Overview

Introduction:
This Reviewer's Manual is intended to provide you with an understanding of the reviewer's role, interaction between CVB personnel, the resources available, and practical aspects of the reviewing/licensing process. It is NOT intended to provide a course of action for all possible scenarios. The content of this manual is intended as a guide and must be considered in conjunction with any extenuating circumstances that may be specific to a given submission.

The goal of the Review and Licensing Process is to:

- Evaluate submission(s) for adherence to regulations, guidelines, and scientific and technical validity.
- License high quality veterinary biologics
- Maintain high quality and/or improve currently licensed veterinary biologics.

This is a team effort made of Legal Instrument Examiners (LIE), Program Assistants (PA), Biologic Clerks (BC), Staff Reviewers, Section Leaders, Laboratory Vet/Micros and Technicians, and IC staff. There is a system of checks and balances to keep track of submissions, enhance consistency, minimize error, expedite review, evaluate product and seeds, and maintain records.

The Regulations:

The Virus-Serum-Toxin Act is found in Title 21 of the U.S. Code, Sections 151-159, and is the basis of CVB authority. Most of the specific information regarding biologics regulation is found in Title 9 of the Code of Federal Regulations (9CFR), Sections 100-124. The regulations are further interpreted by guidance documents; Veterinary Services Memorandums (VSM)s, and CVB Notices.

VSMs are a type of guideline, as defined in 9 CFR 101.2, that define policies and procedures. VSMs are used to establish principles or practices relating to test procedures, manufacturing practices, product standards, scientific protocols, labeling, and other technical policy considerations that are permanent procedures until canceled or replaced by another VSM. All current VSMs pertaining to veterinary biologics are available on the CVB website
https://www.aphis.usda.gov/animalhealth/cvb

CVB Notices typically are used to disperse information and announcements and to specify temporary procedures with impact that does not exceed one year. Notices tend to be published more quickly than VSMs. Content evolving into policy or permanent procedures ultimately should be converted to a VSM. Recent CVB Notices are available on the CVB website. Older notices (except routine notices for products licensed) are available [redacted]

The Strategy:

The strategy for reviewing submissions will vary with the submission but in general the reviewer follows a common path. The reviewer needs to assess the priority of the submission; identify prior correspondence regarding the issue; consult the appropriate regulations, guidelines and literature; determine which other sections need to be consulted and what other actions need to be performed. The reviewer then responds by **explicitly** stating the outcome of the review, making recommendations based on the submitted information, and suggesting ways to remedy deficiencies in the submitted material. It is important for the reviewer to view the process as a cooperative effort between the firm and the agency in order to maintain high quality veterinary biologics and diagnostic kits.

The licensing process is an accumulation of data and information that ideally follows the process described in VSM 800.50 and provides the necessary support to justify licensure. The firm is responsible for carrying out the studies, documenting them, and assuring they were performed as stated, while the reviewer is responsible for assuring the submitted material meets the regulatory requirements. The final product, when ready for licensing, must stand on the merit of the submissions and have appropriate justification for any variances allowed.

Communications Official and Unofficial:

Communication via letter, on APHIS Forms, and as part of the official program at the Public Meeting are official forms of communication. All other interactions, such as phone calls, e-mail, or face-to-face meetings are unofficial until followed by official correspondence. When an unofficial communication has taken place, it is common practice to have the firm make a formal written request, asking for an official response.

One of the most important parts of the reviewer's job is to prepare complete, explicit written responses to submissions. Response letters should include adequate detail to stand alone without referring to the incoming submission. They should enable the submitter to understand the basis for a decision, describe the limitations of that decision, and educate the submitter regarding CVB regulations and policy. Avoid vague phrases such as "This submission is acceptable for the purpose intended."

Regardless of the type of communication, it is essential to maintain notes and logs of important discussions and to ensure that copies of these records are uploaded to the mail log. In particular, use caution when communicating by email. It is a convenient mechanism to interact with your firms, but it bypasses the review to which official correspondence is subjected. Try to use email only for short, simple requests or notifications. Avoid providing regulatory guidance by email. If an email string contains information that should be included in the licensing file, make a pdf copy and upload it to the related mail log. If in doubt about the relevance of an email to the licensing file,

upload it to the mail log. Upload brief descriptions of relevant telephone conversations with a firm to the phone log.

[redacted]

Organizational Strategy of the Review Process:

Review loads can result in a mountain of paper, so it is highly recommended that you stay current on submissions and develop an organizational system for submissions on your desk. It is important to check incoming mail daily to get a general idea of what has been received and how it is to be prioritized. Although all submissions should be processed in a timely and thorough manner, in general the following are considered to be priority items:

- 103.3 requests (shipment of experimental biological products).
- Protocol review
- Test requests
    - Authorization to submit
        - Seeds
        - Prelicensing serials
- Items marked "priority" by the firm

Use of Statistics Support:

The Statistics section provides support in a number of valuable ways that have to do with data interpretation and validation of the firm's conclusions (refer to Section on Statistics of this manual for details). The Statistics section typically evaluates protocols and data packages from:

- Efficacy studies
- Potency tests (if they include data amenable to statistical analysis)
- Field safety studies

It is left to the discretion of the reviewer whether or not a submission merits statistical analysis. Submissions should not be forwarded to Statistics without a preliminary assessment by the reviewer. Some specific submissions do not require statistical analysis, even if they are the type of document that routinely merits statistical review. Examples would include a study protocol that follows widely accepted 9CFR procedure, study results that count the number of live vs. dead animals to meet an accepted 9CFR

standard, or study results that clearly are not acceptable (in which case it is not worth the statistician's time to analyze). Reviewers also should determine whether electronic data files (if applicable) were included and should request any missing items from the firm as soon as possible.

If a submission requires statistical analysis, however, it is important to send it to Statistics as soon as you have completed a preliminary review.. If you question whether a particular submission should be reviewed by Statistics, feel free to consult with one of the statisticians prior to routing to Statistics..

Use of Other CVB Support:

The reviewer may request an opinion on a particular submission from other personnel within CVB (e.g., the designated Agent Expert for the antigen being considered, laboratory personnel, IC personnel). It is common for testing protocols (e.g., Section V, Outline of Production) to be reviewed by laboratory personnel. Other opinions may be sought, depending on the reviewer's discretion. When requesting input from other CVB personnel, the applicable part(s) of the submission should be forwarded with a cover letter or routing comment that explains the review requested. It is often useful to set a deadline for review (e.g., "please reply by (two weeks) if you plan to comment on this") to keep the submission moving forward.

When reviewing submissions for split manufacture (i.e, products for further manufacture (FFM) and those final-use products containing FFM components), the reviewer should routinely consult the reviewer(s) responsible for the other firm(s) participating in the split manufacture before making any pivotal decisions.

Outside consults:

This is atypical but not unprecedented. The key in doing this is to realize that everything is confidential business information and needs to be kept that way. It is feasible to discuss things generically, but submissions must not be given to anyone outside the CVB without written permission from the submitter.

Use of auxiliary opinions in final review:

Always be aware that it is the reviewer who makes the final decision (and is liable for that decision) regarding the acceptability of a submission. Reviewers are expected to evaluate the merits of the submission before accepting another person's opinion.

The content of the response letter should be written by the reviewer, and should not be simply a collection of other documents, copy and pasted into a letter. If you agree with the opinions provided by others and wish to incorporate them into your response, paraphrase their comments in your own writing style. Use "cut and paste" judiciously. Do not forward auxiliary comments in their original format without express permission of the author.

Coordinated Review Team (CRT):

CRTs are formed to address issues associated with the licensure of novel products or to develop new policies. [redacted]

Staff Notes, Staff Meetings, Consistency Questions, and eFOIA:

Staff meetings and consistency questions are a forum for discussion of issues as they arise. Further guidance regarding staff meeting is included in Reviewer Staff meeting chapter of the Reviewers manual (Chapter 1.6)

Reviewers write summaries regarding efficacy studies (including reference qualification studies). The summaries are modeled after those currently posted by the FDA for human biologicals as part of the Freedom of Information Act (FOIA). These CVB documents are found in the CVB Mail Log as the document type Efficacy Licensing Summary. They provide a valuable source of information regarding what other firms have done to meet efficacy requirements, and reviewers are encouraged to use them as a tool to facilitate consistency among firms. For more information see Chapter 4.4.2.