REVIEW MANAGEMENT

PROCEDURES FOR TRACKING AND REVIEWING PHASE 4 COMMITMENTS

CONTENTS

PURPOSE This MAPP describes the policies and procedures to be used by Center for Drug Evaluation and Research (CDER) staff to:

- track Phase 4 Commitments;
- process submissions related to Phase 4 Commitments; and

- review studies and evaluate applicants' responses to Phase 4 Commitments.

BACKGROUND

For many years, FDA has asked for, and obtained, commitments from applicants to conduct postapproval studies. These studies were not considered to be essential for approval of the application but provided additional information or data that could, for example, change the prescribing information or use of the drug or provide additional assurance or verification of product quality and consistency. A company's agreement at time of approval to conduct such studies is a Phase 4 commitment.

In addition to the studies agreed to prior to approval, FDA may ask for studies after approval, often to assess some aspect of safety, but also to evaluate widespread off-label use or to further establish product quality and consistency. These are also called Phase 4 studies.

In 1993, new regulations for accelerated approval under 21 CFR Part 314 Subpart H codified FDA's authority to require Phase 4 studies for certain new drug applications. Under this regulation, when FDA approves an application on the basis of a surrogate endpoint or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity, it can require Phase 4 studies to confirm and describe the clinical benefit of the drug. If the studies do not demonstrate effectiveness, if they reveal safety problems, or if they are not completed with due diligence, FDA can withdraw approval of the drug.

In 1987, the Division of Drug Information and Resources (DDIR) was given the task of administrative tracking of the Phase 4 Commitments. Because each individual reviewing division has handled Phase 4 commitments and submissions of Phase 4 data differently, the task of tracking the status of commitments and the review of submissions is difficult. This guide describes both standardized procedures for tracking incoming and outgoing documents related to Phase 4 commitments and the responsibilities and procedures for review and evaluation of Phase 4 data submissions.

DEFINITIONS

- **Phase 4 commitment** - Commitment made by an applicant in response to a request from FDA to conduct post-approval research; may be a commitment voluntarily made by an applicant before or after approval or a commitment required as a condition of approval under 21 CFR 314, Subpart H.

- **Phase 4 study** - For purposes of this document, a study conducted to fulfill a Phase 4 commitment.

- **Phase 4 submission** - A submission that pertains to or includes data generated in response to a Phase 4 commitment.

POLICY

- Phase 4 commitments and a schedule for fulfillment of those commitments should be agreed upon with the applicant before approval of the application.

- The approval letter should list all Phase 4 commitments and the schedule for completion of each commitment. Statements regarding Phase 4 commitments should not include proprietary information.

- Relevant information regarding Phase 4 study commitments also should be documented in the administrative record. These might include, for example, study objectives, research designs, reporting frequency, and study report formats for clinical studies or test methodology, frequency of testing, and method of data analysis for chemistry commitments. If these details are not determined at the time of approval, this should be noted and a schedule for resolving the issues described in the approval letter.

- A Phase 4 Tracking System linked to the Centerwide Oracle-based Management Information System (COMIS) (see attachment A) will be used to monitor the status of Phase 4 commitments. It will use a standardized coding system to identify the type of each Phase 4 commitment and the fulfillment status of each commitment (CDER Data Standards Manual, see attachments B and C). (For a schematic diagram of the flow of documents between the Division Document Room (DDR) and the Division of Drug Information Resources [DDIR], see attachment D.)

RESPONSIBILITIES AND PROCEDURES

PRIOR TO APPROVAL/AT THE TIME OF APPROVAL

- **Project Management Staff (PM):**

  1. Assures that the applicant of the pending NDA submits a letter of commitment describing any Phase 4 studies they agree to conduct after approval of the application and the schedule for initiation and

completion of those studies and submission of the study results.

2. Describes any Phase 4 commitments in the approval letter (see attachment E) and their schedules for completion.

3. Assures that consulting CDER Offices/divisions that have joint/team responsibility for evaluation of Phase 4 studies have been involved in negotiation of the commitment and copied on the approval letter distribution list.

- **Team Leader and PM:**

1. Involve consulting offices (such as Office of New Drug Chemistry, Office of Clinical Pharmacology and Biopharmaceutics, Office of Epidemiology and Biostatistics/Division of Pharmacovigilance and Epidemiology [OEB/DPE]), as needed, to decide if a Phase 4 commitment will be requested.

2. For Subpart H commitments: Assure that the study protocol is evaluated for its ability to meet objectives and commitments. Where consult divisions are involved, the submission should be sent to the appropriate consult division for evaluation and written review. (For non-accelerated approval: protocols and other information on Phase 4 commitments are often not submitted until after approval. See POST-APPROVAL, Review Team, item 1).

- **Division Document Room:**

1. Enters a flag into the COMIS system to designate NDA approval letters that include Phase 4 commitments.

2. Sends a copy of the approval letter to HFD-80.

- **DDIR:**

1. Monitors COMIS for original approvals that have Phase 4 flags and follows up with the Division Document Room whenever DDIR is not in receipt of an approval letter.

2. Determines the Phase 4 commitment and fulfillment categories for each commitment specified in the approval letter and whether or not it is a Subpart H commitment and enters the proper codes into the Phase 4

tracking system.

POST APPROVAL

- **Project Management Staff (PM):**

1. Requests/confirms that the applicant submits, according to the agreed upon schedule, preliminary concepts and study protocols, data, and interim and final reports for Phase 4 commitments to their Investigational New Drug Application (IND) for the product with a copy of the cover letter to the NDA, except that, if an NDA is not required to meet the Phase 4 commitment (for example, studies regarding chemistry, manufacturing, or controls), information should be submitted to the NDA as correspondence, with the exception of standard stability commitment data which should be included in the NDA Annual Report. Informs that applicant that all submissions, including labeling supplements, relating to Phase 4 commitments should be clearly labeled “Phase 4 Commitments.”

2. Generates a letter documenting any agreement by the applicant after approval to conduct Phase 4 studies (usually epidemiology studies) (Attachment F).

3. Includes DDIR in the distribution list of all Phase 4-related meeting minutes, telephone contact reports, and outgoing correspondence.

4. Works with review team, consulting offices, and applicant to identify and schedule completion dates for outstanding Phase 4 commitments (see Review Team, item 3).

5. Ensures that the review team, including any consulting offices, prepares a schedule for completion of the evaluation of interim and completed study results.

6. Checks all submissions circulated to the PM to confirm that all relevant submissions are clearly labeled "PHASE 4 COMMITMENT" and directed to the appropriate reviewer(s) (including consultant reviewers). Submissions not labeled by the applicant as related to Phase 4 commitments should be brought to the attention of the division document room for correct processing.

7. At least annually, evaluates status of outstanding voluntary Phase 4

commitments and, at least twice annually, evaluates status of outstanding Subpart H Phase 4 commitments using annual reports and other data, and generates "Dunner Letters" (see Attachment G) for overdue outstanding commitments (some studies may be time-sensitive and need closer scrutiny). Various standard reports of Phase 4 commitments are available from the tracking system for this purpose. Status monitoring includes consultation with review team to confirm that each outstanding commitment is still necessary.

8. Generates an acknowledgment letter to the applicant whenever Phase 4 data have been reviewed and a commitment has been fulfilled (see Attachment H) or when the division has concluded that the applicant may be released from the commitment. If a supplement was submitted as a result of the Phase 4 commitment, the final action letter for the supplement should note that we consider the commitment to have been fulfilled. (Like all letters pertaining to Phase 4 commitments, the supplement action letter should be copied to HFD-80 and "Phase 4 Commitments" should be indicated at the end of the letter after the notation of letter type.)

- **Review Team:**

1. Promptly (usually within 30 days) evaluates the study protocol and proposal for its ability to meet objectives and commitments.

2. Works with the PM to prepare an agreed-upon time line for review of Phase 4 submissions, which generally should not exceed 6 months from the time of receipt.

3. Works with the PM in reviewing and judging the applicant's rate of progress in meeting its commitments (see Project Management Staff, item 3).

4. Reviews and evaluates within the agreed upon time line (generally 2 to 6 months from receipt), study reports, results and analyses and develops a written review for filing to the NDA.

5. Where consult divisions are involved, sends submission to appropriate consult division (e.g., consult safety studies to OEB/DPE for evaluation and written review).

6. Brings to the attention of the PM for correct administrative processing

any incoming Phase 4-related document received by the team member that is not identified as a Phase 4-related document.

7. Reviews annual reports to assure that all requested Phase 4 studies are still necessary. If not, documents reason study no longer needed and forwards to PM for letter to applicant.

- **Division Document Room:**

1. Forwards to DDIR a copy of the cover letter of any incoming submissions to INDs/NDAs that refer to Phase 4 commitments.

2. Forwards a copy of all annual reports to DDIR.

3. Forwards a copy of all outgoing Phase 4 commitment-related correspondence to DDIR.

- **DDIR:**

1. Manages the Phase 4 Tracking System, including entering all incoming and outgoing Phase 4-related documents into the Phase 4 database, and selecting and entering appropriate fulfillment status codes.

2. For each NDA with outstanding Phase 4 commitments, checks each annual report to assure that it includes a section documenting the status of each Phase 4 commitment. If this section is missing, generates and issues a dunner letter to the applicant (see attachment I).

3. Works with the PM and members of the review team to identify commitments that have been completed or from which the applicant has been released.

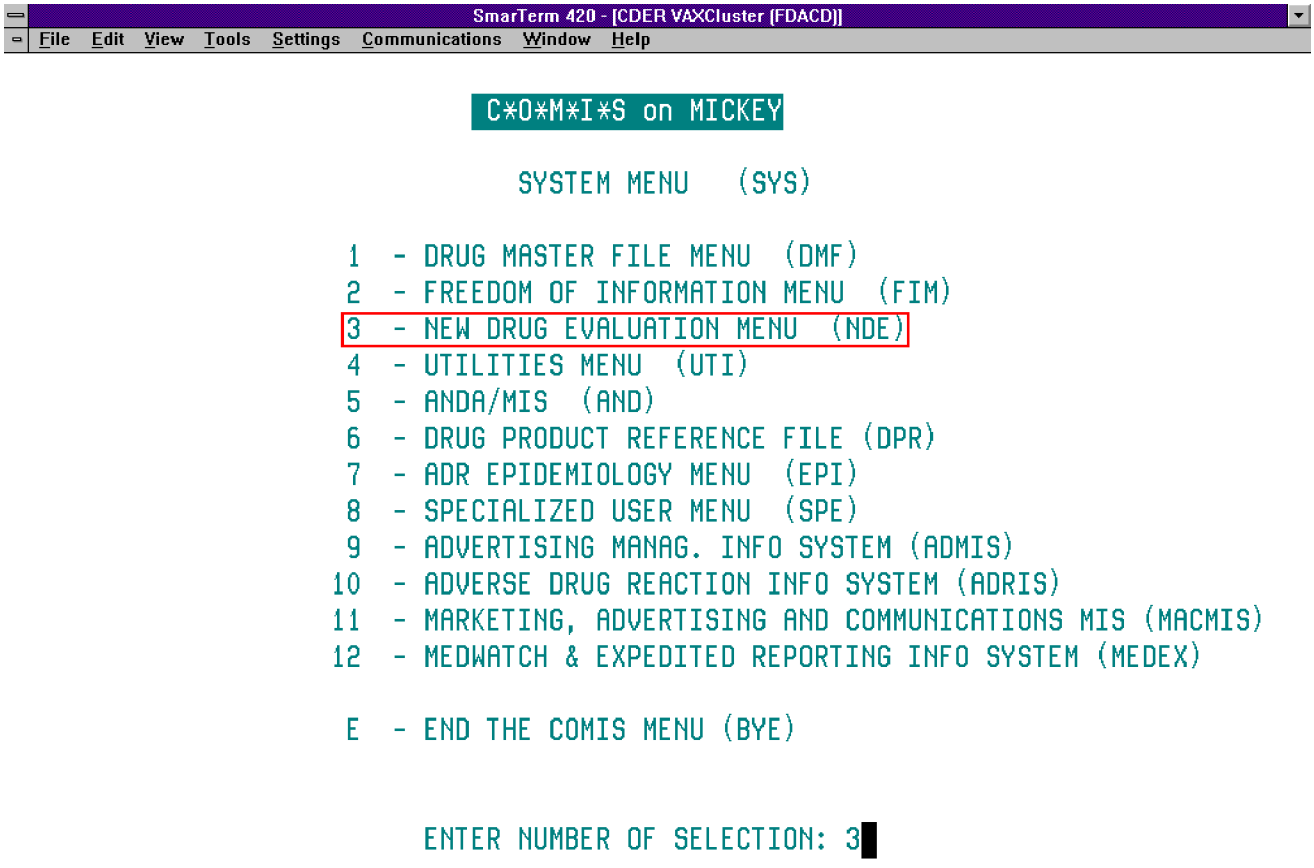
EFFECTIVE DATE

This MAPP is effective October 1, 1996.

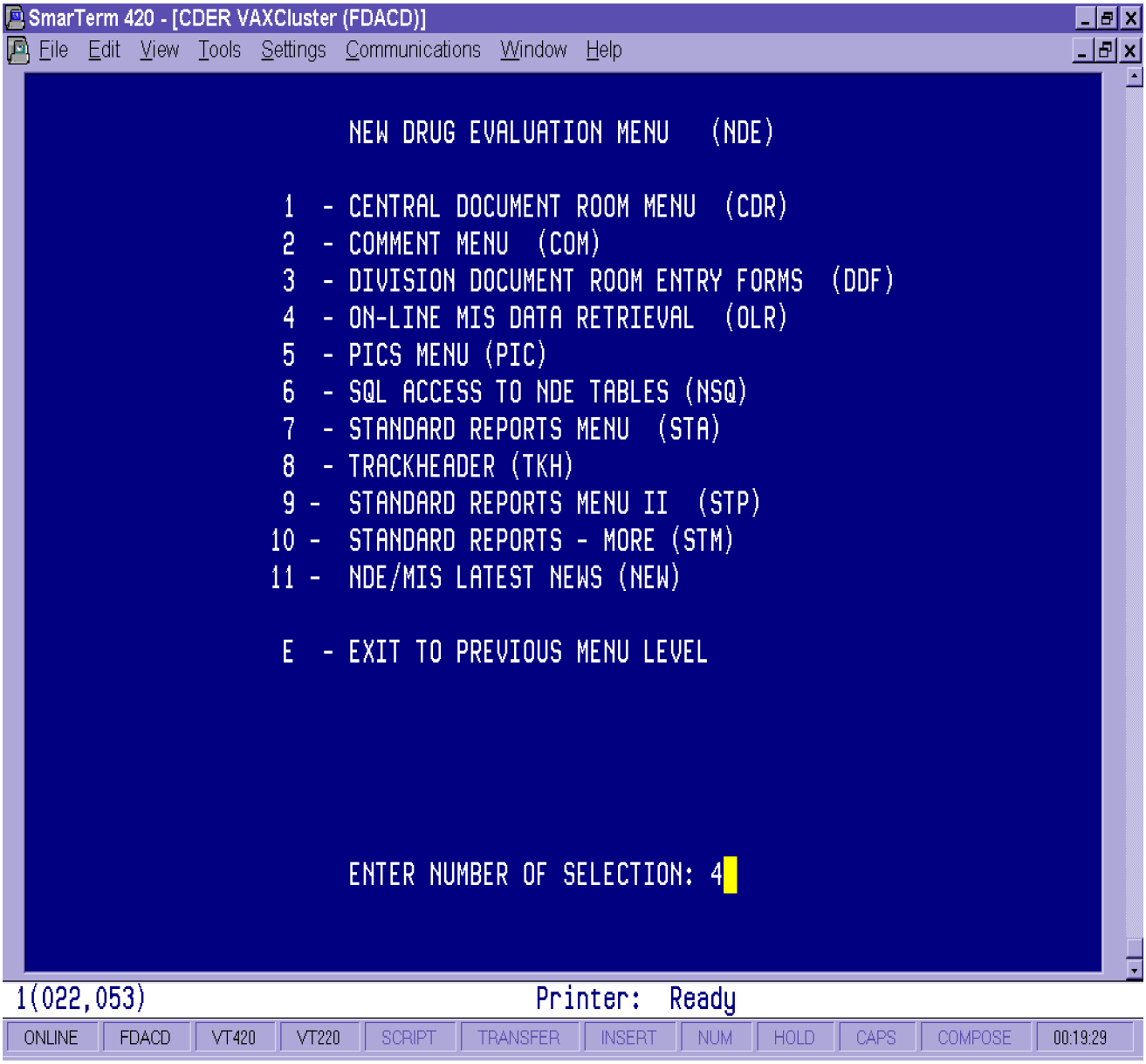
Attachment A

HOW TO ACCESS THE PHASE 4 TRACKING SYSTEM SCREENS AND REPORTS

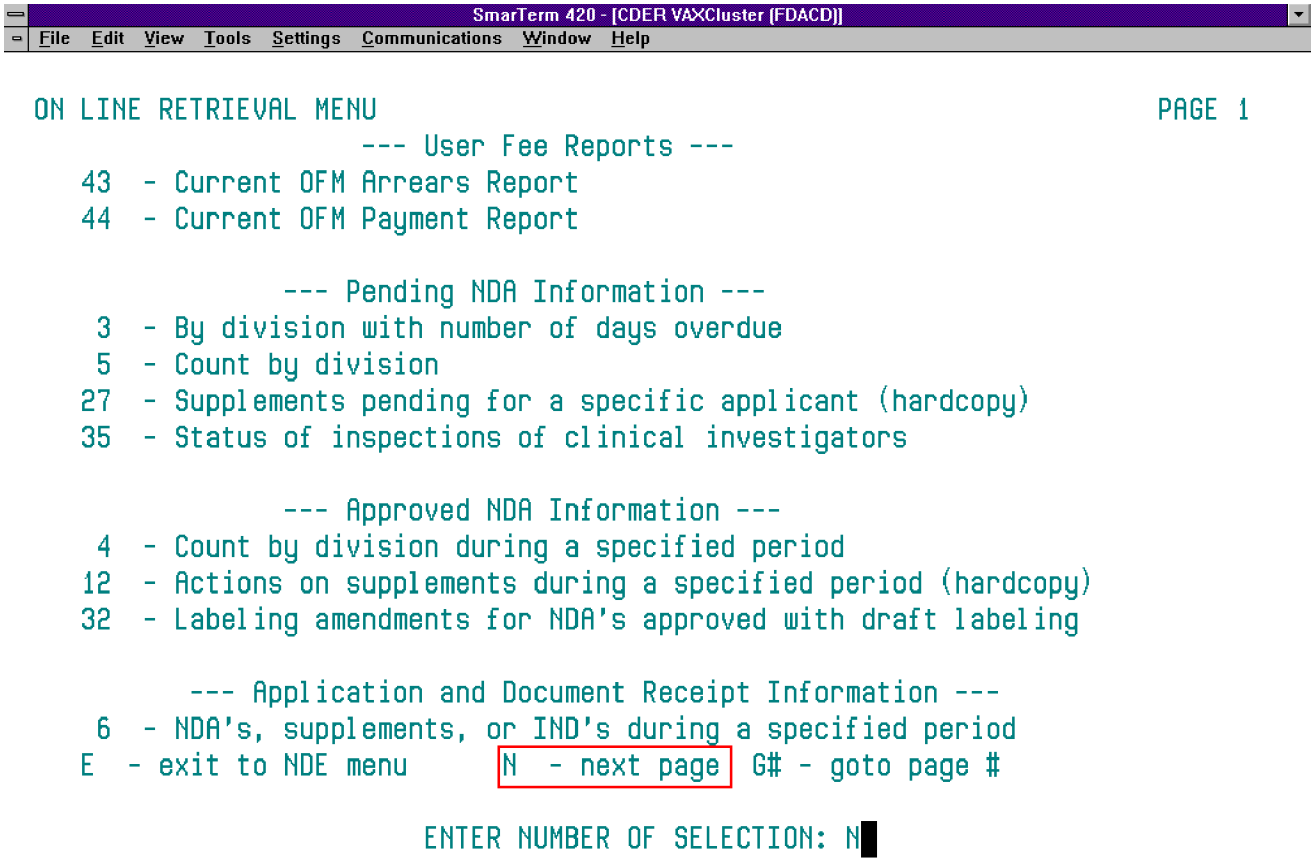
To access the Phase 4 Query System, pick #3 (New Drug Evaluation Menu [NDE]) from the COMIS Main System Menu.



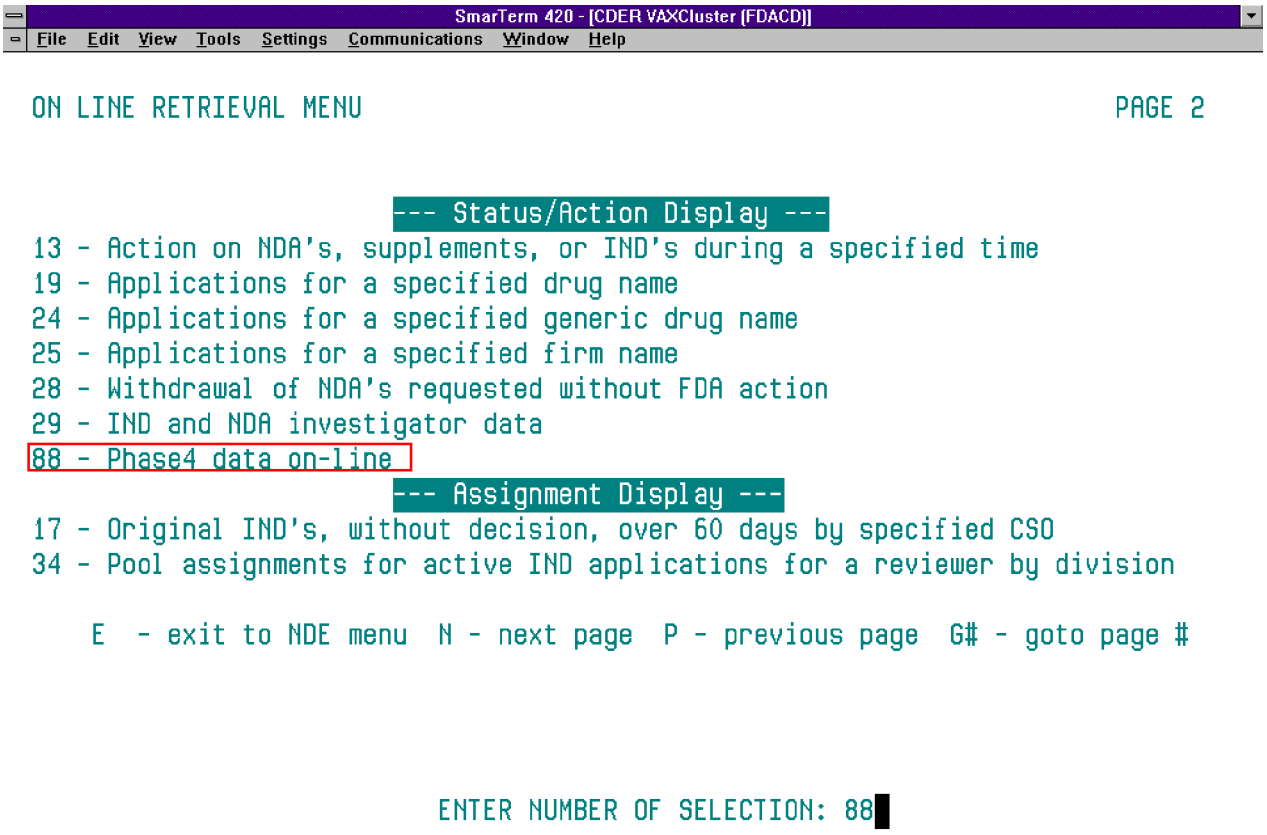
Next, pick #4 from the New Drug Evaluation Menu



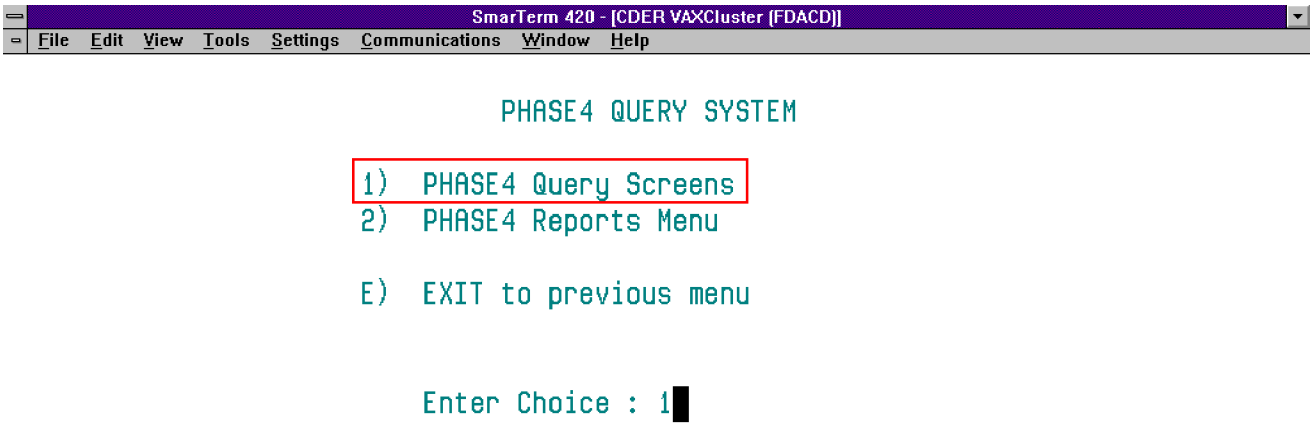
Next, pick N from the On-Line Retrieval Menu



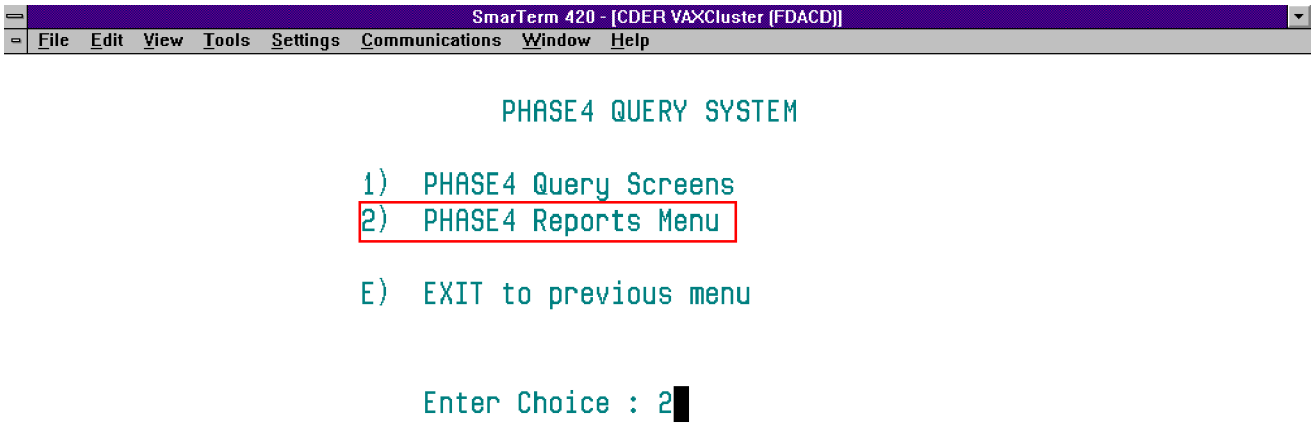
Next, pick #88 from Page 2 of the On-Line Retrieval Menu.



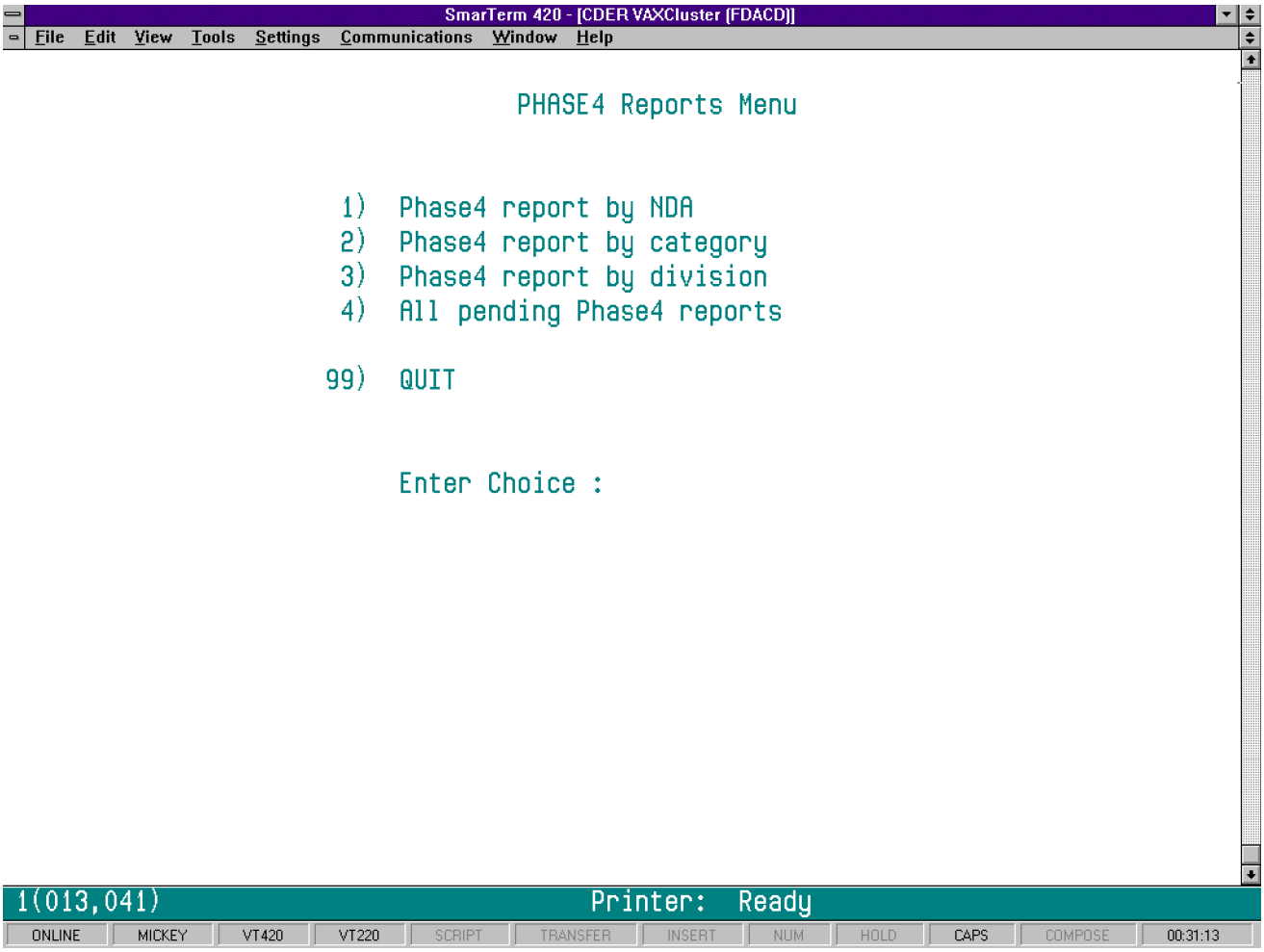
To access the Phase 4 Query Screens, pick #1 from the Phase 4 Query Menu.



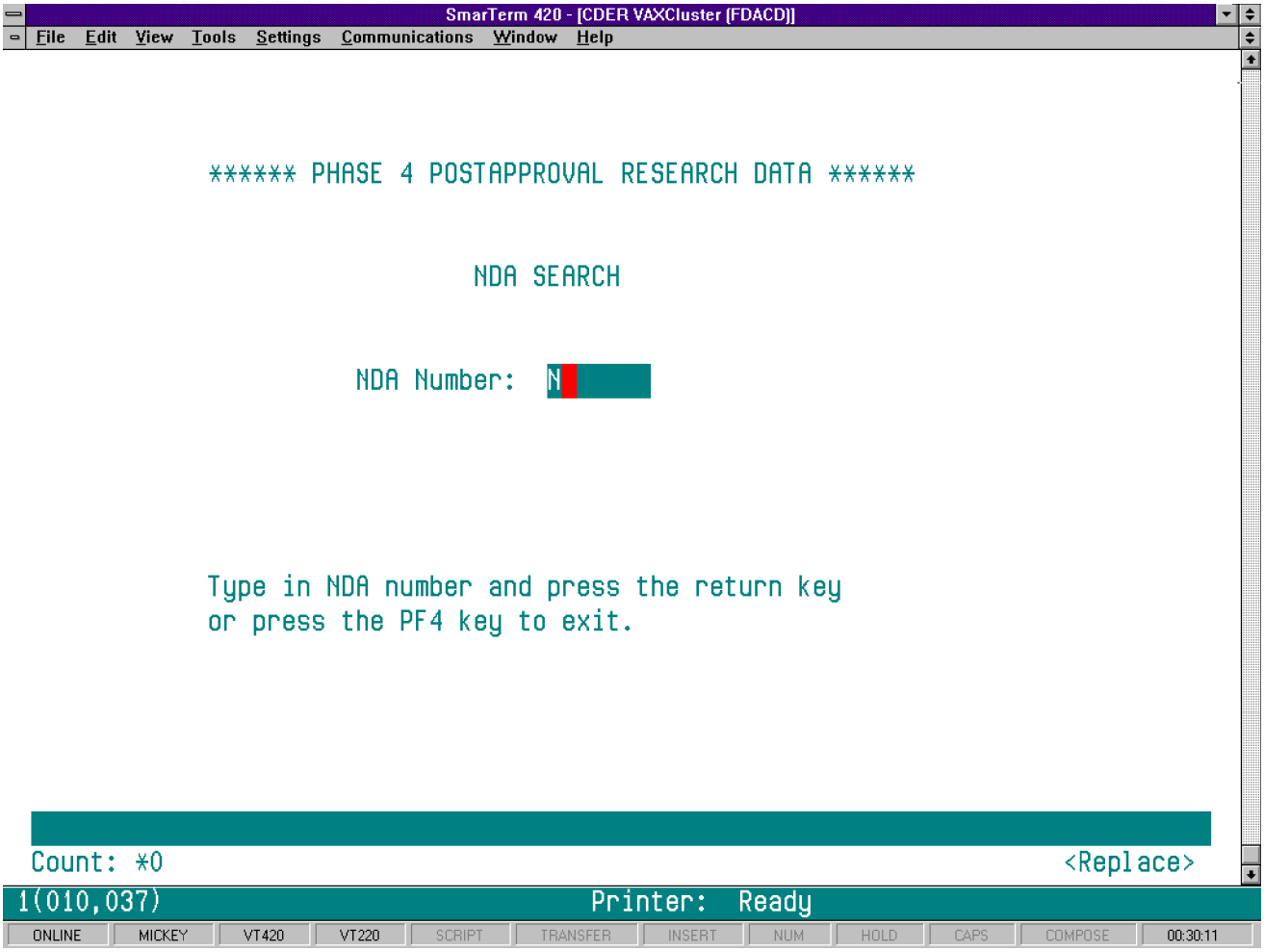
To access Phase 4 Reports, pick #2 from the Phase 4 Query Menu.



Pick the desired report.



To run a query, enter the NDA number.



Attachment B

CDER DATA STANDARDS MANUAL
PHASE 4 COMMITMENT CATEGORIES

FDA Data Element Number. None.

CDER Data Element Number. C-DRG-00901.

Data Element Name. Phase 4 Commitment Category.

Description. This standard provides for all Phase 4 study commitment categories. Phase 4 studies are post-marketing studies that are imposed upon a pharmaceutical firm as a condition for drug approval. Defining the various commitment categories of these studies will permit CDER management to determine trend analysis.

Source. CDER Supervisory Project Managers.

Relationship. Phase 4 Fullfilment Category.

FDA Specifications. None.

CDER Specifications. Phase 4 Commitment Category shall consist of an alphabetic term which has a maximum length restricted to 60 characters, with the comma and hyphen being the only punctuation permissible. Codes representing these Phase 4 Commitment Categories shall consist of three digits.

FDA Approved Date. None.

CDER Approved Date. September 12, 1995.

FDA Revised Date.

CDER Revised Date. December 12, 1995; February 13, 1996.

Data Values.

Name	Definition	Code
ADE/Toxicity, Specified	A study that focuses upon a specific adverse drug experience or a specific drug toxicity in a defined patient population..	001
ADE/Toxicity, Surveillance	A study where no specific adverse drug experience or specific drug toxicity is being investigated in a defined patient population.	002
Animal Study, Other	Any study where animals instead of humans are used.	003
Bioavailability	A study to determine the extent to which an active ingredient of a drug dosage form become available at the site of drug action or in a biological medium believed to reflect accessibility to a site of action.	004

Bioequivalence	A study to determine whether the pharmacokinetics of a drug product is statistically indistinguishable from that of another drug.product with the same active ingredients.	005
Carcinogencity	A study to determine the propensity of a drug to produce or exacerbate tumors or cancer cells.	006
CMC Method Development or Improvement	A study to determine whether a drug or drug product's chemisty, manufacturing, or controls can be alternatively developed or improved upon.	007
Dissolution	A study to determine the characteristics of how a drug product dissolves.	008
Dose-Proportionality	A study designed to establish whether or not proportionate increases in the dose of a drug product are reflected in proportionate increases in pharmacokinetic parameters (i.e., AUC and C_{MAX}).	009
Drug-Drug Comparison	A study to determine the differences and similarities between drugs.	010
Drug-Drug Interaction	A study to determine how a combination of drugs manifests itself over and above that of any particular drug's known effects, including their pharmacokinetics and pharmacodynamics.	011
Drug-Food Interaction	A study to determine how a combination of drug(s) and food manifests itself over and above that of any particular drug's or food's known effects	012
Efficacy	A study to determine a drug's efficacy.	013
Efficacy, Long-Term	A study to determine a drug's efficacy over a long period of time (generally greater than two years).	014
Efficacy, New Indication	A study to determine a drug's efficacy for an indication other than that for which it was originally or supplementally approved.	015
Impurity Identification	A study to identify impurities in the drug product.	016
Literature Search	A computerized survey of the literature using keywords, hypertext, and fuzzy logic to identify applicable books and journal articles.	017
Mutagenicity	A study to determine whether a drug has the potential or ability to cause a mutation in a gene, tissue, organ, or appendage, usually by conducting microbial, insect, mammalian cell, and whole animal tests..	018
Other	Any study that is not already defined by a phase 4 commitment category.	019

Pharmacokinetics	A study to determine the kinetic mechanisms of exogenous drug absorption, distribution, biotransformation, release, transport, uptake, and elimination as a function of dosage, and extent and rate of metabolic processes. The study may also include measurement of the drug's effect upon the body in relation to the concentration time curve.	020
Reproductive Effects, Pregnancy	A study designed to capture and evaluate birth outcomes in women exposed to marketed drugs during pregnancy.	030
Reproductive Effects, Pre-pregnancy	A study to determine the effect of a drug on reproduction (including, but not necessarily limited to, libido, copulation, ovulation, ovogenesis, and spermatogenesis).	021
Special Population, Ages > 60 years	A study to determine a drug's effect in humans 60 years of age or older.	022
Special Population, Ages < 2 Years	A study to determine a drug's effect in humans less than 2 years of age.	024
Special Population, Ages 2 to 6 Years	A study to determine a drug's effect in humans equal to or between the ages of 2 and 6 years.	027
Special Population, Ages 6 to 12 Years	A study to determine a drug's effect in humans equal to or between the ages of 6 and 12 years	028
Special Population, Female	A study to determine a drug's effect in humans of the female gender.	029
Special Population, Other	A study to determine a drug's effect in humans having a particular characteristic (e.g., G6PD deficiency, AIDS, renal failure).	023
Stability	A study over time to determine the propensity of a drug to undergo a chemical or physical change.	025
Teratogenicity	A study to determine whether a drug can cause physcial defects in a developing embryo.	026

Attachment C

CDER DATA STANDARDS MANUAL
PHASE 4 FULLFILLMENT CATEGORIES

FDA Data Element Number. None.

CDER Data Element Number. C-DRG-00902.

Data Element Name. Phase 4 Fulfillment Category.

Description. This standard provides for all Phase 4 study fulfillment categories. Phase 4 studies are post-marketing studies that are imposed upon a pharmaceutical firm as a condition for drug approval. Defining the various fulfillment categories for each study will permit CDER management to determine trend analysis.

Source. DHHS Office of Inspector General, "Postmarketing Studies of Prescription Drugs" dated November 1995.

Relationship. Phase 4 Commitment Category

FDA Specifications. None.

CDER Specifications. Phase 4 Category shall consist of an alphabetic term which has a maximum length restricted to 100 characters, with the comma and hyphen being the only punctuation permissible. Codes representing these Phase 4 Fulfillment Categories shall consist of two digits separated by a decimal.

FDA Approved Date. None.

CDER Approved Date. February 13, 1996.

FDA Revised Date.

CDER Revised Date.

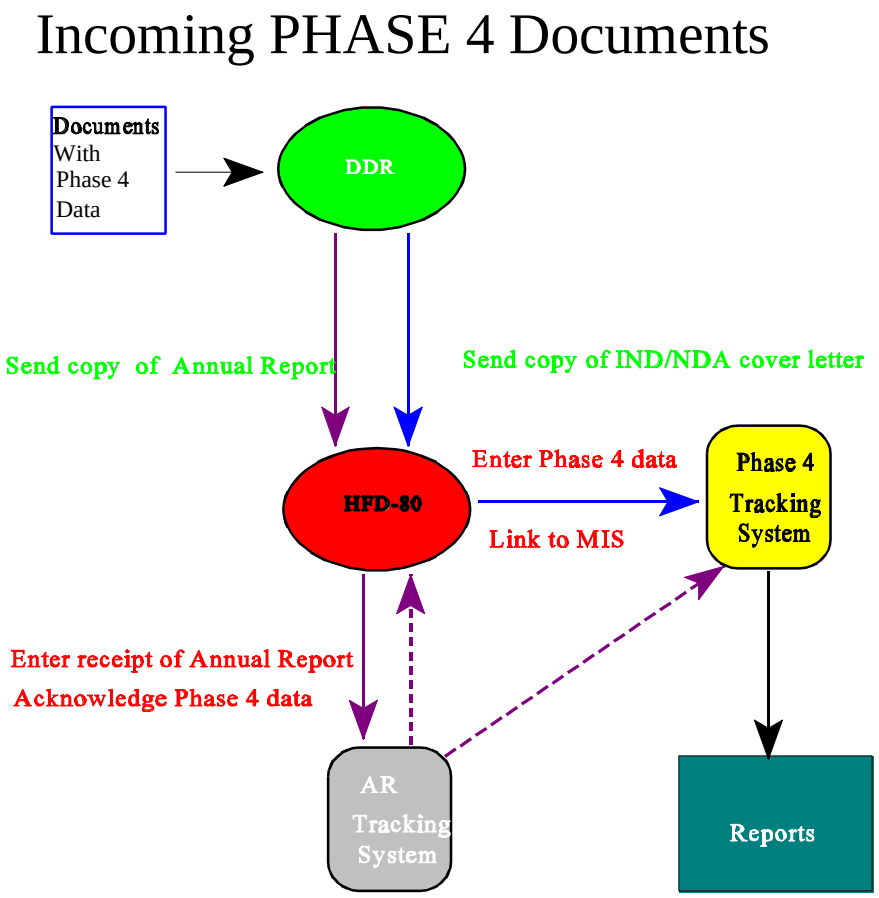
Data Values.

Name	Definition	Code
Study Not Begun, Will Begin in Future	Literal	1.1
Study Not Begun, Company Did Not Agree to Conduct Study	Literal	1.2
Study Not Begun, Company Awaiting Approval of Supplement	Literal	1.3
Study in Progress, Underway	Literal	2.1
Study in Progress, Completed but not Yet Submitted to FDA	Literal	2.2
Study in Progress, Halted	Literal	2.3

Study in Progress, Perpetual	Literal	2.4
Study Submmitted, Accepted by FDA	Literal	3.1
Study Submitted, Not Accepted by FDA	Literal	3.2
Study Submitted, No Determination by FDA	Literal	3.3
Company Released fro Commitment, Drug Not Marketed	Literal	4.1
Company Released from Commitment, Question Answered by Other Studies	Literal	4.2
Company Released from Commitment, reason Unclear	Literal	4.3
Company Released from Commitment, Study Not Feasible	Literal	4.4
Status Unknown, No Information	Literal	5.1

Attachment D

SCHEMATIC FLOW OF PHASE 4 DOCUMENTS



Incoming Phase 4 Documents -

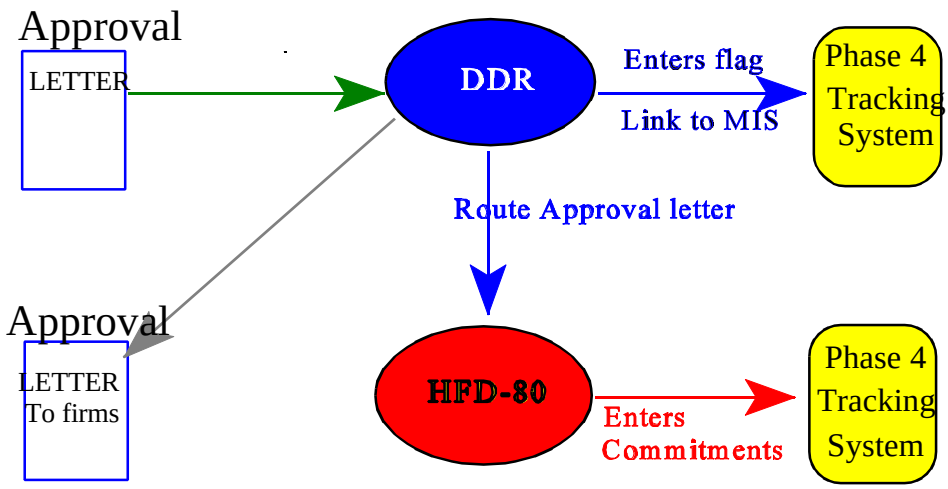
→ If an IND /NDA contains Phase 4 data, DDR will send HFD-80 a copy of the IND/NDA cover letter referring to the Phase 4 data.
HFD-80 will enter Phase 4 data into the Phase 4 Tracking System and link to

→ DDR will send HFD-80 all annual reports. HFD-80 will track annual reports and flag annual reports that have Phase 4 data.

⇢ HFD-80 will enter Phase 4 data into the Phase 4 Tracking system and link to

→ Periodically DDIR will generate reports of outstanding Phase 4 commitments DDIR to then check the documents rooms and work with CSOs to call firms directly to find additional Phase 4 data.

Outgoing PHASE 4 Documents



Approval Letter

Phase 4 commitments will be agreed upon with the firm before approval. The agreed upon commitments will be included in the approval letter.

Approval letter contains paragraph to firm with instructions explaining how to submit Phase 4 data.

Approval letters are send to the division document room.

Approval letter sent to firm

DDR enters a the link to the MIS in the Phase 4 tracking system.
DDR routes a copy of the Approval letter to HFD-80

HFD-80 enters commitments text into Phase 4 tracking system.

Attachment E

SAMPLE APPROVAL LETTER

NDA **NUMBER**

[APPLICANT]
Attention: **[FIRM CONTACT PERSON]**
[ADDRESS]

Dear **[FIRM CONTACT PERSON]**

Please refer to your **[DATE OF APPLICATION]** new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **[TRADE NAME, IF GIVEN, (ESTABLISHED NAME) DOSAGE FORM AND STRENGTH(S)]**.

We acknowledge receipt of your amendment(s) dated **[DATES]**.

This application provides for **[INDICATIONS]**.

We have completed review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated **(DATE OF SUBMISSION)**. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING FOR APPROVED NDA ##-###." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission[s] dated **[DATE(s)]**. These commitments, and their associated schedules for completion, are listed below.

1. **[LIST COMMITMENTS]**

Protocols, data, and final reports should be submitted to IND **##,###** for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment(s), submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly labeled "Phase 4 Commitments." In addition, we request that each annual report to this NDA include a section that summarizes the status of each Phase 4 commitment, identifying each submission and its related commitment. If you feel the situation has changed and the data a Phase 4 study was designed to provide are no longer necessary, fully explain why you believe you should be released from the commitment. All annual reports to this NDA should include an update on Phase 4 studies until you are notified that we consider all commitments to be satisfactorily fulfilled or canceled.

INSERT ADVERTISING PARAGRAPH, IF NEEDED

INSERT METHODS VALIDATION PARAGRAPH, IF NEEDED

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact **[NAME],** Project Manager, phone (301) **[NUMBER]**.

Sincerely yours,

OFFICE OR DIVISION DIRECTOR'S SIGNATURE BLOCK

cc: Orig NDA
HF-2/MedWatch with labeling
HFD-2
HFD-80 with labeling
HFD-10# with labeling
DIVISION FILE
DIVISION/PM
DIVISION/Reviewers and Team Leaders
HFD-40 with labeling
HFD-613 with labeling
HFD-735 with labeling
HFD-560/DBowen with labeling (if OTC drug)
HFD-21 with labeling (if discussed at advisory committee meeting)
HF-35 with labeling (if orphan drug)
DISTRICT OFFICE with labeling
HFD-222/New Drug Chemistry Division Director

DIVISION/drafter/date drafted
typist/dates typed
initialers/date initialed

APPROVAL WITH PHASE 4 COMMITMENTS

Attachment F

SAMPLE LETTER ACKNOWLEDGING PHASE 4 COMMITMENTS MADE AFTER APPROVAL

NDA **NUMBER**

APPLICANT
Attention: **FIRM CONTACT PERSON**
ADDRESS

Dear **FIRM CONTACT PERSON:**

We acknowledge receipt of your letter dated **DATE**, stating your commitment to conduct the following Phase 4 study**[ies]:**

SPECIFY PHASE 4 COMMITMENTS (including schedule for completion)

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter submitted to this NDA. Should an IND not be required to meet your Phase 4 commitment**[s]**, please submit protocols, data, and final reports to this NDA as correspondence. In addition, we request that, under 21 CFR 314.81(b)(2)(vii), you include in your annual report to this application a status summary of each commitment. The status summary should include the number of patients entered in each study, scheduled dates for completion of enrollment, completion of study, and submission of final study report, a list of the dates of all submissions related to this**[these]** commitment**[s]**, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling changes, relating to this**[these]** commitment**[s]** should be clearly designated "Phase 4 Commitments."

If you have any questions, please contact **[NAME]**, Project Manager, phone (301)-**[TELEPHONE NUMBER]**.

Sincerely yours,

DIVISION DIRECTOR'S SIGNATURE BLOCK

Copies: Orig NDA
IND XX-XXX (if needed)
HFD-80
DIVISION FILE
DIVISION PM
DIVISION/Review Team Members

DIVISION/drafter/date drafted
typist/dated typed
initialers/date initialed

GENERAL CORRESPONDENCE (PHASE 4 COMMITMENTS)

Attachment G

SAMPLE DUNNER LETTER FOR FAILURE TO RESPOND TO PHASE 4 COMMITMENTS

NDA **NUMBER**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

APPLICANT
ATTENTION: **CONTACT PERSON**
ADDRESS

Dear **FIRM CONTACT PERSON:**

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADE NAME, IF GIVEN (ESTABLISHED NAME) DOSAGE FORM, STRENGTH.**

Please also refer to your letter of **DATE**, in which you made the following Phase 4 commitment**[s]**:

LIST PHASE 4 COMMITMENT[S]

Our letter of **DATE [, approving this application,]** notes the above Phase 4 commitment**[s]**. To date, we have not received **any/a complete** response to this**[these]** commitment**[s]**. We request that you submit your plan for fulfilling your Phase 4 commitments, or your rationale for why you should be released from this **[these]** commitment**[s]**.

If you have any questions, please contact **[NAME]**, Project Manager, phone (301)-**[TELEPHONE NUMBER]**.

Sincerely yours,

DIVISION DIRECTOR'S SIGNATURE BLOCK

Copies: Orig NDA
IND XX-XXX (if needed)
HFD-80
DIVISION FILE
DIVISION PM
DIVISION/Review Team Members

DIVISION/drafter/date drafted
typist/dated typed
initialers/date initialed

PHASE 4 REPORT REQUEST

Attachment H

SAMPLE ACKNOWLEDGMENT LETTER FOR FULFILLMENT OR NON-FULFILLMENT OF OR RELEASE FROM PHASE 4 COMMITMENT

NDA **NUMBER**

APPLICANT
Attention: **FIRM CONTACT PERSON**
ADDRESS

Dear **FIRM CONTACT PERSON**:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADE NAME, IF GIVEN (ESTABLISHED NAME) DOSAGE FORM AND STRENGTH.**

We acknowledge receipt of your submission(s) dated **[DATE(S)]** regarding your Phase 4 commitment to **[SPECIFY COMMITMENT].**

We have completed review of your Phase 4 data and conclude that your commitment has been fulfilled.

OR

We have completed review of your submission and conclude that you may be released from your commitment because **[INSERT RATIONALE]**.

OR

We have completed review of your Phase 4 data and request that you submit a labeling supplement making the following changes to your labeling:

1. **LIST CHANGES REQUESTED**

OR

We have completed review of your Phase 4 data and request that you submit a chemistry supplement to provide **(INSERT DESCRIPTION OF SUPPLEMENT BEING REQUESTED)**.

OR

We have completed review of your submission(s) and feel that the terms of the commitment have not been met. **[INSERT REASONS FOR FAILURE TO MEET COMMITMENT(S) AND WHAT ACTION THE DIVISION PROPOSES THE APPLICANT TAKE.]**

If you have any questions, please contact **[NAME]**, Project Manager, phone (301)-**[TELEPHONE NUMBER]**.

Sincerely yours,

DIVISION DIRECTOR'S SIGNATURE BLOCK

Copies: Orig NDA
IND XX-XXX (if needed)
HFD-80
DIVISION FILE
DIVISION PM
DIVISION/Review Team Members

DIVISION/drafter/date drafted
typist/dated typed
initialers/date initialed

GENERAL CORRESPONDENCE (PHASE 4 COMMITMENTS)

OR

SUPPLEMENT REQUEST (PHASE 4 COMMITMENTS)

Attachment I

SAMPLE DUNNER LETTER FOR PHASE 4 UPDATE MISSING FROM ANNUAL REPORT

NDA **NUMBER**

APPLICANT
Attention: **FIRM CONTACT PERSON**
ADDRESS

Dear **FIRM CONTACT PERSON**:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADE NAME, IF GIVEN (ESTABLISHED NAME) DOSAGE FORM AND STRENGTH.**

We acknowledge receipt of your Annual Report dated **[DATE].**

A preliminary review of your annual report reveals that it is lacking an update on your Phase 4 commitment**[s]** as specified in our approval letter of **[DATE].** Please provide the requested information within 30 days of the date of this letter.

If you have any questions, please contact **[NAME]**, Project Manager, phone (301)-**[TELEPHONE NUMBER]**.

Sincerely yours,

DDIR SIGNATURE BLOCK

Copies: Orig NDA
HFD-80
DIVISION FILE
DIVISION PM
HFD-80/drafter/date drafted

typist/dated typed
initialers/date initialed

REPORT REQUEST (PHASE 4 COMMITMENTS)