OFFICE OF NEW DRUG CHEMISTRY

Procedures for Assessing Chemistry, Manufacturing, and Controls Data in NDA Annual Reports

CONTENTS

PURPOSE

- This MAPP describes the procedures to be followed when a chemist in CDER's Office of New Drug Chemistry (ONDC) receives an annual report (AR) to a new drug application (NDA).

BACKGROUND

- Important chemistry, manufacturing, and controls (CMC) data on postapproval changes and commercial product quality are routinely reported to the Agency through NDA Annual Reports; therefore, a chemistry reviewer should assess each AR. It is increasingly important to understand the product quality information in ARs, because the Food and Drug Administration Modernization Act and new guidance documents (e.g., SUPAC guidances, FDA guidances for industry on *Changes to an Approved NDA or ANDA*, *BACPAC-1: Intermediates in Drug Substance Synthesis*) recommend that many postapproval changes accompanied by supportive data be reported in an AR.

REFERENCES

- Guidance for industry on *Format and Content for the Chemistry, Manufacturing, and Controls Section of an Annual Report* (September 1994)

- 21 CFR 314.81(b)(2), Annual Reports
- Guidance for industry on *Changes to an Approved NDA or ANDA* (November 1999)
- MAPP 5310.2, Drafting, Circulating, and Signing Chemistry, Manufacturing, and Controls Letters (November 1998)
- MAPP 6010.2, Procedures for Tracking and Reviewing Phase 4 Commitments (November 1996)

POLICY

- Within 2 months of receipt of an annual report, the chemistry reviewer will give the AR a preliminary review to determine whether any reported changes require the submission of a supplement (CBE-0, CBE-30, or PA). If a supplement is required, the chemistry reviewer will write a CMC review or a memorandum to support the decision and issue a letter or fax to the applicant requesting such a submission. When the evaluation of the AR covers only issues related to the appropriateness of filing CMC changes, the chemistry reviewer will write a memorandum, not a CMC review, to prevent the AR from being prematurely closed administratively.

- Within 3 months of receipt, any Phase 4 status reports submitted in the AR will be reviewed and processed according to instructions provided in the MAPP on Procedures for Tracking and Reviewing Phase 4 Commitments. When the evaluation of the AR covers only Phase 4 status reports, the chemistry reviewer will write a memorandum, not a CMC review, to prevent the AR from being prematurely closed administratively.

- Within 12 months of receipt, the chemistry reviewer will fully assess each AR.

- A deficiency letter or fax for an AR will be written when (1) a postapproval change is not adequately supported with data; or (2) there are failures or significant trends in the stability data.

- While it is appropriate to assess each AR, a written review is not necessary if the data and changes reported in the AR are acceptable. A conclusion of *no action indicated* (NAI) is acceptable if a letter or fax does not need to be sent to the applicant or there are no Phase 4 reports to review (i.e., when no regulatory action is necessary).

- Equal credit toward a reviewer's workload will be given for ARs for which a review was completed, for which a letter or fax was sent to the applicant, or for which NAI was determined to be appropriate, provided the action was taken within the time frame stated above.

- If the AR is not reviewed within 12 months of the time of receipt, it should be reviewed as soon as workload permits. However, no workload credit will be given for late reviews of ARs.

RESPONSIBILITIES

- **The Chemistry Reviewer will:**

  Determine whether CMC changes and relevant changes in labeling are appropriate for reporting in the AR according to current guidance and regulation. If there is an incorrect submission of a change, the chemist will prepare a review or memorandum to support the decision and will issue a letter or fax to the applicant requesting the submission of the appropriate supplement.

  Assess relevant data in each AR, which will typically include CMC changes; stability data and/or changes; changes in the "Description," "Dosing and Administration," and "How Supplied" sections of the package insert; changes to the container and/or carton labels, the distribution data, and chemistry literature information.

  Determine whether study reports and data adequately support these changes, and whether the stability data support the expiration dating of the product.

  Prepare a review document, if significant deficiencies are noted (e.g., insufficient data to support change), focusing on the comments that need to be conveyed to the applicant. If the AR contains Phase 4 reports, a review of the report must be conducted.

  Close out the assessment, either as NAI or with a written review, if no comments or significant deficiencies need to be conveyed to the applicant.

  Obtain concurrence from chemistry team leader on written review, and file resulting document in administrative records (e.g., Division Filing System (DFS), application archival copy, division files).

- **The Chemistry Team Leader will:**

  Work with the chemistry reviewer to ensure that consistent deficiency

recommendations are provided to applicants, and concur on written reviews.

Ensure that a letter or fax is issued in a timely manner if deficiencies have been identified by the chemistry reviewer.

Ensure that reviews of Phase 4 reports are completed and appropriately processed.

Resolve any controversial issues through discussion in the appropriate forum.

Bring to management's attention any significant deficiencies identified by the chemistry reviewer (e.g., for recognition during performance evaluations or at All-Hands meetings).

Ensure that late ARs (later than 12 months after the date of receipt) are assessed as soon as workload permits.

- **The Chemistry Deputy Division Director and Division Director will:**

  Resolve any controversial issues brought forward by the chemistry reviewer or team leader through discussion in the appropriate forum.

  Ensure the quality and consistency of the review of ARs across chemistry teams.

  Ensure that workload reports accurately reflect the assessment of ARs performed by chemistry reviewers and team leaders.

  Consider whether significant deficiencies identified by the chemistry reviewer should be presented for training purposes at Division All-Hands, ONDC All-Hands, or ONDC Scientific Rounds.

- **The Office of New Drug Chemistry will:**

  Resolve any controversial issues brought forward by the chemistry reviewer, team leader, or Division Director through discussion in the appropriate forum.

  Ensure the quality and consistency of the review of ARs across chemistry divisions.

  Ensure that periodic reports on workload, including AR reviews completed in 12 months, are prepared for individual chemistry reviewers, teams, and divisions.

  Evaluate and determine which examples of significant deficiencies found in ARs should be presented for training purposes at ONDC All-Hands or ONDC Scientific Rounds.

Include AR workload across chemistry divisions in the overall workload analysis for resources (FTEs).

PROCEDURES

Within 2 months of receipt of an AR submission, the chemistry reviewer performs a preliminary review to determine whether any changes reported require the submission of a supplement.

Within 3 months of receipt of an AR, the chemistry reviewer completes a review of any Phase 4 commitment reports and processes the AR in accordance with Agency guidance.

The chemistry reviewer assesses each AR, either individually or in conjunction with any applicable supplement under review.

After assessing the AR, if the chemist finds no significant deficiencies and there are no Phase 4 commitment reports to review, the chemist closes out the assessment as NAI or prepares a CMC review using the current administrative procedures.

If significant deficiencies are noted (e.g., insufficient data to support change), the chemist prepares a review document or a memorandum. The written review of the AR or the memorandum is to provide information needed to generate a deficiency letter or fax. The type of information that the chemist will typically include in a written review or memorandum will be a summary of data analysis, deficiency comments and recommendations, and administrative data (e.g., application number, date of the AR, applicant's mailing address, contact name).

One acceptable format for the chemist's review of CMC issues is a memorandum with a draft deficiency letter or fax. In this situation, the chemist enters the memorandum and the text of the letter or fax into the appropriate document archive (e.g., DFS) and obtains concurrence from the chemistry team leader. The finalized letter or fax is transmitted to the applicant using standard procedures, and the communication is recorded in the administrative records.

If the chemist writes a CMC review, once the review is finalized and has the concurrence of the chemistry team leader, the chemist enters the review into the document archive and processes the review using standard procedures.

The letter or fax is routed through the appropriate primary reviewers and team leaders for corrections and endorsement. For a letter containing only chemistry

comments and/or deficiencies, the chemistry team leader will be the signatory authority. When comments from multiple disciplines are included, the signatory authority will follow the recommendations in MAPP 5310.2, Drafting, Circulating, and Signing Chemistry, Manufacturing, and Controls Letters.

Standard administrative procedures should be used to ensure that the finalized letter is mailed or faxed to the applicant and noted in the appropriate records.

The Office of New Drug Chemistry will ensure that periodic workload reports are prepared for chemistry teams, including the number of ARs assessed within 12 months of submission. Annual report assignments that were closed by a determination of NAI or by completion of a review will be given equal weight, because both reflect a completed assessment of the information in the AR. Reports of overdue AR assessments will be generated for information purposes, but there will be no penalty (except no credit given) to the chemists, since the AR assignment may not have been closed for a variety of reasons. For example, the assessment may be substantially complete, pending the resolution of one regulatory judgment, or the reviewer may be assessing the AR in conjunction with a supplement.

The chemistry team leader and management staff will discuss whether significant deficiencies identified by the chemistry reviewer should be presented at All-Hands and/or ONDC Scientific Rounds, and will periodically review the workload reports to verify that they accurately reflect the assessment of ARs.

EFFECTIVE DATE

This MAPP is effective upon date of publication.