


1

FDA Cover Letters

☐ Session Objectives

- Attendees will learn
 - The purpose of the FDA cover letter
 - The importance of the FDA cover letter
 - How to prepare cover letters to the FDA
 - How to complete key forms required for submission to the FDA
 - The purpose of the key forms in FDA submissions

 KIOSC
Korean Incubating Organization for Small Church

2

FDA Cover Letters

- ❑ **Purpose of the Cover Letter in FDA Submissions**
 - **Directs submission to the proper Division at the FDA**
 - **Briefly identifies the purpose of the submission**
 - **Identifies the Sponsor's point of contact for the submission**
 - **Authorized Agent for non-US Sponsors**



3

FDA Cover Letters

- ❑ **Importance of the Cover Letter in FDA Submissions**
 - **Informs the FDA to whom the submission is directed**
 - **Pharmacology/Toxicology**
 - **Chemistry/Manufacturing/Controls (Quality)**
 - **Clinical**
 - **Any combination of the above**
 - **Establishes a high level summary of FDA interactions over time**
 - **For both the FDA and the Sponsor**
 - **“FDA Log”: A log of all cover letters sent to the FDA or received from the FDA provides a written history of FDA/IND interactions**



4

>> FDA Cover Letters

❑ Preparation of the Cover Letter to the FDA

- There is no formal or agreed-upon template or standard
- Most Sponsors develop their own style and approach to the FDA cover letter
- Basic information in the cover letter for IND submission:
 - Administrative information: Date, To/From, IND number, serial submission number
 - Purpose: For example, new clinical protocol and manufacturing information
 - Brief summary of the submission



5

>> FDA Cover Letters

Example of Cover Letter for Initial IND Submission:

Program has included a Pre-IND Meeting and the submission of Meeting Minutes to the FDA from the Sponsor



6

>> FDA Cover Letters

- ❑ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)

COMPANY LETTERHEAD/LOGO

<Date>

22 September 2021 (Try to avoid 1/9/2021: Is it January 9th or September 1st?)

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiology and Nephrology Products

Office of Cardiology, Hematology, Endocrinology, and Nephrology

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993



7

>> FDA Cover Letters

- ❑ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)
 - Always check before submission for changes in FDA staff or address
 - <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-offices-and-divisions>



8

>> FDA Cover Letters

☐ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

RE: IND 123,456
 Drug ABC-001 (or generic name)
 Initial IND Submission

Serial No: 0002



9

>> FDA Cover Letters

☐ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

Administrative Information

Dear Dr. Stockbridge:

Reference is made to the Pre-IND Meeting of 15 July 2021, the submission of our draft meeting minutes of 22 July 2021, and the official meeting minutes provided by the Division dated 15 August 2021. Following the successful Pre-IND Meeting and the information provided by the Division, we hereby submit the initial IND for ABC-001 for the treatment of hypertension.



10

>> FDA Cover Letters

☐ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

Administrative Information

Dear Dr. Stockbridge: (continued)

ABC-001, a renin inhibitor, is being developed by the Acme Pharmaceutical Company of Seoul, Korea and will first be studied in a Phase 1, single dose, dose escalating study entitled <title of study>, Study ABC-001-101.



11

>> FDA Cover Letters

☐ “Model” Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

Administrative Information

Dear Dr. Stockbridge: (continued)

All correspondence regarding this initial IND submission should be addressed to <name/title/company>, who will be acting as the authorized agent for Acme Pharmaceutical.



12

>> FDA Cover Letters

☐ "Model" Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

Administrative Information

Dear Dr. Stockbridge: (continued)

Please let me know if any additional information will be necessary with regard to the initial IND. I can be reached by phone at (xxx) yyy-zzzz or via email at jsmith@jsmithconsulting.com.



13

>> FDA Cover Letters

☐ "Model" Cover Letter to the FDA (Division of Cardiology and Nephrology)

Date

Address

Administrative Information

Dear Dr. Stockbridge: (continued)

Sincerely,

Joseph Smith, Ph.D., Founder,

JSmith Consulting, LLC

<address>

<telephone number>

<email>



14

>> Form FDA 1571

- ☐ **Critical form from FDA's perspective**
 - ☐ **Binds the Sponsor to comply with FDA regulations**
- ☐ **MUST accompany every submission to the FDA**
 - ☐ **Including both PIND and IND submissions**
- ☐ **Best to search the following link to make sure you get the latest form:**
<https://www.fda.gov/about-fda/reports-manuals-forms/forms>
- ☐ **Note expiry date in upper right-hand corner**



15

>> Form FDA 1571

- ☐ **Box 1: Name of Sponsor - Acme Pharmaceutical**
- ☐ **Box 2: Date of Submission – note mm/dd/yyyy**
- ☐ **Box 3: Sponsor Address – physical location** (cannot be a post office box)
- ☐ **Box 4: Sponsor's Telephone Number – include country code**
- ☐ **Box 5: Name of Drug** (*Include : Trade, Generic, Chemical, or Code*) – **ABC-001**
- ☐ **Box 6A: IND (or PIND) Number** (*if previously assigned*) – **123,456**
- ☐ **Box 6B: Commercial or Research – Commercial** (Research is for Sponsor-Investigator INDs)



16

Form FDA 1571

☐ Box 7A: (Proposed) Indication for Use – Hypertension

Rare Disease Y/N – No

Orphan Designation Y/N – No

Orphan Designation Number – leave blank in our example

☐ Box 7B: SNOMED CT Indication Disease Term

- Relatively new
- Assigns a code number that provides a standardized way to represent clinical phrases captured by the clinician and enables automatic interpretation (hypertension = high blood pressure)



17

Form FDA 1571

☐ Box 7B: SNOMED CT Indication Disease Term

1. Navigate to <http://browser.ihtsdotools.org/>. (Use Firefox)
2. Under Local Extensions, select 'Go Browsing United States edition'.
3. Select the 'Search' tab located in the upper left hand of page.
4. Enter the disease term in the search field.
5. Check the box 'Group by concept'.
6. Select the single most appropriate term for the indication.
7. Select the 'Expression' tab located in the upper right hand side of page.
8. Copy the entire text that appears under the heading 'Pre-coordinated Expression'.

☐ Box 7B: SNOMED CT: 38341003 | Hypertensive disorder, systemic arterial (disorder)



18

Form FDA 1571

- ☐ **Box 8: Phase of Clinical Study – Phase 1, 2, 3, or other- Phase 1**
- ☐ **Box 9: List numbers of all INDs, NDAs, DMFs, or BLAs, referred to in this application** – leave blank in our example. Do not repeat the IND # from Box 6A
- ☐ **Box 10: Serial Number – 0002** (Note: Form indicates for initial IND it should be 0000 but that is if there is no Pre-IND Meeting or other interaction with FDA)
- ☐ **Box 11: This submission contains all of the following (check all that apply)**
 - Initial IND - YES
 - Protocol Amendment
 - Information Amendment
 - Request for (Meeting, Special Protocol Assessment, etc.)
 - IND Safety Report



19

Form FDA 1571

- ☐ **Box 12: Originals/Combination Products – relates to drug/device combinations.**
Leave blank for our example
- ☐ **Box 13: Select the following if applicable (like emergency research exception)- rare to select any.** Leave blank in our example.
- ☐ **Box 14: Contents of Application – (Select all that apply)**
 - In our example, check 1-9 (except #2 – TOC)
 - #10-12 rarely checked
- ☐ **Box 15: Will any part of study be conducted by Contract Research Organization**
Y/N – In our example, let's check YES
 - If Yes, will obligations be transferred - YES



20

>> Form FDA 1571

☐ Transfer of Obligations

- Sponsor can transfer none, some, or all sponsor responsibilities defined in 21 CFR 312.50-59
 - Transfer should be in writing (appended to the Form FDA 1571)
 - Ideally, limited to those responsibilities defined in 21 CFR 312.50-59
 - Ideally, signed by representative of sponsor and CRO



21

>> Form FDA 1571

- ☐ **Box 16: Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations – Usually the CMO of sponsor or CRO**
- ☐ **Box 17: Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug – Subtle difference from Box 16, but note that Box 17 refers to “safety” in general, which includes toxicology studies. Generally, senior staff (VP of Development, CSO) to whom both clinical and nonclinical departments report or senior staff at CRO.**
 - Nevertheless, often the CMO is listed for Boxes 16 and 17



22

» Form FDA 1571

☐ **Note well the language between Boxes 17 and 18:**

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements..... i.e., 21 CFR 312.



23

» Form FDA 1571

- ☐ **Box 18: Name of Sponsor or Sponsor's Authorized Representative (Authorized Agent) – Joseph Smith, Ph.D. in our example**
- ☐ **Box 19: Telephone Number – of Sponsor (Acme Pharmaceutical)**
- ☐ **Box 20: Facsimile Number – of Sponsor (can leave blank nowadays)**
- ☐ **Box 21: Address of Sponsor – Physical address**
- ☐ **Box 22: Email address – of Sponsor**
- ☐ **Box 23: Date of Sponsor's Signature (dd/mm/yyyy)**
- ☐ **Boxes 24-26, 28: Name/address/email address of Countersigner – Rarely used. If Sponsor wishes to have a second signature. This is not Authorized Agent.**
- ☐ **Box 27: Signature of Sponsor or Authorized Agent – Joseph Smith, Ph.D.**



24

>> FDA Cover Letters and Key Forms

- ☐ Break
- ☐ Questions?



25

>> Form FDA 3674

- ☐ Ensures compliance with clinicaltrials.gov regulations
- ☐ Should be submitted whenever a new clinical protocol is being submitted to the FDA
- ☐ [Clinicaltrials.gov](https://clinicaltrials.gov) requires the Form FDA 3674 to be submitted for “applicable clinical trials”
 - **Controlled** clinical investigations (other than phase 1 investigations) of any U.S. FDA-regulated drug or biological product for any disease or condition
 - ACTs generally include interventional studies (with one or more arms)
 - The trial has one or more sites in the United States
 - The trial is conducted under an FDA investigational new drug application (or investigational device exemption)
 - The trial involves a drug, biological, (or device) product that is manufactured in the United States or its territories and is exported for research



26

» Form FDA 3674

- ☐ Despite the straight-forward definition of “applicable clinical trial”, many sponsors list all studies on clinicaltrials.gov
 - Fear of non-compliance with clinicaltrials.gov?
 - Assist with enrolment into clinical study?



27

» Form FDA 3674

- ☐ Again, make sure the form you are using/completing has not expired
- ☐ Box 1: Name of Sponsor/Applicant/Submitter – Sponsor can get assistance with completion of form and registration with clinicaltrials.gov
- ☐ Box 2: Date of the Application/Submission
- ☐ Box 3: Address (note, P.O. Box is acceptable)
- ☐ Box 4: Telephone and Facsimile Number (OK if Facsimile Number is left blank)
- ☐ Box 5: For Drugs/Biologics, Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Names – ABC-001
- ☐ Box 6: Type of Application/Submission Which This Certification Accompanies
 - IND, NDA/BLA, ANDA, etc.



28

» Form FDA 3674

- ☐ **Box 7: IND, NDA/BLA, etc. number (e.g., IND 123,456)**
- ☐ **Box 8: Serial Number Assigned to Application/Submission Which This Certification Accompanies – Serial Number 0002**
- ☐ **Box 9: Certification Statement (Check only one of the following boxes):**
 - ☐ I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.
 - ☐ I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.
 - ☐ I certify that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met.



29

» Form FDA 1572

- ☐ **Form FDA 1572 is the Statement of Investigator form that accompanies the submission of new investigators conducting studies under an IND**
- ☐ **It is a critical form in that, by signing, the investigator agrees to comply with all applicable regulations under the IND**
- ☐ **Like all forms, it has an expiration date**
- ☐ **Directions for completing the form are available on the FDA Forms link**
- ☐ **Box 1: Name and Address of Investigator – Must be a physical address (not a P.O. Box)**
- ☐ **Box 2: Education, Training, and Experience that Qualify the Investigator as an Expert in the Clinical Investigation – Append Curriculum Vitae**



30

Form FDA 1572

- ☐ **Box 3: Name and Address of any Medical School, Hospital, or other Research Facility where the Clinical Investigation(s) will be Conducted - Physical address**
- ☐ **Box 4: Name and Address of any Clinical Laboratory Facilities to be used in the Study – Physical address/Can be more than one laboratory**
- ☐ **Box 5: Name and Address of the Institutional Review Board (Ethics Committee) that is Responsible for Review and Approval of the Study(ies) – Physical address**
- ☐ **Box 6: Names of Subinvestigators (If not applicable, enter “None”)**
 - Include CV of Subinvestigators
- ☐ **Box 7: Name and Code Number, if any, of the Protocol(s) in the IND for the Study(ies) to be Conducted by the Investigator – Physical address**
 - Name = Title and having a protocol study number (code number) is strongly recommended (like ABC-001-101)



31

Form FDA 1572

- ☐ **Box 8: Provide the Following Clinical Protocol Information (*select one of the following*)**
 - ☐ **Phase 1 Investigations**
 - ☐ **Phase 2 or 3 Investigations**
 - Check appropriate box. No need to include anything else as it will be provided/included in the clinical protocol being submitted
- ☐ **Box 9: Commitments**
 - Eight commitments are listed which summarize the responsibilities of investigators conducting trials under an IND
 - Note the last commitment: *“I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312”*
- ☐ **Box 10: Date (mm/dd/yyyy)**
- ☐ **Box 11: Signature**



32

» Form FDA 356h

- ☐ Form FDA 356h is the “NDA Equivalent” of the IND Form FDA 1571
- ☐ Form FDA 356h must be submitted with the NDA/BLA
- ☐ Note the expiration date (Interestingly, the “current” form that downloads from the FDA Forms link is out of date)
- ☐ There are instructions (5 pages) provided on the FDA Forms link for completing the Form FDA 356h
- ☐ Box 1: Date of Submission (mm/dd/yyyy)
- ☐ Box 2: Name of Applicant (Sponsor)
- ☐ Box 3: Telephone Number (Include country code if applicable and area code)
- ☐ Box 4: Facsimile Number – can leave blank nowadays



33

» Form FDA 356h

- ☐ Box 5: Applicant Address (Note: P.O. Box is listed but my experience is that it needs to be a physical address)
- ☐ Box 6: Authorized U.S. Agent (required for non-U.S. applicants)
- ☐ Box 7: NDA, ANDA, or BLA Application Number
- ☐ Box 8: Supplement Number (if applicable) – This is for previously approved NDA/BLAs that are being supplemented (new claim)
- ☐ Box 9: Established Name (e.g., proper name, USP/USAN/generic name/generic)
- ☐ Box 10: Proprietary Name (Trade Name) (if any)
- ☐ Box 11: Chemical/Biochemical/Blood Product Name (if any)
- ☐ Box 12: Dosage Form (e.g., tablets)



34

» Form FDA 356h

- ☐ **Box 13: Strengths (e.g., 250 mg, 500 mg, 1000 mg)**
- ☐ **Box 14: Route of Administration**
- ☐ **Box 15A: Proposed Indication for Use (also includes information regarding orphan drug designation, if applicable, similar to that in the Form FDA 1571)**
- ☐ **Box 15B: SNOMED CT Indication Disease Term (similar to that used in the Form FDA 1571)**
- ☐ **Box 16: Application Type (NDA, BLA, ANDA)**
- ☐ **Box 17: If an NDA, identify the type - (505(b)(1) or 505(b)(2)**
- ☐ **Box 18: If a BLA, identify the type – 351(a) or 351(k) [biosimilars]**
- ☐ **Box 19: If a 351(k), identify the biological reference product that is the basis for the submission**



35

» Form FDA 356h

- ☐ **Box 20: If an ANDA or 505(b)(2), identify the listed drug product that is/are the basis for the submission**
- ☐ **Box 21: Submission (original, supplement, annual report, etc.)**
- ☐ **Box 22: Submission Sub-Type (presubmission, original submission, etc.)**
- ☐ **Box 23: If a supplement, identify the appropriate category (for CMC supplement)**
- ☐ **Box 24: For Originals and all supplements, is the product a combination product (drug/device, biological/device)**
- ☐ **Box 25: Does the submission contain (only pediatric data, human factors information (devices)**
- ☐ **Box 26: Proposed marketing status (prescription/OTC)**



36

» Form FDA 356h

- ☐ **Box 27: Reasons for Submission – For example, New Drug Application**
- ☐ **Box 28: Establishment Information - Locations of all manufacturing, packaging, and control sites for both drug substance and drug product**
- ☐ **Box 29: Cross References (List related NDA/BLAs, INDs, DMFs, etc. referenced in the current application)**
- ☐ **Box 30: This application contains the following items (*Select all that apply*)**
 - Index, Labelling, Summary, Chemistry Section, Nonclinical Pharmacology and Toxicology Section, Human Pharmacokinetics and Bioavailability Section, Clinical Microbiology Section (for anti-infective drugs), Clinical Data Section, Safety Update Report, Statistical Section, Case Report Form Tabulations, Case Report Forms, Patent Information, Patent Certification, Establishment Description, Debarment Certification, Field Copy Certification, User Fee Cover Sheet, Financial Disclosure Information, Other



37

» Form FDA 356h

- ☐ **Certification: Sponsor certifies that all applicable regulations have been/will be (if the application is approved) met and that the data and information in the submission have been reviewed and, to the best of the Sponsor's knowledge, are certified to be true and accurate**
- ☐ **Box 31: Typed Name and Title of Applicant's Responsible Official**
- ☐ **Box 32: Date (mm/dd/yyyy)**
- ☐ **Box 33: Telephone Number**
- ☐ **Box 34: Facsimile Number**
- ☐ **Box 35: Email Address**
- ☐ **Box 36: Address of Applicant's Responsible Official**



38

>> Form FDA 356h

- ☐ **Box 37: Signature of Applicant's Responsible Official or Other Authorized Official**
- ☐ **Box 38: Countersignature of Authorized U.S. Agent**



39

>> Form FDA 3500A (MedWatch Form)

- ☐ **Note the difference between Form FDA 3500 and Form FDA 3500A**
 - Form FDA 3500 is for voluntary reporting of adverse event information by physicians, pharmacists, consumers, etc. for approved products
 - Form FDA 3500A is for mandatory reporting of adverse event information by Sponsors for approved products
 - FDA also allows sponsors to submit Form FDA 3500A for adverse event reporting to an active IND
- ☐ **There is a link on the FDA Forms webpage to the instructions for completing Form FDA 3500A (it is 14 pages)**
- ☐ **Note the expiration date**



40

» Form FDA 3500A (MedWatch Form)

☐ Section A. Patient Information

- **Patient Identifier in Confidence:** Generally a number that often includes study number, site number, patient number for clinical studies (e.g., ABC-001-101-04-006) or patient's initials-birthdate (e.g., GMH-10NOV1980) for approved products. Sponsor can establish format for patient identifier.
- **Age, Gender, Weight, Ethnicity, Race**

☐ Section B. Adverse Event or Product Problem

- **Type of Report (AE or Product Problem), Outcome Attributed to AE, Date of Event, Date of this Report, Describe Event or Problem, Relevant Tests/Laboratory Data, Other Relevant History Including Pre-Existing Medical Conditions**



41

» Form FDA 3500A (MedWatch Form)

☐ Section C. Suspect Products

- **Name/Strength/Manufacturer or Compounder, List Medical Product and Treatment Given at the Same Time of the Event and Date, Dose, Treatment Dates, Diagnosis for Use/Indication, Product Type (OTC, generic, etc.), Expiration Date, Event Abated after Use Stopped or Dose Reduced, Event Reappeared after Reintroduction,**

☐ Section D. Medical Device

☐ Section E. Initial Reporter

- **Name and Address, Health Professional (Y/N), Initial Reporter also Sent Report to FDA (Y/N)**

☐ Section F. For Use by User Facility/Importer (Devices Only)



42

» Form FDA 3500A (MedWatch Form)

☐ Section G. All Manufacturers

- Contact Office (and Manufacturing Site for Devices) or Compounding Outsourcing Facility, Report Source (e.g., Foreign, Study, Literature, Consumer, etc.), Date Received by Manufacturer, NDA # (or BLA#, IND#, etc.), If IND Give Protocol Number, Type of Report (5-day, 7-day, 15-day, etc.), AE Terms, Manufacturer Report Number (format established by manufacturer, e.g., Acme 12 Oct 21-001)

☐ Section H. Device Manufacturers Only



43

» FDA Cover Letters and Key Forms

☐ Questions?



44



45