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# Manual of Standard Operating Procedures and Policies

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## Regulatory - Vaccines

### Routing and Signature Requirements for Regulatory Letters (Delegation of Signature Authority in OVRR)

SOPP 9201

Version #1

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#### 1. Purpose

Describes the routing and signature authority for regulatory letters in the Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER).

#### 2. Definitions

Some of the regulatory letters available to reviewers are described below.

##### **Approval Letter**

- An approval letter and accompanying issuance of appropriate license(s) will constitute the final action on the outstanding reference number(s) following completion of all aspects of the review process for the license application/supplement, including testing of submitted product lots, pre-licensing inspection, if needed, and evaluation of final printed labeling or a suitable alternative.

##### **Clinical Hold Letter**

- A letter that contains an explanation of the basis for the clinical hold action. A complete clinical hold represents a hold of all clinical work requested under the IND. The clinical hold may be a partial clinical hold where only part of the clinical work requested under the IND, e.g., a specific protocol, is not allowed to proceed; however, other protocols are allowed to proceed under the IND. If only part of a protocol is allowed to proceed, with progress to the next part contingent upon FDA review/approval of additional data, this is also a partial hold. In contrast, if the Agency has told a sponsor that the sponsor needs to review results of a clinical study (or pre-clinical data) before proceeding, there is no clinical hold.

##### **Note: Clinical Hold**

is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing clinical investigation

##### **Complete Response Letter**

- When the complete review indicates that there are deficiencies remaining which preclude the approval of the application or supplement at that time this letter will be issued. The Complete Response Letter will summarize all of the deficiencies remaining, and where appropriate, describe actions necessary to place the application/supplement in a condition for approval.

**Discipline Review Letter**

- This letter is used to convey early thoughts on possible deficiencies found by a discipline review team for its portion of the pending application at the conclusion of the discipline review. These letters are not considered to be action letters because they do not represent a complete review of the submission and therefore do not stop the User Fee Review Clock.

**IND Letters** - A type of regulatory letter used in response to Investigational New Drug (IND) applications.

**Information Request or Deficiency Letter**

- This letter notifies the applicant that CBER needs additional information or clarification of the data submitted to a license application or supplement. Information Request or Deficiency Letters are not considered to be action letters because they do not represent a complete review of the submission and therefore do not stop the User Fee Review Clock.

**License Application Letters**

- The types of letters that constitute complete Agency actions (for performance goal and review clock purposes) in response to the license application or supplement review process are complete response and approval letters. Action letters are the result of complete Agency review of applications or supplements and stop the review clock. Other non-action type letters are also described below.

**Refusal to File Letter**

- When the committee believes that a meaningful review of the application cannot be performed because the application is deficient or incomplete a Refusal to File letter is issued to the applicant. The committee is referred to the CBER Refusal to File Guidance Document, SOPP 8404.

**Response Letter to a Sponsor's Complete Response** - A letter to the sponsor from the FDA in response to a sponsor's complete response in which the sponsor

1. is allowed to proceed under the IND as proposed by the sponsor (i.e., the clinical hold is lifted),
2. is allowed to proceed with specific restrictions not proposed by the sponsor (i.e., a partial clinical hold), or
3. is informed that studies under the IND still may not proceed.

In the latter two cases, the letter will set forth as to why the clinical hold is being maintained. This letter should be issued to the sponsor within 30 days of receipt of the sponsor's complete response.

**Review Letters for INDs and Master Files**

- This letter notifies the applicant that CBER requires additional information/clarification about the data submitted to an IND or Master File. Letters may be issued at any time during the review of a MF or IND and their amendments. The letters may include requests for additional information, clarifications and confirmations of data and proposals, administrative actions and advice from OVRP on product development.

**3. Background**

OVRP issues a variety of regulatory letters, from action letters for product license applications and supplements to clinical hold letters for investigational new drug applications and amendments. It has been the policy in OVRP that all regulatory letters were signed by the Office Director. The exceptions to this were IND administrative letters such as reactivation letters or reference number assignment and filing letters for original applications and supplements. OVRP will delegate signature authority on non-administrative regulatory letters as outlined in this standard operating procedure. The Center Director continues to retain authority to issue biologics licenses for all new biological entities, as per CFR Title 21, Part 601, Subpart A, Section 601.4.

**4. Policy**

It is the policy of OVRR that all regulatory letters, including action letters and administrative letters, will be routed for appropriate review and/or signatures to assure concurrence with the issues described in each letter.

## 5. Responsibilities and Procedures

The Branch Chiefs in the Division of Vaccines and Related Products Applications (DVRPA) will sign above their signature blocks on all administrative regulatory letters such as reference number assignment letters, withdrawal letters for license applications and supplements, and filing letters. Acknowledgement letters for INDs and Master files, administrative letters for INDs (inactivation confirmation, exemption, pre-inactivation, pre-termination, reinstatement, report request, withdrawal confirmation, and waiver denied) will be signed by the DVRPA CSO/CST.

All non-administrative regulatory letters such as complete response letters, clinical hold letters, refusal to file letters, information request letters and approval letters for applications and supplements will be routed in draft via e-mail to members of the review committee, the appropriate branch chief/lab chief, the appropriate Division Director(s), the Office Director, and the Associate Director for Regulatory Policy. E-mail turn-around time for IND letters will be 24 hours. Turn-around time for reviewing all other regulatory letters will be determined on a case-by-case basis with the goal of meeting the appropriate PDUFA and FDAMA milestones. No response received in the designated time frame will be regarded as indicating your concurrence. **All regulatory letters will be issued from DVRPA.**

The following types of letters are covered in this section:

- Complete Response Letters for Original License Applications and Supplements, Approval Letters and Refusal to File letters for Supplements
- Discipline Review Letters for License Applications and Supplements
- Information Request Letters
- Approval Letters and Refusal to File Letters
- Signatures for IND Clinical Hold Letters and Letters in Response to Sponsor's Complete Response
- Review letters for IND / Master Files

### **Complete Response Letters For Original License Applications And Supplements, Approval Letters And Refusal To File Letters For Supplements**

Complete Response letters for original license applications and supplements, Approval letters and Refusal to File letters for supplements will be signed by the Division Director with product responsibility or the DVRPA Division Director for clinical efficacy supplements. If the license application or supplement is a combination product, the complete response letter, or approval letter for a supplement, or refusal to file letter for a supplement will be signed by the chair's Division Director. The routing for sign off on the yellow box copy is as follows:

1. Committee Chairperson
2. Committee members (Members are not required to sign but may if they have special interest. In certain situations, the requirement for signature of all committee members is at the discretion of the chairperson, with concurrence of the Director of the Division with product responsibility. Draft letters are routed to members for review.)
3. DVRPA Regulatory Coordinator
4. DVRPA Branch Chief (Viral, Bacterial, and /or Clinical)
5. Lab Chief in division with product responsibility
6. Division Director of the review division with product responsibility or the chair's Division Director if a combination product, or the DVRPA Division Director if clinical (original and/or yellow box)
7. Appropriate DVRPA CSO/CST for dating and mailing of letters (signature on yellow box is required)

### **Discipline Review Letters For License Applications And Supplements**

Discipline review letters for license applications and supplements will be signed by the primary medical reviewer if clinical, or the chair (when appropriate) for manufacturing. These letters will not be routed to the Division Director(s) for signature. The routing and sign-off on the yellow box copy is as follows:

1. Primary medical reviewer or Committee Chairperson (original and yellow box copy), committee members are not required to sign the letter but may if they have special interest. Draft letters are routed to all members for review, as described in V-R-1-94.)
2. DVRPA Regulatory Coordinator
3. DVRPA Branch Chief (Viral, Bacterial, and/or Clinical)
4. Lab Chief in division with product responsibility
5. DVRPA CSO/CST for dating and mailing of letter (signature on yellow box required)

### **Information Request Letters**

Information Request letters will be signed by the Division Director with product responsibility, or the DVRPA Division Director for clinical efficacy supplements. If the chair and the medical reviewer reside in DVRPA, the DVRPA Division Director will sign the original letter. If only the chair resides in DVRPA, the Division Director with product responsibility will sign the original letter. If the license application or supplement is a combination product, the information request letter will be signed by the chair's Division Director. The routing and sign-off on the yellow box copy is as follows:

1. Committee Chairperson or Primary medical reviewer (Committee members are not required to sign the letter but may if they have special interest. Draft letters are routed to all members for review, as described in V-R-1-94.)
2. DVRPA Regulatory Coordinator
3. DVRPA Branch Chief (Viral, Bacterial, and/or Clinical)
4. Lab Chief in division with product responsibility
5. Division Director with product responsibility, or the chair's Division Director if a combination product, or the DVRPA Division Director if clinical (original and/or yellow box copy)
6. DVRPA CSO/CST for dating and mailing of letter (signature on yellow box required)

### **Approval Letters And Refusal To File Letters**

The Office Director will sign all approval letters and refusal to file letters for original license applications. These letters should be routed to the following for the sign off on the yellow box copy; the order of signature will be dependent on where the letter originates.

1. Committee Chairperson
2. Division Director of the review division with product responsibility
3. DVRPA Regulatory Coordinator
4. DVRPA Branch Chief (Viral or Bacterial)
5. Division Director with product responsibility, DVRPA Division Director, and DMQC Division Director, as appropriate.
6. Office Director, OVRP (signs both original and yellow box copy); if a new facility is involved, the Office Director of OCBQ will also sign the original and yellow box copy
7. Appropriate DVRPA Consumer Safety Officer (CSO)/Technician (CST) for dating and mailing of letters (signature on yellow box is required)

### **Signatures for IND Clinical Hold Letters and Letters in Response to Sponsor's Complete Response**

The DVRPA Division Director will sign IND Clinical Hold letters and letters in response to a sponsor's complete response. The routing and sign-off on the yellow box copy of the letter is as follows:

1. DVRPA, IND Reviewer
2. Director, DVRPA (original and yellow box copy)

3. DVRPA CSO/CST for dating and mailing (signature on yellow box required)

### Review letters for IND/Master Files

The DVRPA Division Director will sign Review Letters for IND/Master Files. The routing for sign-off on the yellow box copy of the letter is as follows:

1. DVRPA, IND/Master File reviewer
2. Director, DVRPA (original and yellow box copy)
3. DVRPA CSO/CST for dating and mailing (signature on yellow box required)

### 6. Contacts

For further information on routing and signature requirements for regulatory letters in OVRP, please contact the OVRP Associate Director for Regulatory Policy at 301-827-0655.

### 7. Effective Date

April 7, 1999

### 8. History

Written/Revised	Approved	Approval Date	Version Number	Comment
Norman Baylor, PhD	Norman Baylor, PhD, Assoc. Dir. for Regulatory Policy, OVRP	April 7, 1999	1	Information previously covered in OVRP's Policy & Procedure Guide, #V-R-1-95

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