NEW DRUG CHEMISTRY

Drafting, Circulating, and Signing Chemistry, Manufacturing, and Controls Letters

CONTENTS

PURPOSE

This MAPP clarifies practices related to implementing the memorandum of understanding (MOU) for the timely routing and sign-off of chemistry, manufacturing, and controls (CMC) letters. It describes the policies and procedures to be used by the Office of Review Management (ORM) review divisions, and the Office of New Drug Chemistry (ONDC) divisions for the drafting, circulating, and signing of the following letters relating to CMC:

- CMC Supplement Action Letters
- CMC NDA and Supplement Information Request (IR) Letters
- CMC IND Information Request Letters
- CMC Drug Master File (DMF) Letters

BACKGROUND

The Center for Drug Evaluation and Research (CDER) was restructured in 1995 to create the Office of New Drug Chemistry in the Office of Pharmaceutical Science. After this restructuring, the review chemists continue to be co-located with the Office of Drug Evaluation (ODE) review divisions in the Office of Review Management. The MOU was created to clarify the way the ONDC and the offices and divisions of drug evaluation (ODEs and respective ODE divisions) would work together to accomplish the new drug chemistry review functions.

REFERENCES

- Memorandum of Understanding Between the Office of Review Management and the Office of Pharmaceutical Science Regarding the Responsibilities of the Offices and Divisions of Drug Evaluation and the Office of New Drug Chemistry (December 1996).
- Final Rule, Delegation of Authority and Organization; Center for Drug Evaluation and Research, 62 FR 2554-58, January 17, 1997.
- Food and Drug Administration Modernization Act of 1997.
- Prescription Drug User Fee Act (PDUFA).

POLICY

- CMC supplement action letters

  Actions on manufacturing supplements that do not require in-vivo biopharmaceutics, pharmacology and/or clinical reviews, and supplements containing labeling changes that are limited to (1) carton and immediate container labels, (2) DESCRIPTION or HOW SUPPLIED sections of the package insert that do not change the packaging or increase the container size in such a way that could result in the administration of an unapproved dose or dosing regimen, or (3) name of the manufacturer are the responsibility of the ONDC chemistry team leader co-located in the ODE division. All other manufacturing supplements will be signed by the ORM Division Director or Deputy Division Director.

  Differences of opinion regarding signatory authority that cannot be resolved at the division level (ONDC and ORM) should be referred to the Director of ONDC and the Director of the appropriate ODE for resolution.

- CMC NDA and supplement IR letters

  IR letters related to manufacturing supplements and pending NDAs will be signed by the chemistry team leader or Chief, Project Management Staff (CPMS) with concurrence from the chemistry team leader when the issues pertain only to chemistry, manufacturing, or controls issues, including validation of sterility, environmental assessment, and stability. IR letters will be signed by the CPMS with concurrence from the appropriate team leaders when there is a combination of chemistry and other issues (e.g., in vivo biopharm, parm/tox, clinical).

  As part of the PDUFA/Modernization Act agreements, comments and/or deficiencies from reviews will be communicated to the sponsor as soon as the review has been completed. All NDA and supplement IR letters will include the following as their last paragraph:

*These comments are being provided to you prior to completion of our review of the application to give you **preliminary** notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not consider your response prior to taking an action on your application during this review cycle.*

- CMC IND IR Letters

  IR letters related only to the CMC section of an IND will be signed by the chemistry team leader.

- CMC DMF letters

  All CMC DMF letters will be signed by the chemistry team leader.

RESPONSIBILITIES AND PROCEDURES

Drafting and circulating CMC letters

- The draft letters, as referred to in this document, should be distinguished from the term *draft letter* formerly used as a title for designating the section of the review that listed deficiencies and comments to be communicated to the sponsor/applicant. In this MAPP, it refers to communications in draft intended for IND sponsors, NDA applicants, or DMF holders that have been put into letter format. An ONDC staff member, project management staff member, or secretary should draft the letter promptly, usually within three working days of receipt of a review that requires a letter unless other priorities supersede this time frame.

- The letter should be circulated, finalized, and issued promptly, usually within three working days of drafting the letter unless other priorities supersede this time frame. All draft letters should be circulated to each appropriate reviewer, team leader, and the project manager. Circulation of letters should be coordinated so that the reviewer and team leader have the opportunity to review all changes made to ensure accuracy of content prior to finalization of the letter. Changes should be minimal and highlighted for ease of identification.

- These time frames should be shortened when needed to meet PDUFA or review team goal dates. Each individual who reviews the letter and the person with the signatory

authority (chemistry team leader or ORM Division Director) is accountable to these time frames.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A

MEMORANDUM OF UNDERSTANDING BETWEEN THE OFFICE OF REVIEW MANAGEMENT AND THE OFFICE OF PHARMACEUTICAL SCIENCES REGARDING THE RESPONSIBILITIES OF THE OFFICES AND DIVISIONS OF DRUG EVALUATION AND THE OFFICE OF NEW DRUG CHEMISTRY

GENERAL COMMENTS

This memorandum of understanding (MOU) is intended to clarify the way that the Office of New Drug Chemistry (ONDC) and the offices and divisions of Drug Evaluation (ODEs and respective ODE Divisions) will work together to accomplish the new drug chemistry review functions.

Generally, ONDC's responsibilities will include developing and instituting new drug chemistry policies concerning pharmaceutical science issues, supervising the new drug chemistry and pharmaceutical science microbiology reviewers, assuring the consistent application of policy to review, and planning and administering the training and professional development of CDER's new drug chemists and pharmaceutical science microbiologists. These functions will be performed in collaboration with representatives of the chemistry function from the Office of Generic Drugs. ONDC also will be responsible for assuring adherence to the PDUFA goals by its reviewers, team leaders, and division directors.

Each Office of New Drug Evaluation (ODE) and its respective ODE Divisions will continue to be responsible for decisions about the approvability of original NDAs, effectiveness supplements, and labeling supplements as was the case prior to this MOU. The ONDC (through its team leaders) is responsible for decisions about the approvability of manufacturing supplements to which final sign-off was previously delegated to the supervisory chemists. The ONDC "team leaders" will be responsible for the final sign-off of action letters for these manufacturing supplements as they were previously as "supervisory chemists." The regulations in the CFR will be changed as soon as possible to reflect this change in nomenclature (as it does not reflect any real change in level of responsibility for manufacturing supplement sign-off). Action letters for those manufacturing supplements that previously required ODE Division Director sign-off will still require ODE division sign-off. The manufacturing supplements requiring ODE Division Director sign-off will be coordinated by the ONDC co-located team leaders and the appropriate ODE division project manager.

Many units outside the Offices and Divisions of Drug Evaluation - including CDER's Office of Compliance, FDA's field organization, and CDER's biometricians, as well as personnel from ONDC, contribute reviews and advisory opinions to the ODE Division Directors and Office Directors; however, it is understood that the present delegations of authority on approvability of NDAs, effectiveness supplements, and labeling supplements are maintained by the MOU (i.e., it is delegated to the ODE Division or Office [as appropriate]). In addition, the present delegation of authority for final decision on IND "holds" to the ODE Division Director level is not altered by this MOU.

PERSONNEL AND STAFFING

1. Work Assignment and Staffing: Primary chemistry reviewers and chemistry team leaders will be assigned to be co-located with an ODE review division. The work assigned the chemistry reviewers will be primarily the chemistry work relevant to the ODE review division's work; however, there may be occasional situations in which the work of other ODE divisions might also be assigned to chemistry reviewers co-located elsewhere, if such work assignment is more efficient from the chemistry perspective. There are a number of options for handling backlogs or unexpected special assignments including: (1) sending work to other teams, (2) temporarily assigning reviewers to a different team, (3) permanently reassigning reviewer(s) to a different team, and (4) overtime. Decision on how best to resolve workload concerns will be made through consultation with the managers and chemists concerned.

   Assignment of a chemistry reviewer to be co-located with a specific ODE division will be the responsibility of the Director of the ONDC and the ONDC Division Directors . The director of any ODE division impacted by primary chemistry reviewer or chemistry team leader location assignments will be consulted before any chemistry personnel assignment to or from the ODE division occurs. It is understood that the usual case should be that there is agreement between the ODE Division Director and the ONDC Division Director on assignments; however, it is understood that the final decision on assignment rests with ONDC. Chemistry assignment disagreements may be appealed to the Director of the ONDC, then to the Deputy Director for Pharmaceutical Science, and then to the Center Director, as needed.

2. Performance Rating: The Agency adopted a new performance evaluation system in October 1996. CDER is in the process of full implementation of this system starting January 1997. Formalization of this element of the MOU will occur at that time. One of the principles that will be adopted throughout the Center is input by team components when an individual works on cross-functional teams. The evaluation of chemists in ONDC will incorporate input from the ODE division director which the chemist supports.

3. Recruitment/Promotion: Final decisions on recruitment and promotion of ONDC reviewers will be the responsibility of ONDC management. It is expected the ODE division staff will be able to interview potential co-located chemistry hires and that the ONDC decision to hire an individual who will be placed in a particular ODE division will be made only after consultation with the potential recipient Division, as noted previously in this MOU. It is also expected that each ODE office will have input into the chemistry team leaders assigned to it, and that individual decisions on chemistry team leaders will be made by the ONDC Division Director with input from the particular ODE Office Director(s) affected by the decision. While final decisions on recommendations for promotions and awards rests with ONDC, it is expected that the ODE Division Directors of co-located employees may also initiate-such recommendations.

4. Staff Development: ONDC is responsible for training, travel, and other educational needs of its staff. This includes the fiscal and administrative responsibilities associated with these functions.

5. Disciplinary Actions: Formal personnel actions will be the responsibility of ONDC. Any conduct issues of concern to the ODE Division Director should be immediately communicated by him/her to the ONDC Division Director who is the responsible supervisor for the group or individual of concern. Likewise, any conduct issues of concern to the chemistry reviewers or team leaders co-located in an ODE division involving personnel in that division should be communicated to his/her ONDC team leader or Division Director for discussion and resolution with the ODE Division Director. As needed, high level leadership

from both OPS and ORM can be incorporated into these discussions.

WORK FLOW

1. Assignment of NDA and IND Reviews: Assignment of chemistry review of NDAs and INDs within each ODE division is the responsibility of the co-located ONDC team leader in conjunction with the ODE Division Director (or his/her designee for this purpose). Timelines, milestones for the completion of items, and priorities will be set by the leadership of the ODE division through discussions and meetings with all affected reviewers and team leaders. Any disagreement should be communicated to the appropriate ONDC Division Director.

2. Manufacturing Supplements: Review assignments for manufacturing supplements are the responsibility of the co-located ONDC team leader. However, the ODE Division Directors will be cognizant of the workload of the co-located chemistry team and the importance of meeting/exceeding PDUFA goals for this type of submission.

3. Priorities: As is the case generally within CDER, completion of user fee impacted work - including INDs and treatment INDs - will be given priority over other activities by ONDC staff.

   In addition, when ODE priorities conflict with manufacturing supplement priorities or other ONDC priorities, it is the responsibility of the leadership of the ODE division and the ONDC to develop a plan to either re-assign work to eliminate the conflict or to mutually agree upon the order in which the priorities will be accomplished. If a mutually agreeable decision cannot be reached, a meeting with both the Deputy Center Director for Review Management and the Deputy Center Director for Pharmaceutical Science should be arranged. If necessary, the Center Director may be required to decide final priorities; however, it is the general understanding that these issues will be solved at the ODE Division Director and ONDC Division Director level.

4. Resource Management: ONDC is responsible for management of its workload and human resources so that resource allocation and workload measures are clear to all.

5. EERs: EER requests and follow-up coordination with the Office of Compliance will be the responsibility of ONDC as part of the overall review of the NDA and IND applications. Policies and procedures for management of the EER process will be developed by ONDC management. Until these policies and procedures are developed and implemented, the current process in each of the ODEs will remain in effect.

PERFORMANCE

1. On a quarterly basis, the Center Director, along with the Senior Center Project Manager, will meet with the leadership of the OPS (including the Office and Division Directors and the chemistry team leaders) and the leadership of the ORM (including the Office and Division Directors) to discuss the performance of the new drug chemistry program. Areas where performance has excelled will be explored for "lessons learned" that can be relayed to other work units. Areas where performance has lagged will be explored in an effort to determine the reasons for the less than adequate performance so that it can be improved.

POLICY JURISDICTION

1. Chemistry Policy: ONDC will be responsible for the development and implementation of policies relevant to the pharmaceutical science aspects of new drug applications with appropriate consultation with other groups.

2. Clinical Holds: IND clinical holds will continue to be the responsibility of the ODE Division Director. Hold recommendations by ONDC team leaders are advisory to the ODE Division Director.

3. NDA Actions: Actions on NDAs, effectiveness supplements, labeling supplements, and manufacturing supplements requiring ODE Division Director sign-off are the responsibility of the ODE or ODE division (as appropriate). The ONDC team leader recommendations on such actions are advisory to the ODE and ODE divisional personnel to whom sign-off authority is delegated. As such, the ODE Office Director or ODE Division Director may overrule the recommendation of the ONDC staff, or may choose to proceed in the absence of a final recommendation by the chemistry team leader if the. ODE Director or ODE Division Director believes it is not necessary to issue an appropriate action letter. Any such actions shall be documented in writing.

4. Meetings: ONDC's new drug chemists and pharmaceutical science microbiologists are responsible for requesting meetings with pharmaceutical firms when necessary to address specific CMC and microbiology issues which affect the approval of NDAs and other types of applications. These meetings should be coordinated with the affected ODE review divisions. ONDC personnel will ensure that the corresponding project manager(s) in the ODE divisions is immediately informed of the need and rationale for the meeting and provide an agenda (and list of proposed sponsor participants, if appropriate) for the meeting. The project manager(s) will then provide the necessary administrative support for these CMC meetings including contacting the firm to arrange the meeting, ensuring appropriate participation, and ensuring that minutes are prepared. The ONDC chemist or microbiologist will work closely with the ODE review divisions and the project manager(s) to facilitate the discussions and ensure the success of such meetings.

5. Sign-offs: Final sign-off for chemistry reviews on NDAs, DMFs, INDs, and supplements is the responsibility of the co-located chemistry team leader in the ODE division.

   Final chemistry sign-off on action packages for non-NME NDAs is the responsibility of the co-located chemistry team leader in the ODE division.

   Final chemistry sign-off on action packages for NME NDAs is the responsibility of the ONDC Division Director who supervises the chemistry team that reviewed the application.

   Final sign-off on letters to sponsors to request chemistry information, action letters on manufacturing supplements (for which the team leader has sign-off authority), and action letters on DMFs is the responsibility of the co-located chemistry team leader in the ODE division.

6. Trade Marks/Trade Names: The ODE division may either decide to adjudicate the trade mark/trade name itself or it may decide to refer it to the Nomenclature Committee for a recommendation. In the case of referral to the Nomenclature Committee, the recommendation of the committee is advisory to the ODE Division.

7. Review of Carton Labeling and Immediate Container Labeling: The review of the carton labeling and the immediate container labeling, as well as certain portions of the package insert, is the joint responsibility of

the ODE Division and the review chemists. This represents no change from the current division of responsibility.

ADMINISTRATIVE SUPPORT

1. Equitable Treatment: ONDC staff co-located in the ODE Divisions are to be treated in the same professional manner as their ODE divisional counterparts and will be considered their professional equals.

2. Space: It is the responsibility of Center management to provide to the ONDC staff co-located in an ODE division an allocation of space coincident with the space provided the ODE Division. These offices are under the management supervision of ONDC.

3. Support Staff: ONDC is responsible for providing secretarial support for its staff. Until such staff is identified and in place, the secretarial staff in the ODE divisions will continue to provide support for the co-located chemistry staff.

   CSOs and project managers in the ODE Divisions will continue to provide project management and related support to the co-located chemistry staff just as they do for other review disciplines in their ODE division for work items for which the division is responsible. These project managers continue to be responsible for the cross-cutting project management of the review of specific applications.

   ONDC is responsible for administrative support/ project management support for activities of their co-located staff which are not ODE divisional activities.

4. Shared Equipment and Supplies: The ODE Division will be responsible for the acquisition of routine office supplies for the ODE staff end for the co-located chemistry staff. It makes no sense to have "ODE paper" and "chemistry staff paper," etc. In addition, it makes no sense to duplicate equipment purchases of faxes, copiers, overhead projectors, etc. These items are for the use of both the ODE Divisional staff end co-located chemistry staff on an equal basis.

   The Office of Management is responsible for assuring a pro-rata share of operating expense dollars to each ODE division that houses co-located chemistry staff to cover the chemistry supplies and other operating expenses of shared equipment.