

---

# Manual of Standard Operating Procedures and Policies

---

## Regulatory - License Applications

### The Responsibilities of the Division of Epidemiology (DE/OBE) in the BLA Review Process

SOPP 8401.6

Version #1

Date: August 27, 2007

---

#### 1. Purpose

The purpose of this SOPP is to describe the procedures for the Center for Biologics Evaluation and Research (CBER) staff for obtaining review from the Division of Epidemiology /Office of Biostatistics and Epidemiology, (DE/OBE/CBER) for Biologics License Applications (BLAs) and efficacy supplements. This SOPP focuses on pharmacovigilance activities in the post-approval period.

#### 2. Definitions

**Pharmacovigilance** - This SOPP uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

##### **Phase 4 study**

- A postmarketing study carried out as a condition of licensure of a new product, e.g., to further assess safety of the product in a broader subject population.

##### **Postmarketing Commitment (PMC)**

- Any commitment by a drug or biologic applicant to conduct a post approval investigation made before or after FDA has granted approval or licensure to market a product or approval of a supplement. The commitment may be to conduct a study or studies; to otherwise gather additional information about the product safety, efficacy, or use; or to further evaluate chemistry, manufacturing, or control (CMC) issues.

#### 3. Background

Postmarketing studies are those performed by a drug or biologics applicant after FDA has granted approval or licensure to market the applicant's product. Such studies are used to gather additional information about product safety, efficacy, or optimal use. Postmarketing studies are also used to

evaluate CMC issues, which are important for ensuring consistency and reliability in drug production.

During product development, a safety/clinical risk assessment should be conducted in a thorough and rigorous manner. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for continuously evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

The decision to approve a drug or license a biologic is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. Once a product is marketed, new information will be generated that can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities.

### **Determining if DE /OBE involvement is needed (examples)**

#### *Needed:*

##### Type of submission

- ICH E2E Safety Specification or Pharmacovigilance Plan for new BLA or approved product (including efficacy supplements, when applicable).
- Proposed evaluations of Risk Minimization Action Plans (RiskMAP) suitability using epidemiological methods.  
(NB: some manufacturers submit combined Pharmacovigilance Plans and RiskMAP's under the general heading of Risk Management Plans)

##### Type of study to be reviewed

- Large observational safety studies (in all cases); adverse event surveillance studies

#### *Not needed:*

##### Type of submission

- Most supplements for manufacturing changes

##### Type of study

- Toxicology studies

## **4. Policy**

### *Manufacturers are expected*

to submit a safety specification and pharmacovigilance plan according to the International Conference on Harmonization E2E guidelines for Pharmacovigilance Planning (<http://www.fda.gov/cber/gdlns/ichpvp.htm>) and/or to make a commitment to conduct a postmarketing safety study as a condition of licensure of a new product (so called "phase 4" studies).

If safety concerns arise prior to licensure that are not completely resolved by the clinical trials but are not

sufficient to prevent licensure, a phase 4 study may be requested by FDA. Phase 4 studies are usually designed prior to licensure of a product and conducted after licensure. These studies generally involve both a study of issues that arose during pre-licensure testing and active surveillance for any unexpected adverse events, in a larger and more diverse population than received the product prior to licensure. *Reasons for requesting a phase 4 study could include the need to study potentially serious adverse events in larger and/or more diverse populations than the ones studied during the clinical trials.*

Phase 4 study protocols are usually submitted with the BLA. Thus, the need arises for the review committee to include reviewers within the Division of Epidemiology (DE/OBE) early in the New Drug Application (NDA) or BLA review process. A DE/OBE reviewer will ordinarily be invited to the pre-NDA or pre-BLA meeting, anticipating the participation at the NDA or BLA stage.

## 5. Responsibilities and Procedures

### Responsibilities of the BLA review committee

- A representative of DE/OBE will ordinarily serve on the committee for a new BLA. Thus, DE/OBE will have already been contacted (usually by the IND primary reviewer or regulatory project manager [RPM]) to provide a representative for the pre-BLA meeting for most new BLAs.
- Once the BLA is submitted, a preliminary review should be conducted by the review committee assigned to the respective BLA to determine whether the submission contains plans for phase 4 studies requiring DE/OBE review.
- Review from DE/OBE may also be requested for certain BLA supplements, e.g., indication for a new subject population.
- Any member of the BLA/BLA supplement review committee (usually the clinical reviewer) may notify the committee chair or RPM/regulatory coordinator of the need for review from DE/OBE.
- The committee chair or RPM/regulatory coordinator of the respective BLA should contact the Director of DE within OBE for assignment of a reviewer (if this wasn't done at the pre-BLA stage).
- The committee chair/RPM/regulatory coordinator should specify the sections of the BLA for which a review is requested, usually the section of the BLA concerning protocols and plans for Phase 4 studies.
- The committee chair/RPM/regulatory coordinator should provide the reviewer within DE/OBE a date by which the review memorandum is requested and should make DE/OBE aware of action due dates and timelines to ensure that the review can be completed in a timely manner.
- The RPM/regulatory coordinator for the BLA should ensure that the reviewer within DE/OBE is routed a copy of the relevant section of the BLA in a timely manner.
- Once a review memorandum is obtained from DE/OBE, the RPM/regulatory coordinator of the respective BLA submission should submit the review memorandum to the official file and also forward a copy of the review to the clinical reviewer and the review committee chair person for the BLA.
- Meetings and telecons pertaining to phase 4 commitments will be organized and recorded, usually by the RPM/regulatory coordinator, for the respective BLA, in consultation with the DE/OBE reviewer. (Certain exceptions are noted in the next section.)

- All regulatory letters pertaining to phase 4 studies will be drafted and issued by the RPM/regulatory coordinator for the respective BLA, in consultation with the DE/OBE reviewer.

### **Responsibilities of the Reviewer within DE/OBE prior to approval of the BLA**

- All reviewers should be held accountable for their timely and complete response to review requests.
- Reviewers within DE/OBE should review the portions of the BLA for which their input is requested within the agreed upon timelines and provide a written review memorandum.
- All reviews of PMC study proposals should include a brief summary describing the portion of the submission that was reviewed.
- In addition to the protocol summary, the review memorandum should contain comments in "letter ready" format to be communicated to the manufacturer, when appropriate.
- The reviewer is responsible for obtaining the appropriate clearances/sign-off, as specified by Office-specific procedures, from the supervisor within DE/OBE.
- Once the review is completed, the reviewer shall then forward the review memorandum and a copy of the reviewed submission, directly to the RPM/regulatory coordinator of the BLA.
- The reviewer within DE/OBE should coordinate with the RPM/regulatory coordinator regarding telecons and/or meetings with applicants, if needed.
- Certain telecons (e.g., requests for information) may be initiated and recorded by DE/OBE without participation of the RPM/regulatory coordinator; however, it is the responsibility of the reviewer within DE/OBE to submit a written telecon memorandum for inclusion in the BLA administrative record.
- If the reviewer within DE/OBE, upon preliminary review of the BLA sections forwarded for review, determines that he/she does not have the expertise to address the specified areas, the RPM/regulatory coordinator of the respective BLA as well as the respective supervisor within DE/OBE shall be immediately notified for review reassignment.

### **Responsibilities of the Reviewer within DE/OBE following approval of the BLA**

Once the BLA is approved and a PMC study is initiated, reports on the status of these studies are submitted periodically by the manufacturer.

- The reviewer within DE/OBE assigned to the BLA should review these reports upon receipt and write a short critique and communicate this to the RPM/regulatory coordinator/committee chair and clinical reviewers, with a copy to the branch chief within DE/OBE. This critique should focus on any safety or methodological questions raised by the report.
- If the reviewer within DE/OBE believes immediate action is indicated, this should be brought to the attention of relevant staff in DE/OBE and the appropriate product office.
- The reviewer should provide a review of the final study report for the BLA administrative record.

## **6. Effective Date**

August 27, 2007

## 7. References

- [International Conference on Harmonisation \(ICH\); Guidance for Industry: E2E Pharmacovigilance Planning - 3/31/2005](#)
- [Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment - 3/25/2005](#)

## 8. History

| <b>Written/Revised</b> | <b>Approved</b>          | <b>Approval Date</b> | <b>Version Number</b> | <b>Comment</b>              |
|------------------------|--------------------------|----------------------|-----------------------|-----------------------------|
| OBE/OVRR               | Robert A. Yetter,<br>PhD | Aug 22, 2007         | 1                     | First issuance of this SOPP |

Updated: August 27, 2007