New Drug Application and Biologics License Application Filing Checklist

This checklist explains how to prepare a New Drug Application (NDA) or Biologics License Application (BLA) for submission to the U.S. Food and Drug Administration (FDA). The checklist covers what must be included in an NDA/BLA, how it should be formatted, and how to submit the completed application to the FDA.

New Drug Applications

If your client is seeking to commercially distribute a new drug product in the United States, the product will first need to be approved by the FDA. This approval is obtained through the submission of an NDA.

The NDA is a comprehensive collection and summary of all the data and information gathered during any animal studies and human clinical trials that were conducted while developing the drug, as well as any other information or data that is pertinent to the FDA's review of the application.

When submitting the NDA, you will want to ensure that the information you are providing is detailed and pertinent enough that the FDA will be able to come to following conclusions:

- That the drug is safe and effective when used as directed, and that the benefits of using the drug outweigh its risks
- That the drug's proposed labeling, including the package insert, is appropriate and in compliance with applicable labeling laws
- That the processes used to manufacture the drug and its quality are sufficient to ensure the drug's identity, strength, quality, and purity

Biologics License Application

If your client is seeking to commercially introduce a new biological product into the United States, FDA approval is required. Biological products are large complex molecules such as vaccines, blood, blood components, and viruses that are introduced into a living system to diagnose, prevent, treat, and cure diseases and medical conditions. To obtain the FDA's approval, your client will need to submit a BLA.

BLAs are regulated under both the Public Health Services Act, and the Food, Drug, and Cosmetic Act. Unlike an NDA, a BLA covers not only the product, but also the process and facility where the product is manufactured.

When submitting a BLA, your client must demonstrate that their product meets safety, purity, and potency requirements, and these requirements should be kept in mind and referenced in the application.

Content of NDA/BLA

Your client will need to include the following information in their NDA or BLA:

- A cover letter
- FDA Application Form 356h
- An index
- A summary
- Technical sections
- Samples and labeling
- Case report forms and tabulations

- Patent information
- Claimed exclusivity
- Financial certification or disclosure statement
- Debarment certification

Cover Letter

The cover letter should serve to introduce the FDA to your client and their product, and should include the following information as applicable:

- Identify a contact person (or persons) for communications relating to the application.
- State and confirm any agreements or prior understandings with the FDA.
  - If you met the FDA prior to your submission and are submitting any information in an alternative form, it should be noted here.
- Any other important information that you think the FDA should be aware of while considering your application.

Application Form

FDA Form 356h must be completed and signed as part of the application process. The form has labeled and coded fields and must be completed in its entirety.

When completing Form 356h, the following should be considered:

- Date of submission
  - This date should match the date on your cover letter.
- Name, address, and contact information of the applicant
  - The applicant is the person or legal entity to whom the license will be issued.
- NDA/BLA number if previously issued
  - Generally speaking, you would only have an NDA or BLA number if you are submitting a resubmission, amendment, or supplement.
  - This should be a six -digit number, if less than six digits, use leading zeroes.
- Supplement number
  - If there was a previously submitted supplement, insert that four -digit number here. If less than four digits use leading zeroes.
- The product's proposed indications for use
  - If more than one indication, use a new continuation page for each additional indication.
  - You will need to state whether the indication is for a rare disease.
    - A disease is considered rare if it has a prevalence that is greater than 1 in 200,000.
  - If you have an FDA Orphan Designation, you will need to provide that number.
  - You will also need to provide any Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes.
    - SNOMED CT is the FDA's required terminology for indication disease terms.
    - As an example, a SNOMED CT code would read as follows: 38341003 | hypertensive disorder, systemic arterial (disorder).
- You will need to identify the application and submission type
  - NDAs
    - 505(b)(1) applications are traditional new drug applications for novel drugs that have not been previously introduced, where the sponsor has conducted full clinical trials.
    - 505(b)(2) applications differ from a 505(b)(1) application in that they allow the sponsor to rely on the FDA's findings of safety and effectiveness for a previously approved drug. For 505(b)(2) applications, your client will need to include the biological reference product and the approved application number that the submission is based on.
  - BLAs

▪351(a) applications are the standard pathway for approval of a drug, where approval is based on independent clinical trials.

▪351(k) applications rely on the FDA's findings of safety and effectiveness for an approved biosimilar. For 351(k) applications, your client will need to name the biosimilar and BLA holder that your client is basing the submission on.

- The reason for submission
  - This will be a very brief, usually one line, statement that summarizes the contents of the application.
- Establishment information
  - Your client will need to provide the establishment information for all locations that are engaged in manufacturing (including packaging, labeling, sterilizing, and micronizing), testing (as it relates to commercial disposition), or storage of the drug product.
  - The full establishment information for all sites involved in the drug product will need to be contained in the body of the application. For the application form, your client will need to provide the following items:

▪The FDA Establishment Registration (FEI) number. If your client does not have an FEI for a facility at the time the application is submitted, the application should still be submitted, however an FEI should be applied for as soon as possible.

▪Master File (MF) or Drug Master File (DMF) number (if applicable).

▪Establishment Data Universal Number System (DUNS) number. If a facility does not already have a DUNS number, one should be obtained prior to submitting an NDA. DUNS numbers can be obtained online through Dun & Bradstreet's website at no cost.

▪The contact information for someone at the facility who will be responsible for communicating with the FDA as it pertains to the application.

▪Manufacturing steps. In this field, your client must provide a brief statement of the specific manufacturing steps, including any quality tests, taken at that facility.

- The applicant, or the applicant's attorney, agent, or other authorized official must sign the application form
  - If the person signing the application form does not reside or have a place of business within the United States, the application form 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 United States.
  - The person who signs this form should also sign all amendments and supplements.

Index

The archival copy of the application must contain a comprehensive index that references, by volume number and page number, the summary, the technical sections, and all supporting information.

Summary

The summary is where will your client give an overview of all the data contained in the application. Some things to remember while drafting the summary are the following:

- The summary should be a comprehensive compilation that covers every aspect of the application, clearly structures the mass of information contained in the application, and then distills that information down into a clear and concise conclusion.
- The summary should provide enough information that the reader feels like they have a firm understanding of the product and the data behind it when they are finished reading.
- The summary should be written at the level of detail required for publication in a scientific or medical journal.
- Date should be presented in tabular and graphic form wherever possible.
- Avoid any editorializing or promotion of the drug. This should strictly be a factual summary of safety and effectiveness data.
- Separate the summary into sections and use headings to make it clearer and easier to follow.
- If only submitting a supplement, a summary is not required.
- If you are resubmitting an application, be sure to update your summary and clearly explain any changes that occurred.

The summary must include the following information:

- The proposed text of the labeling, including:
  - Any required medication guides

- Annotations to the information in the summary and technical sections that support each statement in the labeling

▪An annotated copy of the proposed labeling

- If any labeling requirements were omitted, or if the label contains any variations from what is required under federal law, provide a detailed statement explaining the reasons for those omissions or variations

- For each statement, or related groups of statements in the labeling, provide annotations -volume and page number -to information in the summary and in the technical section that support the statements

- For any serious adverse experience that is described in the summary but not on a label, explain the omission

▪Also explain any omissions of contraindications, warnings, or precautions present in similar drugs

- A statement identifying:
  - Pharmacologic class of the drug
  - The intended use of the drug
  - Potential clinical benefits of the drug product
  - Include a discussion of the scientific rationale for the drug
- A brief description of any known marketing history, either by the applicant or any other person, of the product outside the United States, if applicable, including:
  - A list of the countries in which the product has been marketed
  - A list of any countries in which the product has been withdrawn from marketing for any reason related to safety or effectiveness

▪Provide a specific reason as to why the product was withdrawn

  - A list of countries in which applications for marketing are pending
- Include separate summaries for each of the technical sections
- Include the following in the conclusion:
  - A brief statement explaining the benefit/risk assessment of the drug and the toxicity of the drug during the clinical and preclinical studies
  - A brief benefit/risk assessment of the drug based on the results of human effectiveness studies and the toxicity of the drug in human and animal studies
  - A description of any postmarketing clinical studies that will be conducted upon approval, and the reasons for the studies

Technical Sections

The technical sections are where all the data and studies that were conducted during the development of the product are compiled and summarized. The technical sections must be comprehensive and thorough, and data should be presented in tabular or graphic form wherever possible.

- **Chemistry, manufacturing, and controls section.**

-This section describes the composition, manufacture, and specification of the drug substance and the drug product. The following information needs to be included:

▪The environmental assessment should be included here, or, if an environmental assessment was not conducted, include a statement explaining why an assessment was not required.

▪If possible, your client should consider submitting the complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the application. The FDA will generally review these prior to receipt of the full application, potentially shortening the approval time.

- **Nonclinical pharmacology and toxicology section.**
  - This section describes the animal and in vitro studies that were conducted.
  - The FDA has an industry guidance to assist in the content and format of this section.
- **Human pharmacokinetics and bioavailability.**
  - In this section, provide any relevant studies related to the absorption of the drug, and its bioequivalence to existing drugs.
  -The FDA has an industry guidance to assist in the content and format of this section.
- **Microbiology.**

- A section describing the microbiology data is required if the application is for an anti -infective drug.
- The FDA has an industry guidance to assist in the content and format of this section.

- **Clinical data.**
  - In this section, provide the statistical data results of the clinical trials.
  - The FDA has an industry guidance to assist in the content and format of this section.
  - FDA Form 3674 is required.

Samples and Labeling

This section explains the requirements for samples and labeling.

- Include the following:
  - Copies of the label and all labeling for the drug product in SPL format (.XML file) and Microsoft Word format (.docx file)
    - 4 copies of a draft label -or -
    - 12 copies of the final printed labels

This includes any required medication guides and package inserts.

- Three copies of the analytical procedural and related information from any tests conducted on the drug product or substance contained in the chemistry, manufacturing, and controls technical section
  - This needs to be detailed enough that the FDA, given a sample of the drug product or substance, would be able to duplicate and validate any of the tests that were conducted on the drug.

- The FDA will request samples, and once requested, they must be submitted directly to the designated government laboratory. The FDA will use the samples to try to duplicate and/or validate the analytical procedures contained in your technical sections.
  - Your client will likely be sending samples to two or more FDA labs.
  - Once requested, your client must provide four samples of each of:
    - The drug product
    - The drug substance used in the drug product from which samples of the drug product were taken
    - Any reference standards or blanks

Case Report Forms and Tabulations

Additional data and content must be included in the application.

- The application must contain the following:
  - Case report tabulations of all studies
  - Case report forms
- The FDA may reach out to request additional tabulations or forms. If this is the case, your client will have 30 days to respond.
- Your client should meet with the FDA before submitting the NDA to discuss whether the tabulations and forms that have been prepared are sufficient and formatted correctly.

Patent Information

If your client is submitting a 505(b)(2) application, they will need to provide any applicable patent information, including:

- FDA Form 3542a
- The patent number and patent certification with respect to each patent issued for the listed drug
  - This includes expired patents.

If there are no relevant patents, a certification stating as much should be submitted.

Claimed Exclusivity

If your client believes their product is entitled to exclusivity, it must be claimed in the application, and your client must provide sufficient proof that it qualifies. The following exclusivities may apply:

- 351(k) application
  - 12 years
- Orphan drug
  - 7 years
- New chemical entity
  - 5 years
- Generating Antibiotics Incentives Now (GAIN)
  - 5 years
- New clinical investigation
  - 3 years
- Pediatric exclusivity
  - 6 months
  - Attached to existing exclusivity

Financial Certification or Disclosure Statement

The NDA must contain any applicable financial certifications or disclosure statements of financial or proprietary interests that any clinical investigators may have in the product.

- If there are no financial arrangements, submit FDA Form 3454.
- If there are financial arrangement that need to be disclosed, submit FDA Form 3455.

Debarment Certification

Your client must submit a signed certification that they did not and will not use in any capacity the services of any debarred persons in connection with the application.

- Use the following language in the certification:
  - "[Client name] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."
    - ▪You may not use any language that indicates a lack of knowledge or responsibility (i.e., "to the best of my knowledge").
- If foreign, both the applicant and the U.S. agent must sign this certification.

Format of an Application

The FDA's Comprehensive Table of Contents Headings and Hierarchy is a highly detailed table of contents that should be followed when submitting the application.

If submitting an original NDA, prepare and submit three copies, as follows:

- Archival copy
  - This will be the official, complete, copy of the application.
  - The archival copy may be submitted in paper or electronic format.
    - ▪Electronic submissions must be in Electronic Common Technical Document (eCTD) format.

▪If submitting in paper format, the labeling, including any package inserts, must be submitted in electronic format.

- Review copy
  - For the review copy, separately bind each technical section, and attach to each a copy of the application form and the summary.
- Field copy
  - The field copy is a separately bound copy of the NDA that includes at least the technical sections, application form, and summary.
  - Include a certification that the technical sections are true copies of the archival copy.
  - This copy should be mailed to the applicant's home FDA district office.