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United States Department of Agriculture
Center for Veterinary Biologics

Standard Operating Policy/Procedure

Outlines of Production & Special Outlines

Date: **August 14, 2023**

Reference Number: CVB-SOP-0067.03

Contact: Center for Veterinary Biologics, 515-337-6100

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Animal and Plant Health Inspection Service
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INTERNAL USE ONLY

Source Document: CVB-MAN-5100, *CVB Operations Manual*, Chapter 7

Table of Contents

1. Overview

The Outline of Production (OP) is a detailed written description in outline format of how a serial of product is formulated, tested, packaged, dated, and recommended for use. With respect to product formulation, the Outline can be thought of as a recipe that defines manufacture in a sufficiently detailed and restricted manner to ensure that all serials of the product will be consistent and essentially identical to the serial(s) used to establish product efficacy and safety. It is also, in essence, our contract with the manufacturer regarding accepted manufacturing practices for a product. Therefore, it is important the Outline be complete, clear, and legally defensible. Guidelines for writing Outlines of Production for various categories of biological products are found in 9 CFR 114.9 and Veterinary Services Memorandum 800.206.

Special Outlines (SO) detailing individual processes which may apply to more than one product are reviewed and processed in much the same way that OPs are. The general sections of this chapter apply to SOs as well as OPs, except where specifically noted.

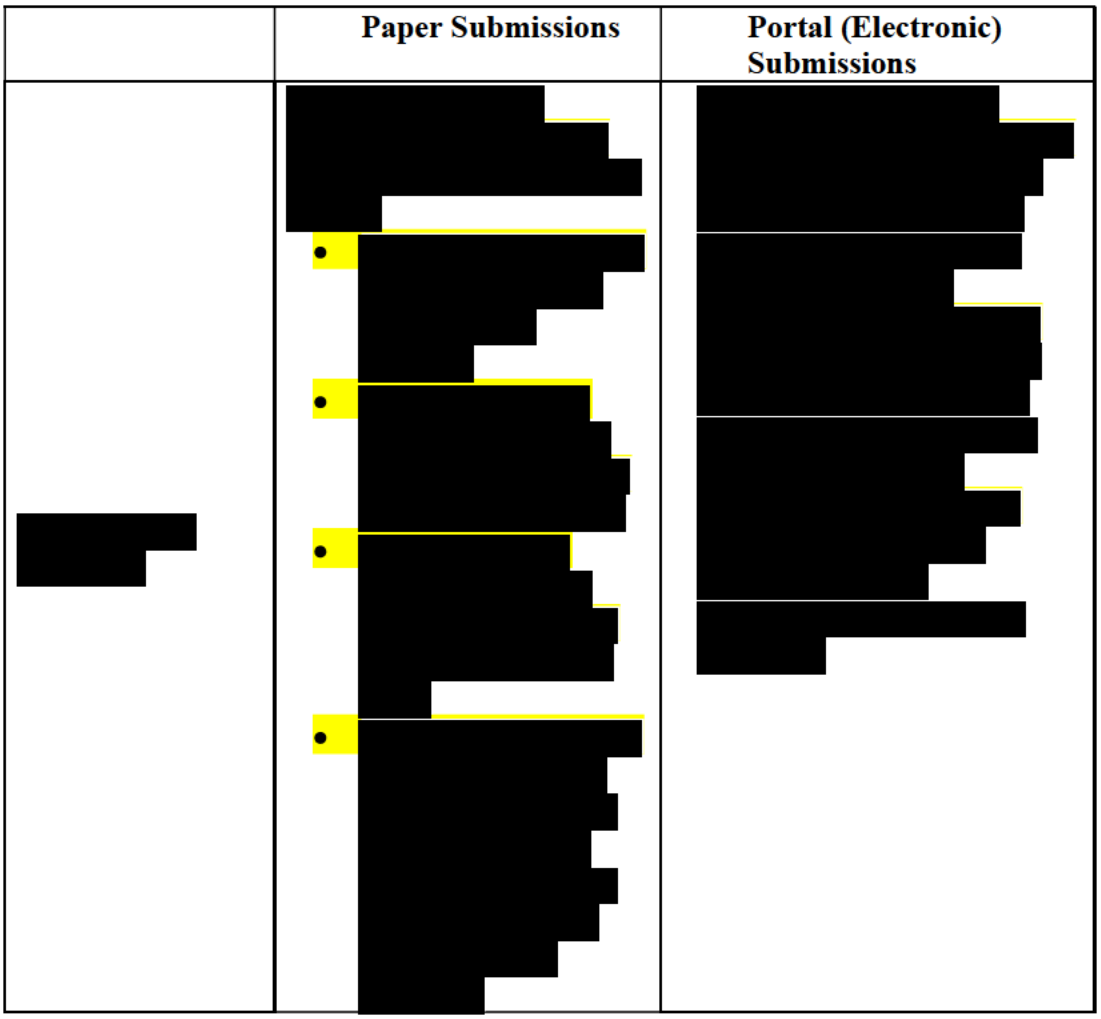
2. Flow of Information

	Paper Submissions	**Portal (Electronic) Submissions**
Submission	An OP must be submitted with an accompanying APHIS Form 2015. Two paper copies of the OP must be submitted, both with original signatures. The firm may voluntarily submit additional copies for processing if they need them. The APHIS Form 2015 can be accessed here. [redacted]	Electronic OPs are submitted under APHIS Form 2049 via the portal. APHIS 2015 is not required, and the Outlines themselves are not signed by the firm. Portal user guides 18-20 contain the instructions the firms use to prepare and submit OPs electronically. Templates for submitting OPs can be found in portal user guide B.
Initial Routing	[redacted]	

	Paper Submissions	Portal (Electronic) Submissions
	[redacted]	
[redacted]	[redacted]	[redacted]

	Paper Submissions	**Portal (Electronic) Submissions**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

	Paper Submissions	Portal (Electronic) Submissions
[redacted]	[redacted]	[redacted]

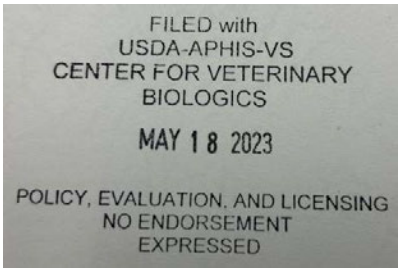

Paper Submissions
Portal (Electronic) Submissions

	Paper Submissions	Portal (Electronic) Submissions
[redacted]	[redacted]	[redacted]

Physical Stamp Examples:

#5 Stamp

#6 Stamp



Electronic Stamp Examples:

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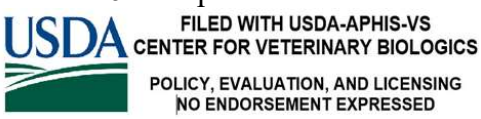
#6 Stamp



3. Definitions

APHIS Form 2015: Also called a 2015. Transmittal of Labels and Circulars or Outlines. This form must accompany all *paper* submissions of Outlines, Special Outlines, or labeling materials. The top part of the form is filled out by the firm to identify the accompanying submission. The bottom part is filled out by the CVB, and the form is returned with the firm's copy of the reviewed document.

APHIS Form 2049: The transmittal form for electronic submissions. The 2049 interface is what the portal user completes prior to making a submission. It is not a separate form.

Special Outline: An auxiliary Outline that describes a particular manufacturing process or testing method. Special Outlines (SOs) often apply to a group of products and, thus, are cited in Outlines to avoid repeating the same text in numerous locations. Special Outlines are numbered and are cited in Outline(s) of Production. Hard copy SOs may follow any format the manufacturer chooses, but it is recommended they use a format similar to what is found in the NCAH Portal User Guide. NCAH Portal users should use the SO template and guidance found at the NCAH Portal User Guide website. It is recommended SOs that describe a potency assay list the product codes the SO applies to after the title page. SOs may include product codes in the title and add additional codes after licensure of new codes. A list of applicable product codes should appear after the title page unless all codes are stated in the title of the SO.

Combination package: A product license that consists of two or more *individually licensed* components, packaged together. The license for the combination package authorizes the licensee to package the components together and to label the product with instructions to mix the component products prior to administration. Note this is not the same as a combination product which is a multivalent product in a single vial.

4. General Review Guidelines

1. Check all references to other documents (SOs, other Outlines).
   a. Does the referenced document really exist? Beware of documents that may have become obsolete since the last Outline revision.
   b. Does the referenced document contain information that is sufficient and correct?
   c. Watch for "circular" references (e.g., Outline of Production says information is in Special Outline, but Special Outline says the same information is found in the Outline of Production).
   d. Ensure that the referenced document contains the pertinent information and does not simply reference a third document as the source of information. Avoid creating "document chains."
   e. Avoid duplication of information—If information is in the Special Outline, it does not need to be repeated in the Outline of Production. When information is duplicated and subsequently amended, it is very easy to forget to update one of the locations where the information is found.

2. Pay particular attention to syntax that may allow for variable production or testing methods. Ensure that the language used is appropriate for the purpose. "**Should**" means that the procedure/value is *recommended*, but not necessarily mandatory.

3. Deviations from the described procedure are not necessarily out of compliance. Likewise, "**may**" permits a procedure, but does not require it.
   a. Shall/Must/will" means that the procedure/issue is mandatory. Deviations are out of compliance. Example: Use "must/will" to describe serial release test parameters.
   b. Use care with the phrase "or equivalent." Since this phrase is open-ended and subject to interpretation, do not permit the use of this phrase in situations where an alternative, not yet reviewed or approved by the CVB, might make a critical difference to the outcome of the procedure. Example: "Read the ELISA plate with the Dynatech 3000 ELISA reader or equivalent" is appropriate, as another brand of ELISA reader could reasonably be expected to give equivalent results. "Use Reference Bacterin 309 or equivalent" is not appropriate because Reference Bacterin 309 is the only approved reference. New references, even though they

may be formulated to be equivalent to #309, must be approved by the CVB before they are used (and incorporated into the Outline). New references are to be lot number controlled and new or replacement references are to be documented on when the CVB accepts the use of the reference.

c. "and" vs. "or": And means that both conditions must be met. Or means that either condition (but not necessarily both) must be met.

4. [redacted]

   Review amended paper pages in the context of the entire Outline. (Only Complete Revisions are allowed for electronic Outlines.) It is permissible to ask firms to submit other paper pages (or a complete revision) if deficiencies are noted on pages that are not currently under official review. [redacted]

5. When possible, support requests for revisions with citations from the regulations or guidance documents. (Example: "Revise section VI.C to include the component codes for this combination package, per VSM 800.206.)

6. In general, "either/or" options are not acceptable in Outlines of Production because manufacturing and testing procedures should not be subject to variability. If an ingredient or process is optional (e.g., adding extra nutrient solution during fermentation), then the conditions under which it is added or utilized should be clearly defined (e.g., add an amount not to exceed X mg/L if the pH drops below 6.9). Data may be necessary to demonstrate that the quality of the product is not affected by optional ingredients or procedures.

   Alternative procedures or tests are often proposed for globally marketed products to satisfy the various regulatory requirements of different importing countries. If alternative procedures or tests clearly are not interchangeable, then it is likely that two separate product licenses are needed—one for each method.

   Only one Master reference and one Working reference per fraction should be indicated in an Outline although if a fraction uses multiple potency tests, it is possible each test

requires a different reference. When a new reference is needed, the new reference is added to the outline by replacing the designation of the old reference with any other changes associated with the new reference. If alternatives are acceptable (e.g., two manufacturing sources of a chemically identical adjuvant), then the acceptable alternatives should be clearly specified.

7. Temperatures and processing times usually should be expressed as an acceptable range of degrees or time units. Due to normal, minor fluctuations in temperature, even under controlled conditions, a firm may be out of compliance with an Outline that specifies only a single acceptable temperature. Likewise, it may be difficult to time an incubation down to the minute every time. Also, refrain from using "room temperature", "on ice", etc., this should be listed as a specific temperature range and unit of measure.

8. If there is allowable variability in a formulation step, the OP should include a range that defines both a minimum and a maximum value rather than a one-sided bound. Statements that only have a one-sided bound such as "Gentamycin is added at a concentration not to exceed 30 mcg/mL." allow the manufacturer to omit gentamycin entirely and are therefore not acceptable. An example where one-sided bounds may appropriate is the serial release specification such as "The relative potency at the time of release is RP $\geq$ 1.2."

   All minimum-maximum ranges should be reasonable. [redacted]

9. Ensure the OP written by the firm follows the appropriate guidelines established in 9 CFR Part 114. If extra sections or subsections are needed beyond what is provided in the guidelines, add them at the end of each section or subsection.

10. All changes made to an OP are to have comments provided as to why the change is occurring and/or reference previous submissions of CVB accepting the change. Paper submissions will include a summary of changes document. Portal submissions will have comment "bubbles" added to the proposed change. Changes made to an OP without firm comments are at risk of being returned unprocessed.

Requirements for firms to review/revise Outlines

Per 9CFR 114.8(d), firms are required to review their Outlines annually. If that review reveals inaccuracies, insufficiencies, or items that do not meet current standards, the firm is expected to submit revisions accordingly.

There is no written policy regarding whether a firm should submit amended paper pages or a complete paper revision, and individual firms vary widely in their approach to this. *In general*, if the amended paper pages account for at least half of the total paper Outline, a complete revision, instead of individual pages, should be submitted. The portal does not allow revisions of individual pages so only complete revisions are accepted electronically, even if only one page has been changed.

CVB evaluates submissions from manufacturers in which the manufacturer requests permission to change or update one or more aspects of the manufacturing, testing, or distribution methods in a filed Outline of Production. Once CVB has finished reviewing the request, a response letter to the manufacturer either approving or denying the request is returned to the manufacturer. If the request is approved, the response letter will instruct the manufacturer to submit an updated Outline of Production which will become the new CVB-approved version of the Outline of Production after review. Center for Veterinary Biologics-Inspection and Compliance (CVB-IC) makes decisions about serial release and compliance during inspections based on information in the filed Outline of Production. During the time period between CVB approval of a change and approval of a subsequently submitted updated Outline of Production, CVB-IC has experienced delays releasing products to market and has observed unintended compliance issues during inspections.

In order to address this issue, CVB will not consider a change in manufacturing, testing, or distribution methods to be in effect or applicable for regulatory purposes unless the change is in the CVB-approved Outline of Production. The manufacturer is responsible for updating the Outline of Production with accurate and sufficient information, including any changes to manufacturing, testing, or distribution addressed in the acceptance letter. The Outline of Production must be updated to include the date of the CVB approval letter and the associated mail log number in the appropriate sections. Product may be prepared and tested by the manufacturer prior to the approval of the data and Outline of Production but must not be submitted for market release until the updated Outline of Production is filed with CVB.

The reviewer has the authority to request a complete review, and if necessary, revision to address inadequacies or insufficiencies at any time; such a request is probably warranted if the Outline is several years old and does not meet current standards for content or format.

Special considerations for Outline changes for Rabies Vaccines

In the past, we did not allow Outline changes (even very minor ones) for licensed rabies products without redoing full efficacy studies. We had publicly assured State and Federal public health authorities that even the most minor production procedure changes for rabies products will be supported by full efficacy data. However, Center for Veterinary Biologics Notice 06-23, Production changes for Rabies Vaccines, is now rescinded. Now minor changes, associated with data to support equivalency, are allowed post licensure. [redacted]

[redacted]. An Outline revision will only be approved upon satisfactory completion of the plan as provided in a response letter to each submission.

Specific Review Considerations

Vaccines, Bacterins, Toxoids, Antigens

References: 9CFR Section 114.9(d)

This 9CFR section contains the sections and subheadings that must appear in all Outlines of Production. Hardcopy Outlines should be formatted according to 9 CFR Part 114.9. NCAH Portal users should use the OP templates and guidance in the NCAH Portal User Guides. This does not preclude a firm from adding additional subheadings, as appropriate, to specific Outlines of Production per VSM 800.206.

Veterinary Services Memorandum 800.206
This guidance document provides details regarding what should be included in Outlines of Production.

Cover page

Paper: Typically, the cover page of the Outline is replaced only with complete revisions. In certain circumstances (e.g., change of Establishment name), it may be prudent to submit amended cover pages even though the Outline has not been completely revised. If this occurs, the amended cover page should continue to list the date of the last complete revision. Underneath this date, the firm should add a statement "Cover page updated<date>." (This explains why the revision date on the cover page and the date of the CVB approval stamp may be widely disparate.)

Electronic: All submissions are complete revisions. Follow the NCAH Portal User Guides.

Section I

1. Ensure that Section I contains all of the information specified in VSM 800.206. When the Master Seed is the property of another firm in an FFM relationship, complete seed information is included in the FFM firm's Outline. Therefore, complete information may be in the FFM or FUP outline, but not always both. Similarly, complete information may not always be in a combination package Outline of Production. The CVB should not require release of confidential business information between firms. Note that in general Master Seed should be sourced from the United States or countries considered free, low risk, or not affected with foreign animal diseases of concern (as

defined in VSM 800.51, Section IV.A) and with negligible or controlled risk of bovine spongiform encephalopathy (BSE), according to APHIS' Animal Disease Status designations.

2. This section should be completed in all Outlines and should not cite another Outline (except in certain split manufacture scenarios).

3. For products licensed based on Production Platform technology, indicate in Section I.A. that this product is licensed based on production platform technology specific for gene(s) of the XYZ protein, derived from the ABCD pathogen, and utilizing JKLQ Technology developed by XXX corporation. The XYZ protein sequence from different ABCD pathogen isolates may be exchanged as per VSM 800.213.

4. In Section I.E of the Outline of Production of a Production Platform technology product, include a table of approved sequences (constructs). An example of the appropriate information to include in the table is summarized below.

Plasmid Designation	Firm Designation code	CVB Identity Code	Gene Source/date of accession	Number of Nucleotides	Map Location
pPlasmid ABCD	mmddyyyyxyz1	Est#_product Code_mmddyyyy-xyz1-001	ZZZZz (GeneBank accession No.)	10000	Addendum 1
pPlasmid-ABCD	mmddyyyy-xyz2	Est#_Product Code_mmddyyyy-xyz2-002	ZZZZx (GeneBank accession No.)	10032	Addendum 1
pPlasmid-ABCD	mmddyyyy-xyz3	Est#_Product Code_mmddyyyy-xyz3-003	ZZZZy (GeneBank accession No.)	10044	Addendum 1

Section II

Sections II-IV can be difficult to review because the subheadings required by 9 CFR 114.9 do not always lend themselves to describing production in a stepwise manner. Ensure that all critical production steps are covered in these sections and that it is possible to understand how the product is made, even though the descriptions may not be optimally organized.

Section-Specific Reference: VSM 800.65 (products made with eggs, poultry)

1. All outlines must address the source of ingredients of animal origin in Section II. Often this is specified in Section II.C. The following statement is acceptable:

   Ingredients of animal origin are sourced from the United States or countries considered free, low risk, or not affected with foreign animal diseases of concern (as defined in VSM 800.51, Section IV.A) and with negligible or controlled risk of bovine spongiform encephalopathy (BSE), according to APHIS' Animal Disease Status designations. Each lot of ingredient additive of animal origin used to prepare an administered biological product must be sterilized or tested as prescribed in 9 CFR 113.53, unless a risk-based exemption is provided by the CVB upon request by the firm.

   The firms also may generate their own versions of this statement, and the following guidelines apply:
   a. The CVB considers minimal risk regions with regard to BSE to include the United States, Canada, Australia, and New Zealand. Control measures in place assure the safety of bovine derived materials sourced from these countries. Regions where BSE exists, or regions that have import requirements less restrictive than those that would be acceptable for import into the United States are not acceptable sources of ingredients of animal origin. If it is not possible to adequately evaluate the control measures of another country, then it is advisable to not use ingredients of animal origin from that country.
   b. The statement should not include any disclaimers that it only pertains to ingredients purchased after a country is officially declared at risk for BSE. (i.e., We do not want them to continue to use ingredients purchased the day before an announcement is made.)
   c. If in doubt, use the default statement listed above.
   d. The statement should be included even for those products containing only highly processed ingredients of animal origin (e.g., casein digest). Although ingredients such as these were not the primary target of concern when we implemented this policy, it is easier to be all-inclusive now.
   e. A comprehensive list of all ingredients of animal origin used in production of biological products should be maintained. This list should include the name of the material, the supplier, the country of origin, and the date of purchase of each lot. This list may be reviewed, and certification of materials required at the time of inspection by the CVB-IC, or as requested by the CVB. This list may be referenced in the Outline of Production or in a Special Outline. Even if the list is not referenced in the Outline of Production, however, it should be maintained and available upon request.
   f. Section A Ingredients of Animal Origin statements in VSM 800.51 should be referenced in the ingredients of animal origin statement in the Outline of Production.

2. Range of subcultures or passages to be used in production (Section II.B). Some of the Standard Requirements (9CFR 113) specify the maximum number of passages from Master Seed that may be used in production. If there is no Standard Requirement, or if the Standard Requirement does not address passage levels, then the maximum allowable passage is based on the passage level used in the serial that was used to demonstrate efficacy. [redacted]

3. Composition and reaction of media used for seed and production cultures. If the product utilizes a Master Cell Stock, ensure that the lot number of the approved cell and the CVB approval date are listed.

   [redacted]

   Note that CVB will not consider licensure of a product which uses starting material from a country that is not considered "free, low risk, or not affected with foreign animal diseases of concern". This guidance, including a list of the foreign animal diseases of most concern to CVB, may be found in Veterinary Services Memorandum (VSM) 800.51. While this memorandum does not explicitly include the term Master Cell Stock in the Ingredients of Animal Origin (IAO) section, the MCS is one of the foundational components of a product and must be held to the highest of standards to mitigate the risk of introduction of foreign animal disease (FAD) into the United States. [redacted]

4. Character, size, and shape of containers used for growing cultures (Section II.D). Be aware of changes in technology (e.g., movement of virus production from roller bottles into bioreactors, switch of bacterial production from small containers to large, automated fermenters). Such changes often need to be supported by data that demonstrate that the firm can make quality product by the new technology.

Section III

Section-specific reference: VSM 800.56 (disposal methods, Section III.E)

1. [redacted]

Section IV

Section-specific reference: VSM 800.51(additives, adjuvants)
VS Memo 800.117 (inactivation studies)

1. For the inactivation procedure (IV.A), the inactivation time is to be clearly specified.

2. Degree of concentration (IV.C): Ensure that the maximum permissible degree of concentration is specified. The method of concentration (e.g., centrifugation, ultrafiltration) should be listed and should not be interchangeable. Changes may be made with prior approval based on data. Filtration procedures should specify a molecular weight cut-off. Centrifugation should specify a g-force (not RPM, which is rotor-dependent).

3. Assembly of units (IV.E): Firms are encouraged to include concentrations (e.g., ≥107.8 pfu/ml), as well as the volume, of each antigen.

4. Volume of maximum serial: Be aware of large increases in maximum serial size. Large changes in production scale may affect the quality of the finished product; a request for supporting data may be justified. [redacted]

5. Volume of fill: The volume of fill should include some overage so that the full quantity indicated on the label is recoverable by the end-user.

6. Moisture testing (lyophilized products): Moisture testing should be addressed in Section IV (in-process test), despite the fact that it is listed in Section V in the Outline Guide in 9CFR 114.9. For bacterial products, 9 CFR 113.64(e)(2), requires data from 10 serials to support the moisture level cited in the outline post-licensure.

7. Antibiotic content: Ensure that antibiotics are consistent with the regulations set forth in 9CFR 114.10. Only certain antibiotics may be used, and multiple antibiotics may be used only in specific combinations. Include an acceptable concentration range, with a lower, as well as upper, limit. Dilution of preservative data should be consistent with

the maximum level of antibiotic cited in the Outline of Production. The reviewer should collaborate with the firm regarding designing the appropriate dilution of preservative study for autogenous products. [redacted] Acceptable antibiotic combinations are described in 9 CFR 114.10.

8. [redacted]

Section V

Section-Specific References: CVB Notice 06-24 (Purity Testing of Avian-Origin products)
CVB Notice 12-21
CVB Notice 13-18 (Inactivation of USDA RelPot software and SAM 318)
VS Memo 800.120
VS Memo 800.119

Tests of completed product are described in Section V. Section V tests are reported on APHIS Form 2008 during the serial release process. In addition to purity and safety tests, there should be a potency test for each antigen listed in the true name of the product. The descriptions of the tests should include enough detail that a person who is reasonably skilled in general laboratory techniques could reproduce the assay (see CVB Notice 23-08). Tests should indicate if they are performed on final and/or bulk stage of product. Assays should be adequately controlled. Control preparations should be clearly defined, and criteria for a valid test should be specified. If a control preparation is used, there should be a validity criterion associated with it.

1. Section V.A:

   Outlines must specify the maximum volume of media to use in sterility testing. This volume is based on the results of a "dilution of preservative" study conducted in accordance with 9 CFR 113.25(d) and SAM 903. This study should be repeated whenever a significant Outline change involving preservatives or additives (type, percentage) occurs. The Outline of Production should include the ML # and/or date the dilution of preservative data was accepted by the CVB. See Section IV.7 above on maximum antibiotic levels in the Outline of Production.

   a. If the product is in a category that requires Mycoplasma testing (9CFR 113.28), the product may be exempted from testing if the conditions set forth in VS Memorandum 800.86 are met. Some formalin inactivated poultry products have a

firm specific general exemption to this testing that may date to the 1970s. VS Memo 800.119 also contains guidance on exemptions from codified testing.

b. Modified live products of avian embryo origin that are administered via wing-web or Coccidia Vaccines are eligible for an exemption to 9CFR 113.27(a); they may be tested for purity by 9CFR 113.27(e) instead. If firms are exporting to countries that accept a higher titer, include this information in this section. The firm will need to provide some type of supporting documentation to include.

2. Section V.B: Stepwise procedures for safety tests are sometimes contained in Special Outlines (SO). When this occurs, ensure that criteria for a valid test, criteria for a satisfactory test, and retest provisions remain in each applicable Outline of Production and are not duplicated in the SO. For killed poultry products, the potency birds are the safety birds prior to challenge. If multiple fractions have potency test birds, all the birds are considered safety test birds. This could also be applicable to aquaculture species and minor species. If safety test exemptions are granted, this testing may still occur for serial release in case a specific serial needs to be tested for any of a number of reasons or the exemption is temporarily or permanently retracted.

3. Section V.C: Sufficient details for potency testing are to be included so that they can be easily repeatable with technicians at the firm and at the CVB-Laboratory. See CVB Notice 23-08 for details. Stepwise procedures for potency tests are often contained in a SO. When this occurs, ensure that the following information remains in each applicable Outline of Production *instead* of the SO:

   a. Identification number(s) of Reference Preparation(s) (include both the Master and Working References)
   b. Expiration date(s) and storage conditions of Reference Preparations
   c. Release and throughout dating potency specifications
   d. Criteria for a valid test
   e. Retest provisions
   f. Include the date and Mail Log number when references are approved by the CVB.

   The Special Outline should refer the reader to the Outline for the above information (e.g., "Refer to the applicable Outline of Production for the product being tested for reference information.") This practice is necessary for CVB-IC to find commonly referenced release information quickly and efficiently during reviews of APHIS Form 2008. Do not duplicate this information in the Outline and the SO.

   Section V.C. should contain efficacy study information. [redacted]

Relative Potency (RP) Release Values

a. RP values should only include a single decimal place (i.e., a RP value of 1.2 is appropriate, but approving a value of 1.23 would not be appropriate) since the significance of decimal places beyond the first one is questionable.
b. If the first non-significant digit is a 5 or greater, round up (for example if the RP is calculated as 1.25, round up to 1.3). Note that this is for general regulatory purposes only.

4. Combination packages: Outlines for combination packages (2 licensed products that are packaged together, usually as lyophilized component and liquid component) should not have any testing requirements in Section V because combination packages are not tested as a package. Section V for these Outlines should say "Not Applicable because this is a combination package consisting of Product Codes X and Y". It should not refer to testing of the component products or describe any other type of testing.

5. Ensure that all test procedures are adequately described. It is insufficient to say, for example, that potency will be evaluated by an "agglutination test." The Outline (or associated SO) should have enough detail that an experienced laboratory technician could perform the test with the correct reagents, procedure, and controls.

6. Conditionally licensed products are not required to have a fully validated potency test that is correlated to efficacy. Outlines for conditionally licensed products should, however, have some kind of test to ensure batching consistency (e.g., pre-inactivation titer). These tests are often performed in-process (Section IV), but they should be cited in Section V.C and reported on APHIS Form 2008.

7. Batching consistency results for Prescription Products should be cited in Section V.C and report on APHIS Form 2008, similar to conditionally licensed products.

8. During annual review of Outlines, please remind firms that still use RelPot Software and/or SAM 318 for calculating relative potency that this method has been inactivated in 2013, and per CVB Notice 13-18. Firms should submit proposals to transition to alternate methods.

Section VI

Section-specific reference: VS Memorandum 800.202, GLC Section 4.2

1. Section VI.A
   a. For prescription product and autogenous serials in which less than 50 vials are manufactured, no confirmatory testing is done, and thus no samples need to be submitted.

2. Section VI.B
   a. The expiration date should be calculated from the date of initiation of the first potency test. An Outline should list only one dating period.
   b. The appropriateness of the dating period should be confirmed with real-time data (9CFR 114.13). When confirmatory data have been accepted by APHIS, the acceptance ML# and/or date should be recorded in Section VI.C. Outline reviews performed by Reviewers is a good time to identify that confirmation of dating studies are complete and recorded appropriately in the Outline.
   c. Combination packages: this section must identify the component products contained in the combination package. See VS Memorandum 800.206 for standard syntax.
   d. Typically, diagnostic test kits are initially assigned 12-month dating, killed/nonviable products are initially assigned 24-month dating, and modified live products are initially assigned 18 months dating at licensure, pending confirmation of dating.

3. Section VI.C
   a. This section should include all approved species of animals, routes/schedules of administration, duration of immunity (if applicable), and label claims. If appropriate, this section may contain approved label text verbatim. However, be aware that the firm may have approved claims that it does not elect to place on its labels (or only on certain labels). Poultry products for manual administration may have that route only indicated on smaller dose sizes. In these cases, the Outline and the labels may not agree exactly.
   b. Label claims should be updated to be consistent with single tier requirements for products licensed prior to November 1, 2016, and eligible for the claim per VSM 800.54. Permission may be granted to continue using 4-tier language indefinitely for certain export markets and wording should be maintained in the Outline. It is recommended that firms include in their Outline what countries the 4-tier language applies to.

c. [redacted]

4. Section VI.D
   a. If the licensee has licensed premises in multiple geographically separated locations, the location, and the description of each step of production that occurs should be specified.
   b. If production steps are to be moved to a new alternate location, CVB approval of transfer of technology is necessary prior to implementing the change and submission of the APHIS Form 2008 of the affected serials in case confirmatory testing of those serials is necessary.

Split Manufacture (FFM)

References: VS Memorandum 800.61 (split manufacture, FFM)
CVB Notice 13-06

1. The Outlines for FFM products are similar to those for final product, as applicable.

2. Generally FFM Outlines only have inactivation testing listed in Section V (although exceptions exist). If the FFM licensee performs other tests that ordinarily would be in Section V, they are placed in Section IV of the FFM Outline as in-process tests with a notation that they are reported on an APHIS 2008 for the FUP. The Outline for the final-use product (FUP) that contains the FFM may include, in its Section V, a reference to Section IV of the FFM Outline.

[redacted]

[redacted]

3. FFM Outlines and Outline for final use products that contain FFM should contain information about transfer of the FFM product from one manufacturer to the other, per VS Memorandum 800.61.

4. Split manufacture outlines (FFM and the final use product (FUP)) should clearly specify which steps are done by each licensee. Often firms attempt to write Outlines in a split manufacture, so each component Outline covers complete product manufacture, from start to finish. The FFM Outline should describe only those procedures performed by the FFM licensee. Outline sections not applicable to the FFM product should state "Not applicable"; they should not describe downstream procedures performed by the next licensee.

   The FUP outline should simply cite the FFM Outline for all steps performed by the FFM licensee; it should not describe those steps in a manner that suggests they may be performed by the FUP licensee. The composition and form of the product received from the FFM licensee should be adequately described, and complete Outline information from that production point onward should be included.

Combination Package Outlines

A combination package does not undergo testing and is not subject to release by CVB IC because it is made up of individual licensed products. Each component product is subject to serial release. It is critical to ensure that individual components included in a combination package are subject to serial release, since the combination package is not subject to serial release, although some flexibility may be considered regarding how this is accomplished. If one of the component products is manufactured by another firm, typically the firm that licenses the combination package has a final use product license associated with the antigens manufactured.

When licensing a combination package that includes live desiccated vaccine, ensure the inactivated liquid product is not viricidal, as per 9 CFR 113.35. Check to make sure the antibiotics in the combination package comply with 9 CFR 114.10.

Special Outlines

Reference: CVB Notice 14-16

Sometimes a Special Outline that describes a serial release test is in sufficiently acceptable format to be processed, but it still needs minor revisions, or the described procedure still needs validation or confirmatory testing before it is acceptable for official use. To

document that the SO is not yet ready for use in serial release, it is stamped with a #5 stamp.

Improvements are sometimes made to testing methods already used for licensed products. Ideally the firm should create a new SO when substantial assay improvements are proposed. In this way, the new method can be kept separate from the method currently being used for serial release. If, however, the firm has a strong preference to retain the existing SO #, new SO versions created during assay development and validation may need to remain unprocessed. Do not replace a SO currently approved for serial release with a version having a #5 stamp. The firm needs to retain an approved version of a test method to continue serial release while any assay improvements are being reviewed and approved.

Antibody Products

References: Outline guide in 9CFR 114.9(c)
VS Memorandum 800.100
Chapter on Antibody Products in this manual

Diagnostic Test Kits

References: VS Memorandum 800.73
Outline guide in 9CFR 114.9(f) and VS Memorandum 800.206
CVB Notice 02-08
Chapter on Diagnostic Test Kits in this manual

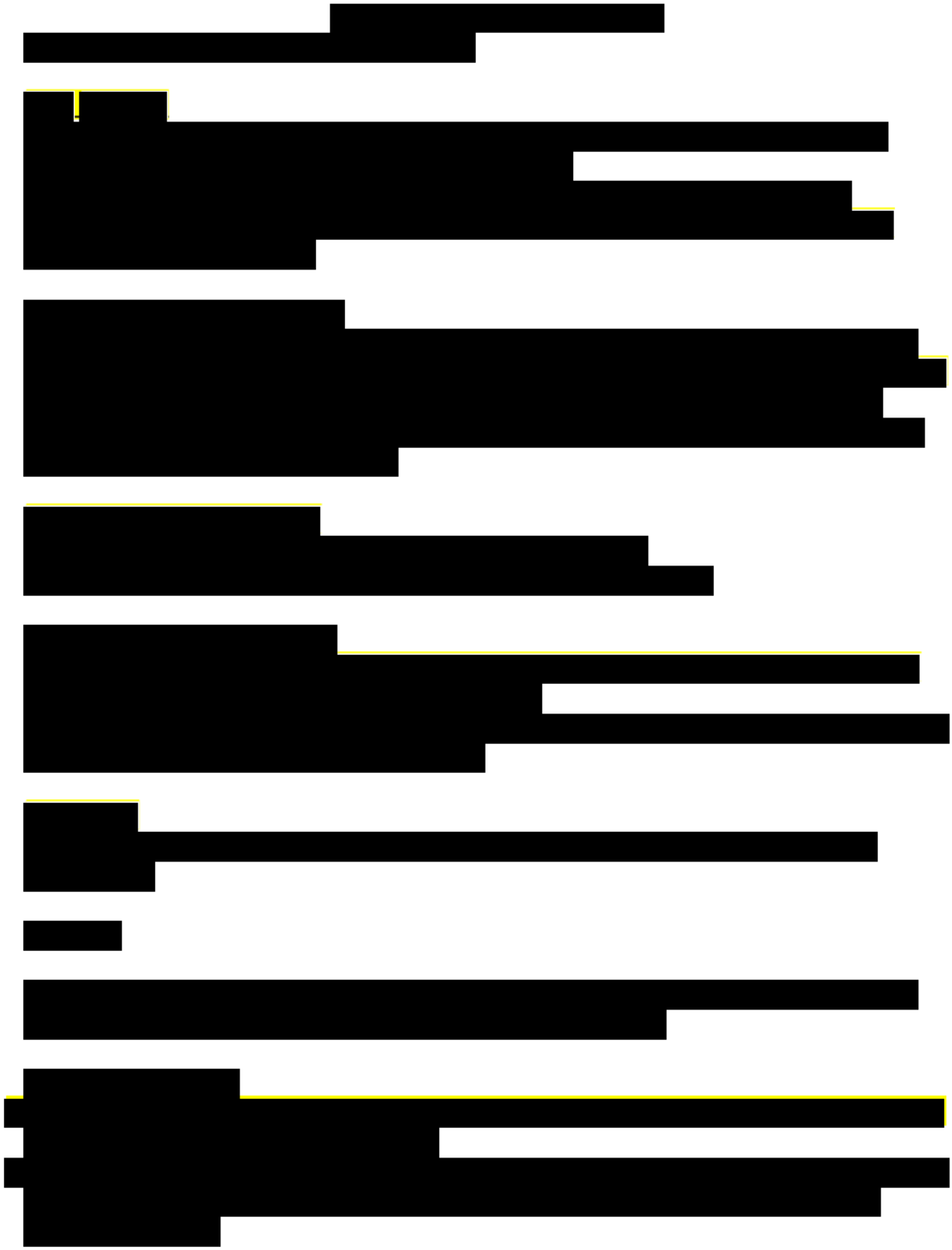
Allergenic Extracts

References: Outline guide in 9CFR 114.9(e)
VS Memorandum 800.106

Production Platform Products
References:VS Memorandum 800.213
Prescription Platform Products
References: VS Memorandum 800.214

Estimating Relative Potency

See above comment for Outlines of Production, Sec. V, point #8, regarding inactivation of RelPot software and SAM 318.



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