Even then, the bank would need to validate their normal procedures in addition to the validation of irradiation of corneas. Irradiation affects some structural components which then could alter the microorganism growth potential.

Spiking studies are NOT generally recommended, due to the potential of contamination of the hood or clean room.
Could the bank use a risk benefit approach?

The FDA follows a risk based approach in 1271 Standards. That’s why corneas as a non-sterile tissue with a low rate of infectious problems is held to a different standard compared with devices, drugs, and some tissues, except as related to communicable diseases.

How do FDA inspectors determine the appropriateness of a validation study?

The FDA does not tell eye banks how to validate, only when they must validate. CBER is involved in training of field investigators on validation, and they have resources at CBER if there are questions.

CBER reviews any actions which rise to a level above a Form 483.

Do all eye bank employees doing processing have to be involved in the validation?

No – All employees should be involved in competency training for procedures they perform. That competency training should involve culturing corneas if they perform any procedures requiring cultures for contamination or cross-contamination or if they will perform validation procedures. Not every employee is required to participate in the validation processes. (MS C2.000 – Training, Certification and Competency Reviews of Personnel)

What is the frequency of revalidation?

There is no need to revalidate unless there are changes to an eye bank’s procedures. Over time, there can be drift, so it is wise to revalidate if a significant amount of time has passed (i.e., 8 years).

For environmental monitoring, the bank must begin with frequent testing until a baseline/frame of reference has been established. Then the bank can reduce testing, as indicated by these results.

What are validated microbial methods?

It is recommended that eye banks utilize a laboratory that is familiar with the culturing of allograft tissue and uses established and published methods. The best source for eye banks is USP Chapter <71> Sterility Tests, which contains relevant information including bacteriostasis and fungistasis testing, or FDA CFR part 600.

Is an eye bank required to use an FDA registered and approved microbiological laboratory for validation testing?

FDA does not approve microbiological laboratories. Those that perform such testing on HCT/Ps during processing must register with FDA and be compliant with applicable regulations, as microbiological testing is considered processing. An eye bank is not required to use such laboratories for validation activities; however, it would save a lot of work that would need to be done to validate the microbiological method used.