OUTLINES OF PRODUCTION
& SPECIAL OUTLINES

Overview

The Outline of Production 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 that 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 are reviewed and processed in much the same way that Outlines are. The general sections of this chapter apply to Special Outlines as well as Outlines, except where specifically noted.

Flow of Information

Paper Submissions	**Portal (Electronic) Submissions**
Outlines of Production must be submitted with an accompanying APHIS Form 2015. Two paper copies of the Outline must be submitted, both with original signatures. The firm may voluntarily submit additional copies for processing if they need them. CVB Notice 09-08 includes additional details regarding the availability of the APHIS Form 2015 in electronic format.	Electronic Outlines of Production 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 17-20 describe the instructions the firms use to prepare and submit Outlines.
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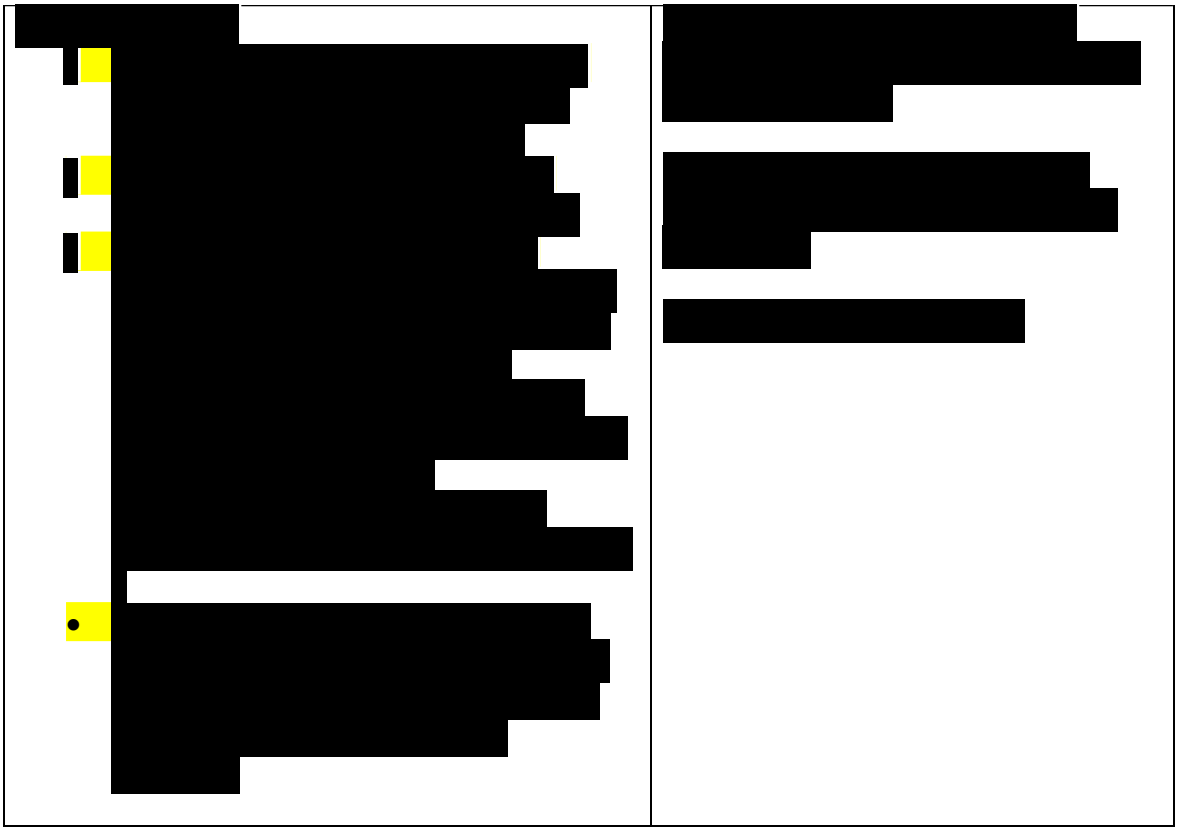

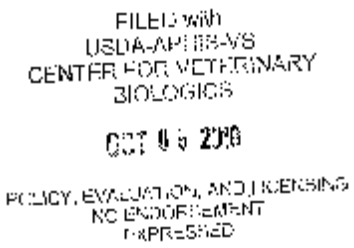

#6 stamp

#5 stamp

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, but they are not associated with any particular product code except when they are cited in an individual Outline of Production.

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.

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."

2. 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.

3. Pay particular attention to syntax that may allow for variable production or testing methods. Ensure that the language used is appropriate for the purpose.

    a. "**Should**" means that the procedure/value is *recommended*, but not necessarily mandatory. Deviations from the described procedure are not necessarily out of compliance. Likewise, "**may**" permits a procedure, but does not require it.
    b. "**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.
    c. 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 <u>not</u> appropriate because Reference

Bacterin 309 is the only approved reference. New references, even though may be formulated to be equivalent to #309, must be approved by the CVB before they are used (and incorporated into the Outline).

d. "**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 paper 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 alternatives are acceptable (e.g., two manufacturing sources of a chemically identical adjuvant), then the acceptable alternatives should be clearly specified. 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 and/or tests are often proposed for globally marketed products to satisfy the various regulatory requirements of different importing countries. If alternative procedures and/or tests clearly are not interchangeable, then it is likely that two separate product licenses are needed—one for each method.

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.

8. Most ranges should define a minimum and a maximum value. Example: "Gentamycin is added at a concentration not to exceed 30 mcg/mL." This statement allows the manufacturer to omit gentamycin entirely and is therefore not acceptable.

All minimum-maximum ranges should be reasonable [redacted]

[redacted]

Requirements for firms to review/revise Outlines

Firms are required to review their Outlines annually. If that review reveals inaccuracies 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. Only complete revisions are accepted electronically.

The reviewer has the authority to request a complete revision 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 general, we do not allow Outline changes (even very minor ones) for rabies products without redoing full efficacy studies. We have 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, or will be considered on a case-by-case basis only after consultation with and concurrence from the National Association of State Public Health Veterinarians' Rabies Compendium Committee (see Center for Veterinary Biologics Notice 06-23, Production changes for Rabies Vaccines).

Specific Review Considerations

Vaccines, Bacterins, Toxoids, Antigens

References:

9CFR Section 114.9
This 9CFR section contains the sections and subheadings that should appear in all Outlines of Production. This does not preclude a firm from adding additional subheadings, as appropriate, to specific Outlines of Production.

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.

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.

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	mmddyyyyxyz 1	Est#_productCode_mmddyyyy-xyz1-001	ZZZZz (GeneBank accession No.)	10000	Addendum 1
pPlasmid-ABCD	mmddyyyy-xyz2	Est#_ProductCode_mmddyyyy-xyz2-002	ZZZZx (GeneBank accession No.)	10032	Addendum 1
pPlasmid-ABCD	mmddyyyy-xyz3	Est#_ProductCode_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) and with negligible or controlled risk of bovine spongiform encephalopathy (BSE), according to APHIS' Animal Disease Status designations.

The firms also may generate their own versions of this statement, but 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 Center for Veterinary Biologics-Inspection and Compliance (CVB-IC), or as requested by the CVB. This list may be referenced in the Outline of Production. Even if the list is not referenced in the Outline of Production, however, it must 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.

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]

[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.

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)

Section IV

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

1. 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).

2. Assembly of units (IV.E): Firms are encouraged to include concentrations (e.g., $\geq 10^{7.8}$ pfu/ml), as well as the volume, of each antigen.

3. 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.

4. 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.

5. 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.

6. 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.

Section V

Section-Specific References:

CVB Notice 06-24 (Purity Testing of Avian-Origin products)
CVB Notice 12-21
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. 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:

a. Outlines must specify the 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 were accepted by the CVB.

b. 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.

c. Modified live products of avian embryo origin that are administered via wing-web are eligible for an exemption to 9CFR 113.27(a); they may be tested for purity by 9CFR 113.27(e) instead.

2. Section V.B: Stepwise procedures for safety tests are sometimes contained in Special Outlines (SO)s. 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.

3. Section V.C.: Stepwise procedures for potency tests are often contained in 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)
b. Expiration Date(s) of Reference Preparations
c. Minimum potency values (may have separate values for release and through dating)
d. Criteria for a valid test
e. Retest provisions

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 <u>not</u> duplicate this information in the Outline and the SO.

Section V.C. should contain efficacy study information.. For live products, release titers are based on the titer used in the efficacy serial + "adequate overage to compensate for adverse conditions." The general historical convention, unless otherwise specified in the Standard Requirement for a specific product, is:

--Live virus vaccines: Titer throughout dating = efficacy titer + 0.7 $\log_{10}$. Release titer = throughout dating titer + 0.5 $\log_{10}$ for loss over dating, which may be subsequently adjusted based on a stability study.
--Live bacterial vaccines: Throughout dating titer = 2x efficacy titer. Release titer = 3x throughout dating titer for loss over dating.

Relative Potency (RP) Release Values
-- RP values should only include a single decimal space (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 spaces beyond the first one is questionable.
-- 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.

F. Section VI

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

1. Section VI.B
    a. For prescription product 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.C

    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.

c. Combination packages; this section must identify the component products contained in the combination package. See VSMemorandum 800.206 for standard syntax.

d. Typically, killed/nonviable products are assigned 24 month dating at licensure, pending confirmation of dating. Modified live products are typically assigned 18 month dating. Diagnostic test kits are typically assigned 12 month dating.

3. Section VI.D

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). 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. Outline of Production updates may be done at any time, effective immediately provided it is done by the time single-tier labels appear on released product. Section VI should list the single-tier effectiveness statement for the product. Keep the 4-tier language in the Outline of Production as well during the implementation period. The implementation period spans from now until October 31, 2020. Permission may be granted to continue using 4-tier language indefinitely for certain export markets. .

c. Poultry products recommended for in-ovo administration: The CVB allows this class of products to be labeled with instructions to mix the product with another specified product, even though the two products are not marketed together. Normally recommendations to mix individual products is permitted only with licensed combination packages.

2. Section VI.E:

a. If the licensee has licensed premises in multiple geographically separated locations, the location at which each step of production typically 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. 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.

Occasionally the FFM licensee performs final product testing on samples provided by the FUP licensee. If this occurs, the FUP Outline should mention in Section IV that the samples are shipped to the FFM licensee for testing. Section V should state that testing is performed by the FFM licensee and should cite the FFM Outline for the specific test protocol.

The FFM Outline should include a statement in Section IV that the FFM licensee receives test samples from the FUP licensee. The testing should be described in Section IV of the FFM Outline and should include validity criteria, release values, and information regarding test references.

3. FFM Outlines and Outline for final 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. The component products are 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 dessicated vaccine, ensure that 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 process, 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: specific Outline guide in 9CFR 114.9
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
CVB Notice 02-08
Chapter on Diagnostic Test Kits in this manual

Allergenic Extracts

References: Outline guide in 9CFR 114.9
VS Memorandum 800.106

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