



FDA Responses: Licensure, Validation, and Donor Testing

October 1, 2024

Below is a summary of two letters from the Food and Drug Administration (FDA) responding to questions from America's Blood Centers (ABC). The questions represent concerns raised by ABC member blood centers relating to the licensure process, validation data, and donor testing. ABC's first letter, sent to FDA on July 2, requested clarification on licensure, validation, and donor testing requirements. FDA responded to ABC's letter on July 26. ABC's second letter, sent on August 20, requested further clarification regarding donor testing requirements. FDA responded with its second letter on September 14.

Licensure and Validation Data

I. ABC Question: What is the process that centers should use when opening a new fixed site to trigger an inspection?

Summary of FDA Response (July 26 FDA letter):

- “Blood establishments seeking approval to license blood components manufactured at a new facility without an inspection history must submit a Prior Approval Supplement (PAS) to FDA, in accordance with 21 CFR 601.12(b). Blood establishments may contact FDA if there are questions on what to include in the PAS.”
- “FDA staff...will confirm receipt of the PAS submission and will send a subsequent communication informing the blood establishment of when the inspection will be scheduled. With this process, most inspections occur within approximately six months of our receipt of the PAS.”

II. ABC Question: Why does a PAS need to be submitted prior to undergoing an initial inspection?

Summary of FDA Response (July 26 FDA letter):

- “For new facilities without an inspection history, blood establishments seeking approval to license blood components at such new facilities must submit a Prior Approval Supplement (PAS) to FDA, in accordance with 21 CFR 601.12(b).”
- “CBER's review of new applications and supplements includes a compliance status review (compliance check) of each manufacturing location(s) included in the application, or for supplements, each location affected by the changes in the supplement before approval.”
- “FDA relies on recent inspectional history to complete a compliance check of a manufacturing facility; consequently, FDA cannot approve a submission as a CBE-30 for a new facility that does not have an inspectional history. In this case, the blood establishment must submit a PAS” to trigger the initial inspection.

- “Licensed establishments seeking to add a new facility with a recent FDA inspection indicating compliance at the new facility may submit a CBE-30 under their approved comparability protocol (21 CFR 601.12(e)).”

III. ABC Question: What are the QC requirements for validating an automated collection device?

Summary of FDA Response (July 26 FDA letter):

- Please refer to the [FDA Guidance – Collection of Platelets by Automated Methods](#). “FDA intends to clarify recommendations for process validation in future guidance.”
- “Validation of a new automated collection device should be performed according to a predetermined, statistically valid plan based on the binomial distribution. The plan should describe both the number of components from consecutive collection procedures to test and the number of allowable failures.”
 - An example of an acceptable plan includes the “testing of 60 components from consecutive collection procedures with no failures.”
 - “It is acceptable to combine several types of apheresis platelet collection procedures (i.e., singles, doubles, and triples) in one validation plan, as long as the testing is performed on consecutive collections.”
 - FDA “recommend[s] testing a representative number from each collection type to reach the required totals, taking into account the types of collections you routinely perform. For example, if you collect singles, doubles, and triples routinely, you may include 20 components from each collection type in your plan, for a total of 60 components.”

IV. ABC Question: Under what circumstances will FDA permit 60 consecutive collections for validated an automated red blood cell collection device?

Summary of FDA Response (July 26 FDA letter):

- “FDA recommends the use of a statistically valid sampling plan based on the binomial distribution for process validation for Apheresis Red Blood Cells.
 - For example, if you test according to a plan based on the binomial distribution, you may test 60 components from consecutive double red cell collections for process validation.
 - Such a plan could involve testing each component from 30 consecutive double (2-unit) apheresis red cell collections; or testing each component from 25 double (2-unit) apheresis red cell collections and each component from 10 single apheresis red cell collections. Blood establishments should include the process validation statistical sampling plan in their Prior Approval Supplement (PAS) submission for Apheresis Red Blood Cell collections.”

V. ABC Question: What are the QC requirements (i.e., amount of data) to be included in the 2 months’ data gathering period following validation (July 26 FDA letter)?

Summary of FDA Response:

- “Quality control testing should be performed according to a pre-defined statistical plan such as the binomial distribution, or the hypergeometric distribution. Because the number of collections differ among different fixed sites, blood establishments may contact FDA if there are questions on QC requirements and amount of data to be included in their submission.”

Donor Testing

I. ABC Question: Please clarify whether FDA requires notification of a reactive treponemal test for syphilis screening that confirms negative in cases when the donor is reentered per guidance using the sample from the index donation and, therefore, is eligible to return to donate.

Summary of FDA Response (July 26 FDA letter):

- Under 21 CFR 610.41, blood establishments “must defer donors testing reactive by a screening test for evidence of infection due to a relevant transfusion-transmitted infection(s) [(RTTI)].” “Reasonable attempts” must be made to notify the donor of the deferral due to testing results.
- The [FDA Guidance](#) titled, Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis (2020), “recommends deferring donors with reactive treponemal screening test results....The deferred donor is eligible for reentry, by performing a second (different) FDA-cleared treponemal test on the index donation or follow-up sample.”
 - Blood establishment’s procedures that include a step to defer the donor “must notify the donor of the deferral and provide the results of RTTI tests that were the basis for the deferral.”

II. ABC Question: Inspectors are informing blood centers that CBER has changed their perspective on the need to conduct infectious disease testing on Quantity Not Sufficient (QNS) units. Blood centers are reportedly being told that they must test for infectious disease markers any time tubes are collected from a donor regardless of the outcome of the collection. The standard up to this time has been to not test a sample if a collection fails and does not result in a transfusable product. QNS units do not result in a donation and should not be required to be tested. Please clarify whether blood centers need to test all QNS units for infectious disease marker.

Summary of FDA Responses:

- **(July 26 FDA Letter)** The FDA has not changed their “interpretation of the requirement to test donations for RTTIs under 21 CFR 610.40. Under 21 CFR 610.40(a)(1), blood establishments that collect blood and blood components must test each donation for evidence of infection due to HIV, HBV, and HCV and, if a reactive screening test result is obtained, perform further testing in accordance with 21 CFR 610.40(e).”
- **(September 14 FDA Letter)** FDA “recognize[s] that there are occasions when there may be insufficient volume of donated blood to perform RTTI testing, as required. We recommend that blood establishments define in their SOPs when the collected volume of donated blood is insufficient and they cannot perform RTTI testing (i.e., “QNS”). The rationale should not be based on the intent to discard any donation that will not be used for transfusion or further manufacturing, as the regulation requires the testing of each donation. The blood establishments’ SOPs should define when a donation results in an insufficient volume of blood collected after

phlebotomy. We also encourage blood establishments to inform the donor that RTTI testing will not be performed because the collected volume is insufficient.”