Public Webinar: FDA Review of Biologics License Applications for Blood and Source Plasma

Question 1: For first-time BLA applicants, what are the most common deficiencies identified during FDA's review?

Response: We refer you to our presentations from this morning to address your questions in detail. We intend to make the slides available to the public after the webinar. We strongly recommend that first-time BLA applicants contact us for information on what is needed in a BLA. Common deficiencies include missing or inadequate standard operating procedures and documentation, as well as insufficient evidence of compliance with CFR requirements. We also observe failures to comply with cGMP processes because the establishment did not implement a Blood Establishment Computer Software (BECS) system for donor and product management. Relying solely on manual paper systems is problematic because they often lack the necessary controls to prevent errors, ensure product safety, and maintain records as required in 21 CFR 606.160. Additionally, applicants sometimes fail to provide adequate data demonstrating their product's efficacy, safety, purity, and potency.

Question 2: What general timelines should applicants expect from original BLA submission through licensure decision?

Response: As for timelines, applicants can expect acknowledgement of their BLA submission within days of receipt (approximately two weeks). The FDA typically makes a filing decision within approximately 60 days to determine if the application is complete for substantive review. If an inspection is needed, applicants receive at least 30 days' advance notice. The entire review process from original BLA submission to final licensure decision generally takes about 12 months, though this timeline depends on resource availability and the completeness of the application.

Question 3: When submitting a BLA supplement that references a prior application, what are FDA's expectations for resubmitting unchanged labeling versus cross-referencing labeling from a previous submission, particularly when adding new apheresis collection sites and the product label does not change?

Response: For a supplement to an approved BLA, FDA allows applicants to cross-reference the STN (Supplement Tracking Number) under which the container labels were previously approved, provided that the applicant can attest there are no changes to the previously approved container label. This means you do not need to resubmit unchanged labeling in its entirety; instead, you may reference the prior submission where the labeling was approved.

However, it is important to note that during an FDA inspection, inspectors may request to review the actual container label to verify compliance and confirm that it matches the previously approved version. Therefore, while cross-referencing is acceptable for submission purposes, you should maintain readily accessible copies of the approved labeling and be prepared to present them during inspection.

Question 4: How should a new establishment with limited operational experience prepare for and demonstrate readiness for an FDA inspection?

Response: New establishments should prepare for FDA inspection by ensuring the facility is operational for minimum 3 months with comprehensive operational data before submitting the BLA. Before inspection, the facility must have manufacturing actively ongoing, personnel fully trained and competent, operations and processes validated, all operations compliant with applicable CFR requirements, and the facility registered per 21 CFR 607.21.

Preparation involves establishing that the facility is fully operational. This includes comprehensive staff training, complete equipment and system validation, and implementation of all required SOPs, collecting operational data (facility metrics, deviations with CAPA, adverse reactions, reactive test results), and organizing your documentation (have documentation readily accessible).

Demonstrating readiness during inspection requires showing active operations, staff competency, validated equipment, functioning quality systems, and complete organized documentation with traceability from donor to product. Key personnel must be available to explain quality systems, deviation management, and regulatory compliance. The key is demonstrating procedures are actively used and effective, not just documented.

Question 5: Please describe FDA's current practices regarding pre-license and pre-approval inspections (PLI/PAI), including typical inspection notification timelines and the most common inspectional citations observed at new blood collection establishment?

Response: We refer to our presentation on inspections. Pre-license inspections (PLI) are conducted before approval of a new BLA, while pre-approval inspections (PAI) are conducted for major changes with substantial potential to affect product safety or effectiveness and new facilities under an existing license. The facility's Authorized Official is notified by email approximately 30 days in advance of the inspection, after the establishment has been in operation long enough (a minimum of 3 months) to demonstrate compliance with regulations.

As discussed during the presentation these are some of the more common citations which are related to the donor notification process, not testing subsequent units collected after a reactive test result on the index unit, insufficient personnel, and failure to follow SOPs. Other citations were discussed during the presentation.

Question 6: Can a single submission request approval of both a new facility and licensure of products collected at that facility, or does FDA prefer these actions to occur separately or in a specific order?

Response: Yes, a single BLA submission simultaneously requests both approval of a new facility and licensure of the blood products that will be collected at that facility.

Question 7: Please provide guidance on addressing Certificates of Inspection (COI) during BLA review.

Response: FDA does not accept Certificates of Inspection for our BLA review.

Question 8: For establishments that already hold an approved BLA, may a comparability protocol reference the existing licensed application rather than being included in a new BLA?

Response: Yes, a comparability protocol (CP) may reference an existing licensed application and is submitted as a Prior Approval Supplement (PAS) under 21 CFR 601.12(e). The CP establishes specific tests, validation studies, and acceptable limits to demonstrate that specific types of manufacturing changes do not adversely affect product safety or effectiveness. Once approved, the CP allows for a reduced reporting category (e.g., PAS to CBE-30) when implementing the specific changes covered by the protocol.

However, a CP is not appropriate for changes requiring pre-approval inspections. Therefore, while a CP can be useful for certain repetitive manufacturing changes across existing facilities, adding a new collection facility with no inspectional history still requires a standard PAS with pre-approval inspection, as the CP pathway is not applicable for this type of change.

Question 9: What is the current FDA-recommended process for adding a new collection facility to an existing establishment license and licensing products collected at that site?

Response: Adding a new collection facility to an existing establishment license requires a Prior Approval Supplement (PAS) under 21 CFR 601.12(b) because this represents a major manufacturing change with substantial potential to affect product safety, purity, and potency. The facility must be operational for a minimum of 3 months with established, validated operations before submitting the PAS.

If the new facility has an inspectional history to demonstrate compliance and has an approved comparability protocol under 21 CFR 601.12 (e), a lower reporting category, such as a CBE-30, may be appropriate because the use of the protocol mitigates the potential risk associated with the change.

If the new facility has no inspectional history, FDA must conduct an inspection to determine compliance with current good manufacturing requirements. FDA will request facility-specific information from the blood establishment for operational data and schedule the inspection date.

Question 10: Why is the addition of a new blood or apheresis collection center generally considered a "major change" requiring a Prior Approval Supplement (PAS) under 21 CFR 601.12(b), when the new site will operate under the same approved policies, procedures, quality system, and organizational oversight as existing licensed facilities?

Response: The addition of a new blood or apheresis collection center represents a major manufacturing change with substantial potential to affect product safety, purity, and potency. The implementation of manufacturing in a new facility includes validation among other actions. Therefore, FDA expects submissions to include applicable validation and quality control data. As we noted earlier, blood establishments that already hold an approved BLA may request for approval of a comparability protocol. Once approved, the CP allows for a reduced reporting category (e.g., PAS to CBE-30) when implementing the specific changes covered by the protocol.

However, adding a new collection facility with no inspectional history still requires a standard PAS. FDA relies on the inspectional history of a facility to complete a compliance check; consequently, FDA cannot approve a submission for a new facility that does not have an inspectional history. In this case, FDA will conduct an inspection before approval.

Question 11: Are there any circumstances under which adding a new blood or apheresis platelet/RBC collection site could be considered a moderate change appropriate for a CBE-30 supplement under 21 CFR 601.12 (c) and an inspection would not be performed?

Response: Yes, if the facility has recent inspectional history to demonstrate compliance and has an approved comparability protocol under 21 CFR 601.12 (e), a reduced reporting category, such as a CBE-30, may be appropriate because the use of the protocol reduces the potential risk associated with the change.

Question 12: We understand the requirement to notify CBER of substantial changes in SOPs, materials, testing, or equipment for processing source plasma donors. Could you clarify whether minor changes, such as formatting adjustments to internal process documentation or forms used for donor processing, require notification?

Response: Minor changes, that have minimal potential to have an adverse effect on the safety or effectiveness on the product – like administrative changes such as reformatting documents or adjusting the layout of forms - do not require prior notification to CBER. Under 21 CFR 601.12, you must report such changes in your Annual Report. FDA has published specific guidance ("Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture," December 2014) to assist blood establishments in determining the appropriate reporting category.

If you are still uncertain of the reporting category, you may contact us for clarification.

Question 13: What are common reasons BLAs are delayed or do not result in approval on first review? When is formal resubmission of a BLA required?

Response: The most common reason that a BLA takes longer to review or does not result in approval is that FDA receives an incomplete submission.

If the submission is incomplete, FDA may issue a Refuse to File letter. As outlined in the presentation, RTF stops the review process entirely, requiring resubmission of an entirely new BLA with a new review timeline.

After RTF, the applicant must submit an entirely new BLA (not an amendment) with all original content plus corrections to all identified deficiencies, a new STN is assigned, and a new review timeline begins**.**

Once FDA files an application, the CSO will review all documents submitted. If deficiencies are identified and they cannot be adequately resolved through information requests, FDA will issue a complete response letter. Common Reasons for FDA issuance of a complete response letter include manufacturing and quality system deficiencies, donor and product safety concerns (inadequate screening procedures, testing issues), personnel and training deficiencies (insufficient qualified staff, inadequate training documentation, improperly licensed medical personnel), documentation and compliance issues (SOPs not followed in practice, inadequate records, regulatory non-compliance), operational performance problems, and inability to demonstrate consistent compliance.

After a complete response letter is issued**,** the applicant must resubmit the application or supplement addressing all deficiencies identified in the CR letter or withdraw the application or supplement.

Question 14: Form 356h is required to be submitted by all blood establishments when applying for a supplement to their BLA. The form contains many fields that are confusing and may not apply to blood and blood products.

a. **Can you explain the rationale and applicability of form 356h to blood and blood products?**

   Response: Form 356h is the standard form used across FDA for all biologics license applications and supplements, including those for blood and blood components. While the form was designed to accommodate the full range of biological products regulated by FDA, it serves as a consistent framework for all BLA holders to communicate changes. The rationale is to maintain a standardized submission format that allows FDA to locate key information.

b. **Is it possible to create a form specific to blood products?**

Response: As stated earlier, the form applies to all biologic products that FDA regulates. FDA does not plan to create specific forms for blood establishments. You may complete sections applicable to your submission

c. **What are the minimal requirements for blood products that should be included on the form? Can you clarify which entries on the current form are necessary or applicable specifically for blood products?**

Response: Complete only the fields relevant to your submission. At minimum, you should include applicant information, supplement type, a clear description of the proposed change, and any applicable manufacturing information.

Fields that don't apply to blood components (such as clinical or nonclinical study sections) can be marked "not applicable." The goal is to provide FDA with enough information to understand your change without forcing irrelevant data into inapplicable fields.

Question 15: Is there a pre-BLA process available for blood centers to address questions and receive feedback in real-time?

Response: Yes, there are mechanisms available for blood establishments to submit questions and receive feedback before submitting a BLA or BLA supplement. For specific questions regarding your future submission, you can request a formal Type C meeting with FDA. You can contact your Regulatory Health Project Manager (RPMH) or the RPMH Staff Chief Cherry Geronimo (Cherry.Geronimo@fda.hhs.gov) to obtain guidance on how to submit this request. For Type C meetings, you must submit your questions and relevant background information in advance so FDA can review the materials and provide written responses before the meeting. This proactive approach allows you to clarify expectations and ensure your submission is complete and compliant.

Question 16: What is the best way for a blood center to obtain the latest status of their submission?

Response: All questions related to your submission should be directed to the RHPM assigned to your application. Your RHPM is your primary point of contact and can address specific questions about your submission. If we need additional information from you, the RHPM will proactively communicate this to you.

As we stated in our presentation, while blood and Source Plasma establishments are not subject to user fees, we commit to completing reviews within the timelines established for user fee drug products.

Question 17: Please describe best practices for communicating with the RPHM about my submission.

Response: The review process is intended to be interactive as this allows for timely review of applications. The CSO reviewing your supplement will request for additional information or clarification by sending communications through the RHPM. When the RPHM requests additional information, we recommend that you provide comprehensive responses and address the underlying question(s). If a request is unclear, please ask for clarification before responding. If your response is inadequate or needs further clarification, you may receive additional questions. The CSO cannot proceed with approval until all questions are resolved satisfactorily.

Note that if deficiencies remain in the submission, we may issue a complete response letter and stop the review clock. See 21 CFR 601.3

Question 18: What is the most effective way for firms to stay up to date on FDA guidance updates, regulation changes, etc., that directly impact the Source Plasma industry? Are there specific resources or tools you can recommend?

As you heard in Jennifer Scharpf's presentation, FDA publishes relevant communications to blood establishments through various channels, including Federal Register Notices and via the FDA website.

We recommend you check the Blood Guidances and CBER Safety Communications websites occasionally. Also, you may sign up to receive CBER updates via the FDA website. Scroll to the bottom of any CBER webpage and submit your email address to receive notification of CBER news and new document posting.

Question 19: How does FDA respond to complaints from Congress on behalf of their constituents and from blood donors requesting removal from the National Donor Deferral Registry (NDDR) and reentry as donors?

We explain to the Congressman or their representative that FDA recommends, but does not require blood establishments to perform donor requalification and removal from donor deferral registries, as appropriate, when a donor tests falsely reactive on a screening test for an RTTI. Additionally, we share the relevant guidance document that provides the requalification method for donor reentry and suggest that their constituent or blood donor contact the blood establishment's responsible physician to discuss requalification testing and removal from the donor deferral registry, including the National Donor Deferral Registry.