



Biologic License Application (BLA) Checklist

Under the Public Health Services Act, the Federal Food and Drug Administration (FDA) has been given the authority, concurrent with its authority under the Food Drug and Cosmetic Act, to regulate biologics. The FDA regulates a wide range of biologics, including, but not limited to, vaccines, blood and blood by-products, certain monoclonal antibodies, tissue and cellular products. Within the FDA, the Center for Biologics, as well as the Center for Drug Evaluation and Research, can be responsible for the regulation of biologics.

Biologics are evaluated for market by the FDA through the filing of a Biologic License Application (BLA). A BLA, although similar to a New Drug Application (NDA), has its own set of intricate requirements. It is difficult to know whether an applicant has included all of the information required, and provided that information in an acceptable format, under the applicable regulations. The following checklist is intended to act as a general guide and reminder of the types of information which must be included in a BLA, however, applicants must be cognizant that unique and specific information will be required depending on the type of BLA (e.g., blood, vaccines). Although it is always helpful to have legal counsel assist in a final review of the application prior to its filing, this checklist provides a basic summary of the materials the FDA requires for each application as set forth in the current regulations. Prior to any such filing, all applicable regulations should be checked to ensure that there have been no material changes to the application process or procedures.

1. Safety, Purity, Potency

- An applicant (and, by logical extension, the application) must demonstrate: (i) the product is safe, pure and potent; (ii) the facility(ies) for production meet the standards designed to assure that it continues to be safe, pure and potent.
- Safety – Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.
- Purity – Purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes, but is not limited to, relative freedom from residual moisture or other volatile substances and pyrogenic substances.
- Potency – Potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

2. CBER or CDER

- An applicant must determine which division of the FDA to submit its application, as the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) share responsibility for BLAs.



- CBER regulates: (i) allergenics; (ii) blood and blood components, including pharmaceutical products made from blood; (iii) devices (used to safeguard blood, blood components and cellular products from HIV, hepatitis, syphilis and other infectious agents: reagents used to type blood; machines and related software used to collect blood and blood components); (iv) gene therapy; (v) human tissues and cellular products; (vi) vaccines; and (vii) xenotransplantation products (i.e. use of live animal cells, tissues or organs to treat human diseases).
- CDER regulates: (i) monoclonal antibodies for in vivo use; (ii) proteins intended for therapeutic use that are extracted from plants, animals or microorganisms, including recombinant versions of these products; and (iii) other non-vaccine therapeutic immunomodulators.

3. Archival and Review Copies of BLA

- Federal regulations require the submission of two copies of a BLA – archival and review.
- The archival copy is a complete copy of an application submission and must be bound in a BLUE cover jacket.
- The archival copy should include a cover letter to: (i) confirm any agreements or understandings between the FDA and the applicant; (ii) identify a contact person regarding the application; (iii) identify the reviewing division of the FDA and the HFD number; and (iv) convey any other important information about the application.
- The review copy is divided into six technical sections (“review sections”) and should be submitted with each review section separately bound in a specific color: (i) Chemistry, Manufacturing and Controls (CMC) – RED; (ii) Nonclinical Pharmacology and Toxicology – YELLOW; (iii) Human Pharmacokinetics and Bioavailability – ORANGE; (iv) Microbiology (if required) – WHITE; (v) Clinical Data – LIGHT BROWN; (vi) Statistical – GREEN.
- Each review section should contain the following: (i) a copy of the cover letter attached to the archival copy; (ii) a completed application form FDA 356h; (iii) a copy of the summary (defined below); (iv) a copy of the general index of the entire application; (v) an index specific to that particular review section; (vi) letters of reference or authorization, if appropriate; and (vii) patent information.
- Applicants may request supplies of the jackets (with appropriate color coding) from the FDA or an applicant may obtain jackets from commercial sources if it meets FDA specifications.
- The Application (archival and review copy) must be bound on the left side of the page and use U.S. standard-size loose leaf page size (8.5” x. 11”). The pages must be hole punched 8.5” centered and should be bound in the volume format with fasteners rather than three-ring binders.
- Volumes submitted should be no more than two inches thick. The front cover of each volume should display the name of the applicant, the name of the drug, the application number, if preassigned, and the appropriate heading identifying the submission. The lower right hand corner of the jackets should be marked “__ of __ volumes” with the correct number of volumes and specific volume, while the upper right hand corner of the jackets should be marked “Volume __” with the correct specific volume.



4. The Application Form

- Every application must be accompanied by a completed application form FDA 356h.
- The application form should be signed by the applicant, or the applicant's attorney, agent or other authorized official.
- If the person signing the application form does not reside or have a place of business within the U.S., the application must contain the name and address of, and be countersigned by, an attorney, agent or other authorized official who resides or maintains a place of business within the U.S.
- The application form along with the cover letter, letters of authorization (if any), Index and Summary should be packaged together and bound in a single volume. These items will also be included with each separate review section.
- Patent information on the applicant's drug and any patent certification with respect to the drug should be submitted on a separate piece of paper and attached to the application form.

5. Index

- An application must contain an index of all the elements of the application.
- For each element of the application, the index must identify the volume and page number.
- Each review section must contain an index specific to that review section.

6. Summary

- An application must contain a summary, usually between 50 to 200 pages in length (no actual page requirements), integrating all of the information in the application and providing a general understanding of the drug and its application.
- The summary should be written in approximately the same level of detail required for publication in recognized scientific and medical journals.
- The summary must present the most important information about the biologic and the conclusions to be drawn from this information, a factual summary of safety and effectiveness data and a neutral analysis of this data, an annotated copy of the proposed labeling, a discussion of the product's benefits and risks, a description of the foreign marketing history of the drug (if any) and a summary of each technical section.
- Information in the summary should be presented in the following order: (i) Proposed Text of Labeling for the Drug – Annotated; (ii) Pharmacological Class, Scientific Rationale, Intended Use and Potential Clinical Benefits; (iii) Foreign Marketing History; (iv) Chemistry, Manufacturing and Controls Summary; (v) Nonclinical Pharmacology and Toxicology Summary; (vi) Human Pharmacokinetic and Bioavailability Summary; (vii) Microbiology Summary (if required); (viii) Clinical Data Summary and Result of Statistical Analysis; (ix) Discussion of Benefit/Risk Relationship and Proposed Postmarketing Studies.



7. Chemistry Section

- Chemistry, Manufacturing and Controls Section (CMC) – An application must present chemistry, manufacturing and control information for both the drug substance (unformulated active substance which may be subsequently formulated with excipients to produce the drug product) and the drug product (the finished dosage form of the product).
- CMC for Drug Substance – Production of a drug substance, whether by fermentation, cultivation, isolation or synthesis, usually starts with raw materials. The quality and purity of the drug substance cannot be assured solely by downstream testing, but depends on proper control of the manufacturing and synthetic process as well. The CMC for drug substance should include the following information: (i) description and characterization; (ii) manufacturer; (iii) method of manufacture; (iv) process controls; (v) manufacturing consistency; (vi) drug substance specification; (vii) reprocessing; (viii) container and closure system; and (ix) drug substance stability.
- Manufacturer – Information on the manufacturer should include: (i) identification of the manufacturer including name(s), address(es) and other pertinent organization information; (ii) floor diagram(s) (a simple floor diagram of the general layout of the facilities); (iii) manufacture of other products (list of all additional products that are manufactured or manipulated in the same areas used to produce the drug substance); and (iv) contamination precautions.
- Method of Manufacture – Information on the method of manufacture should include: (i) raw materials (a list of all materials used in the manufacture of the drug substance, and their test and specifications); (ii) flow charts (a complete visual representation of the manufacturing process); and (iii) detailed description of the drug substance.
- Process Controls – Information on process controls should include: (i) in-process controls (description of the sampling procedures and the test methods used); (ii) process validation (summary report, including protocols and results, for each validation study of each critical process or factor that affects drug substance); and (iii) control of bioburden (documentation of control of extraneous bioburden)
- Manufacturing Consistency – Information on manufacturing consistency should include: (i) reference standards; and (ii) release testing.
- Drug Substance Specification – Information on drug substance specification should include: (i) specifications; and (ii) impurities profile.
- CMC for Drug Product – This section should contain information on the final drug product including all drug substances and excipients (inactive components) in the final product. The CMC for drug product should include the following information: (i) composition and characterization; (ii) manufacturer and facilities; (iii) manufacturing methods; (iv) drug product specifications; (v) container and closure system; (vi) microbiology; (vii) lyophilization; and (viii) drug product stability.
- Composition – A list should be provided of all components in the drug product including: (i) drug substance; (ii) excipients; (iii) adjuvants; and (iv) preservatives.
- Characterization – The application should also contain a description of the specifications and tests for all ingredients including: (i) description of the drug product (physical state, color, clarity); (ii) identity; (iii) purity and impurities; and (iv) potency.



- Drug Product Specification – This section should include the following information: (i) sampling procedures; (ii) specification and methods; and (iii) validation results.
- Environmental Assessment – Applicant should submit an environmental assessment or a request for a categorical exclusion with the basis for the exclusion. An environmental assessment should include a description of the action that is being considered and should address all the components involved in the manufacture and disposal of the product.
- Samples – FDA will generally ask for submission of samples directly to specific laboratories. If requested, the applicant must submit four samples of the following: (i) the drug product proposed for marketing; (ii) the drug substance used in the drug product from which the samples of the drug product were taken; (iii) reference standards and blanks.
- Methods of Validation Package – An application should include information such as the statement of composition, new drug substance and drug product specifications, certificates of analysis for each sample submitted and the regulatory analytical methods including the following: (i) a tabular listing of all samples to be submitted; (ii) a listing of all proposed regulatory specifications; (iii) information supporting the integrity of the reference standard; (iv) a detailed description of each method of analysis; (v) information supporting the suitability of methodology for the new drug substance; and (vi) information supporting the suitability of the methodology for the dosage form.
- Four copies of the Methods Validation Package should be included with the initial submission – one copy with the archival copy and three with the CMC Section of the review copy.

8. Establishment Description

- General Information – For each manufacturing location, a floor diagram should be included in the application. In the floor diagram, and/or in an accompanying narrative, the following information should be provided: (i) product, personnel, equipment, waste and air flow; (ii) illustration or indication of which areas are served by each air handling unit; and (iii) air pressure differentials between adjacent areas.
- Water System – The application should contain information on water purification systems including: (i) general description; (ii) validation summary; and (iii) routine monitoring program.
- HVAC System – The application should contain information on the heating, ventilation and air conditioning systems, including: (i) general description; (ii) validation summary; and (iii) routine monitoring program.
- Computer Systems – The application should contain information on computer systems which control critical manufacturing processes.
- Contamination/Cross Contamination Issues – The application should contain the following information regarding methods to prevent contamination and cross contamination to supplement information requested in the CMC: (i) cleaning procedures and validation; and (ii) containment features.

9. Nonclinical Pharmacology and Toxicology Section

- An application should list all nonclinical studies, with volume and page numbers, in the application's table of contents and replicated at the beginning of this review section.



- A pharmacology/toxicology summary is required as part of the application and should provide an integrated discussion of all pertinent findings, including interstudy and interspecies comparisons, with appropriate cross-references to the review section.
- Data location cross-references should be included when correlations or comparisons are made among different types of data.
- A recommended order for submission of various types of studies is: (i) Pharmacology Studies; (ii) Acute Toxicity Studies; (iii) Multipledose Toxicity Studies; (iv) Special Toxicity Studies; (v) Reproduction Studies; (vi) Mutagenicity Studies; and (vii) Absorption, Distribution, Metabolism, Excretion (ADME) Studies.
- Reports of studies related to safety should contain a GLP (Good Laboratory Practice) statement.

10. Human Pharmacokinetics and Bioavailability Section

- Typically, an application should include in the Biopharmaceutics Section studies of five general types: (i) Pilot or Background Studies; (ii) Bioavailability/Bioequivalence Studies; (iii) Pharmacokinetic Studies; (iv) Other In Vivo Studies; and (v) In Vitro Studies.
- The section should include the following information: (i) a summary of studies; (ii) a summary of data and overall conclusion; (iii) drug formulation; (iv) analytical methods; (v) dissolution; and (vi) individual study reports format and other considerations.
- Individual Study Reports Format and Other Considerations – The study reports submitted in this section should contain the following information: objective, dosage form(s) studied, principal investigator, clinical facilities, facilities where collected samples were assayed, all individual data needed for conclusions, including demographic information, concomitant medication, if any, blood/urine levels, abnormal laboratory test values and adverse reactions, all presented in coherent tables, with an analysis of the data and conclusions. In addition, documentation should be provided of the sensitivity, linearity, specificity and reproducibility of the analytical method, including sample chromatographs, recovery studies, etc. Data analysis should include appropriate statistical analyses usually involving analysis of variance, calculations of power analysis, 95% confidence intervals and ratio analysis (75/75-125 Rule). The details of pharmacokinetic parameter calculations, including pharmacokinetic models and equations utilized, should be adequately described and referenced.

11. Microbiology Section (necessary only for submissions to CDER and if anti-infective agent)

- The application should include a technical section describing: (i) the biochemical basis of the drug's action on physiology; (ii) the antimicrobial spectrum of the drug, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use; (iii) any known mechanisms of resistance to the drug including results of any known epidemiologic studies demonstrating prevalence of resistance factors; and (iv) clinical microbiology laboratory methods needed to evaluate effective use of the drug.
- Specifically, the section should include the following information: (i) mechanism of action; (ii) pharmacokinetics; (iii) antimicrobial activity; (iv) enzyme hydrolysis rates; (v) miscellaneous studies; (vi)



assessment of resistance; (vii) clinical laboratory susceptibility test methods; (viii) in vivo animal protection studies; (ix) in vitro studies conducted during the clinical trials; (x) conclusions; and (xi) published literature.

12. Clinical Data Section

- The application should generally describe the clinical investigations of the drug, including the following: (i) a description and analysis of each clinical pharmacology study of the drug; (ii) a description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study; (iii) a description of each uncontrolled clinical study, a summary of the results and brief statement explaining why the study is classified as uncontrolled; (iv) a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained by the applicant from any source including information derived from clinical investigations, commercial marketing experience, reports in the scientific literature and unpublished scientific papers; (v) an integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications; (vi) a summary and updates of safety information; (vii) a description and analysis of studies or information related to abuse of the drug; (viii) an integrated summary of the benefits and risks of the drug; and (ix) a statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations, or was not subject to the regulations, and that it was conducted in compliance with the informed consent regulations.

13. Statistical Section

- The application should include a statistical evaluation of clinical data, including the following: (i) information concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies; (ii) information concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

14. Case Report Forms and Tabulations

- An applicant should submit case reports for: (i) all patients who died during a clinical study; and (ii) patients who did not complete a study because of any adverse event, whether or not the adverse event is considered drug related by the investigator or sponsor, including patients receiving reference drugs or placebo.
- An applicant must submit case report tabulations for individual patients for: (i) the initial clinical pharmacology studies; (ii) the adequate and well-controlled clinical studies; and (iii) the safety data.



15. Labeling

- Container Label – The container label should include: (i) the proper name of the product; (ii) the name, address and license number of the manufacturer; (iii) the lot number or other lot identification; (iv) the expiration date; (v) the recommended individual dose, for multiple dose containers; (vi) the statement “Rx only” for prescription biologicals; and (vii) if a Medication Guide is required, then a statement instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed.
- Package Label – The package label should include: (i) the proper name of the product; (ii) the name, address and license number of the manufacturer; (iii) the lot number or other lot identification; (iv) the expiration date; (v) the preservative used and its concentration, or if no preservative is a safety factor, the words “no preservative”; (vi) the number of containers, if more than one; (vii) the amount of product in the container expressed as number of doses, volume, units of potency, weight, equivalent volume or such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; (viii) the recommended storage temperature; (ix) the words “Shake Well,” “Do Not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; (x) the recommended individual dose if the enclosed container(s) is a multiple-dose container; (xi) the route of administration recommended, or reference to such directions in an enclosed circular; (xii) known sensitizing substances, or reference to an enclosed circular containing appropriate information; (xiii) the type and calculated amount of antibiotics added during manufacture; (xiv) the inactive ingredients when a safety factor; (xv) the adjuvant; (xvi) the source of the product when a factor in safe administration; (xvii) the identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation; (xviii) minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the word “No U.S. standard of potency”; and (xix) the statement “Rx only” for prescription biologicals.

16. Patent Information

- An applicant must submit information on each patent that claims the drug or a method of using the drug that is the subject of the BLA and with respect to which a claim of patent infringement could reasonably be asserted.
- An applicant must submit basic information about each patent, including the following: (i) patent number and the date on which the patent will expire; (ii) type of patent; (iii) name of patent owner; (iv) if the patent owner or applicant does not reside or have a place of business within the U.S., the name of the agent of the patent owner or applicant who resides or maintains a place of business within the U.S. authorized to receive notice of patent certification.



Life Sciences

The Troutman Sanders Life Sciences Practice Team serves a diverse group of clients within the life sciences and high technology industry from discovery and development onward through clinical testing and regulatory approval to sales and marketing. Members of the practice team provide counsel to the firm's life sciences clients in the areas of corporate, finance, intellectual property protection, clinical development, federal regulatory pre- and post-approval issues, compliance, commercialization and risk management (including litigation). The life sciences industries the firm serves include the following:

- Pharmaceutical
- Biotechnology
- Medical Devices
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- Dietary Supplements
- Over-the-Counter Medicines
- Cosmetics
- Animal Feed
- Tobacco

The Troutman Sanders Life Sciences Practice Team represents companies within the life sciences industry through all stages of development including the following:

- Corporate Issues
- Financing
- Intellectual Property Protection
- Clinical Development
- FDA, FTC, USDA, DEA Regulations
- Post-Approval or Commercialization Issues
- Risk Management and Litigation

For more information on how the Troutman Sanders Life Sciences Practice Team can assist you, contact Diane Romza-Kutz at 312.759.1922 or diane.kutz@troutmansanders.com.