



New Drug Application (NDA) Checklist

New Drug Applications (NDA) are very complex and detailed. It is difficult to know whether a company has included all of the information that is required by the applicable regulations. The following checklist is intended to act as a guide and reminder of the types of information which must be included in every NDA. 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. Archival and Review Copies of NDA

- Federal regulations require the submission of two copies of an NDA – 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 understanding between the FDA and the applicant; (ii) identify a contact person regarding the application; (iii) identify the reviewing division of the FDA and include 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, and the application number, if preassigned. 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.



2. 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.

3. 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.

4. 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 product 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 drug product 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.



5. Chemistry Section

- Chemistry, Manufacturing and Controls (CMC) Section – An application must provide a section on the method of preparation of the drug substance, the control testing used to monitor its identity, strength, quality and purity. The section must include the following information: (i) physical and chemical characteristics; (ii) stability; (iii) name and address of the manufacturer; (iv) manufacturer of the drug substance; (v) process controls; (vi) drug substance controls; (vii) solid-state drug substance forms: relationships to bioavailability.
- 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.

6. 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 technical 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 technical 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; (vii) Absorption, Distribution, Metabolism, Excretion (ADME) Studies.

7. 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.

8. Microbiology Section (if required)

- If the drug is an anti-infective agent, the application must 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.

9. 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.

10. Statistical Section

- The application must 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.

11. Case Report Forms and Tabulations

- An applicant must 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.

12. Labeling

- Applicants must provide either draft labeling or final printed labeling.
- An applicant who submits draft labeling must submit four copies. One copy should be placed in the archival copy while the other copies should be placed in the chemistry, pharmacology and clinical review sections. If additional copies are submitted, they should be placed in the other review sections of the application.
- An applicant who submits final printed labeling must submit 12 copies of the final printed labeling. One copy should be mounted, bound and inserted in the archival copy while the remaining eleven copies of the final printed labeling should be mounted, bound and submitted in a separate jacket clearly labeled "Final Printed Labeling."

13. 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 new drug application or amendment or supplement to it 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.
- For each formulation, composition or method of use patent, in addition to the patent information, the applicant shall submit a declaration as to coverage as to formulation, composition or method of use of a drug product.

If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted, the applicant must so declare. This declaration must be signed by the patent owner, or the applicant's or patent owner's attorney, agent or other authorized official.

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 group 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
- Biologics
- Veterinarian Medicine
- Food
- 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.