

CHAPTER 4 VACCINES

INTRODUCTION

Vaccines in *USP–NF* traditionally have referenced 21 *CFR* 600–680 and resulted in the so-called “short monograph” that, in addition to a product description, also included the following items: Packaging and Storage, Expiration Date, and Labeling. In 1997, FDA decided to remove items related to specific vaccines from *CFR* and replace them with private licensing agreements. As a result, USP decided to develop public vaccine monographs. The present guideline applies to new vaccines, as well as those that already have a “short monograph” in *USP–NF*. It is designed to assist industry and other organizations in developing monographs for their new vaccines, including those produced by biotechnological processes. It is useful at the development stage to ensure that analytical procedures for purity, quality, and potency are developed and validated as an integral part of vaccine manufacture.

Although the number of manufacturers is limited, vaccines usually are marketed globally. It is advantageous to have common international standards for each product. In order to help accomplish this, USP encourages vaccine manufacturers to submit Requests for Revision for vaccine monographs for their products, as a means of working toward a uniform global standard. The European Pharmacopoeia recently has published several vaccine monographs. Specifications in these monographs do not always conform to those contained in the biological license approved by FDA. Although USP is a national pharmacopoeia, its standards are recognized in numerous countries. Monographs in *USP* may help U.S. manufacturers minimize regulatory impact on global distribution of their products. An article recognized in the pharmacopoeia can be described as “USP” on its label.

In addition to the recommendations in this document, a vaccine monograph also must conform to the requirements discussed in the *General Notices* chapter of *USP–NF*.

VACCINE PRODUCTS

Vaccines are defined as preparations containing antigenic substances that induce a specific and active immunity against an infective agent. They may contain: 1) live microorganisms attenuated by treatments designed to reduce their virulence but retain their immunogenicity; 2) microorganisms inactivated by chemical or physical means; or 3) antigens produced by microorganisms (as is or after detoxification) or biotechnological processes.

Name Sponsors submitting a Request for Revision for a USP vaccine monograph should provide a proposed name. The name of a vaccine monograph should provide a unique identity for the vaccine, differentiating it from

other vaccines, including related ones. The disease that a vaccine is designed to prevent should be the first word(s) in the name, e.g., *Cholera Vaccine*. Additional differentiation can be achieved by including: 1) viability information (live, attenuated, inactivated) for virus vaccines, and, if necessary, strain; 2) expression system (yeast, *E. coli*) and then adjuvant nature (aluminum hydroxide, aluminum hydroxyphosphate sulfate) for recombinant protein and DNA vaccines; 3) serotype or group for polysaccharide vaccines; and 4) nature of the conjugate and then the adjuvant for polysaccharide–protein/peptide conjugate vaccines. The name of adsorbed vaccines should end with *Adsorbed*. For combination vaccines, the title includes names of each vaccine present connected with “and.”

Definition Vaccines are defined by their nature, functional properties, microorganism used, and, when appropriate, production method, conjugation (polysaccharide–protein/peptide), and adjuvant type. A Request for Revision should include biological potency limits in the Definition. Limits of potency for each component (serotypes or different vaccines) in a multivalent vaccine should be indicated. The Request for Revision should indicate antimicrobial agent(s) present in the vaccine product.

PACKAGING AND STORAGE

The Request for Revision should indicate the type of container used for the vaccine product. When container type (plastic or glass) is not included, USP will assume that either is adequate. The Request for Revision also should indicate the storage temperature, using the temperature definitions under *General Notices*. Storage temperatures should conform to the requirements of 21 *CFR* 610.53. If necessary, the Request for Revision also should indicate a requirement to protect from light and freezing.

OTHER REQUIREMENTS

Expiration Expiration dates in the Request for Revision should conform to the table listed in 21 *CFR* 610.53. The establishment of an expiration date should be based upon stability data that have received appropriate regulatory evaluation and approval.

Labeling The Request for Revision should provide labeling information conforming to requirements in 21 *CFR* 610.60 and 606.61, with instructions for use, storage temperatures, recommended dose, and route of administration. For multiple-dose containers, the individual dose also should be provided. Cautionary statements, such as “avoid freezing” or “avoid exposure to light” should be included in the labeling, when applicable. The Request for Revision should indicate any preservatives used and their concentration. Similarly, antibiotic name and amount per dose should be provided, if present. Chemical method(s) used to inactivate microorganisms or virus should be indicated in labeling, which should be provided in the Request for Revision. The Request for Revision should indicate minimum potency of active component(s) in the product, using appropriate units.

REFERENCE STANDARDS

The Request for Revision should indicate which monograph tests require Reference Standard material(s). Reference Standards for tests in a USP monograph frequently are available from CBER (U.S. Reference Standards) and WHO (WHO International Reference Standards). For some monograph tests, official USP Reference Standards are available, e.g., Bacterial Endotoxins. In addition, vaccine manufacturers often use qualified internal standards that have been calibrated against public standards. The Request for Revision should indicate the names of USP Reference Standards to be used for excipient and adjuvant tests, if available from USP. The source of Reference Standards, including official USP Reference Standards, should be included and clearly identified in the test protocol.

SPECIFICATION

Although USP intends to develop monographs that are as comprehensive as possible, it recognizes that some information needed in a Request for Revision may be proprietary. When proprietary information is provided and so identified, USP treats this information confidentially. Nonetheless, procedures in the specification should be sufficiently detailed so that any competent analyst with the appropriate equipment and reagents may conduct the analysis. Where this is not the case, the general technique and acceptance criteria should be provided in the Definition (see above).

The Request for Revision also must include copies of the validation packages for the procedures included in the Request for Revision, as appropriate. The validation data must be consistent with the requirements as described in General Chapter *Validation of Compendial Methods* <1225>, unless the General Chapter does not include the type of procedure included in the Request for Revision (e.g., bioassay, serological procedures). In such cases, ICH, CBER, or another appropriate validation guideline should be followed and should be cited in the Request for Revision. The validation data will be held confidentially by USP and will be made available only to appropriate expert committee members, on a confidential basis, as part of the Request for Revision evaluation (see *USP Document Disclosure Policy*, available at <http://www.usp.org/aboutUSP/governance/policies/documentDisclosure.html>).

Identification Test The Identification test usually includes multiple procedures and should conform to the requirements of 21 *CFR* 610.14. These procedures should adequately identify the vaccine as designated in the labeling, using appropriate physicochemical, immunological, molecular biological, or other procedures, and differentiate it from any other vaccine. This includes a vaccine for the same disease that is a different chemical entity. The procedures should demonstrate that the vaccine contains the specified serotype(s) or antigen(s).

Antimicrobial Preservatives Content Where applicable, the Antimicrobial Preservatives Content test should be conducted using a suitable chemical or physicochemical procedure (see General Chapter *Antimicrobial Agents—Content* <341>). When the test is needed but the General Chapter does not provide a suitable procedure, the Request for Revision should include a validated procedure. The minimal content is based upon the minimum amount shown to be effective (see General Chapter *Antimicrobial Effectiveness Testing* <51>).

Adjuvants If an adjuvant is present in a vaccine, the Request for Revision should include a procedure to quantitate adjuvants. When an aluminum compound is used as an adjuvant, the amount per recommended individual dose must conform to the requirements of 21 *CFR* 610.15.

IMPURITIES

Product-related impurities include residual proteins or DNA in a polysaccharide vaccine. Where these may affect the vaccine's safety or efficacy, the Request for Revision should include procedures and limits for them. Similarly, a vaccine may contain process-related impurities (e.g., benzonase) that are added during fermentation or upstream purification processes and cleared downstream. However, traces almost invariably are present in a vaccine. As for product-related impurities, the Request for Revision should include procedures and limits if they may affect the vaccine's safety or efficacy.

Related Substances Protein-, polysaccharide-, and DNA-based vaccines may contain related substances that are either degradation or truncated products that are co-purified with active antigens. The degradation/truncated product may be produced by the microorganisms in which the vaccine is expressed or as a result of the manufacturing process. The Request for Revision should contain a procedure and limits for these related substances if they may affect the vaccine's safety or efficacy.

ASSAY TEST

For the Assay test, the Request for Revision may include a potency procedure determined by either an *in vitro* procedure or in animals, as compared to a USP Reference Standard for the vaccine. The *in vitro* test may be a procedure for measuring antigen content, e.g., ELISA, or cell-based procedure, e.g., TCID₅₀. In addition, the Request for Revision also

may include a physicochemical procedure, e.g., HPLC, electrophoresis, of colorimetric methods, for the antigen mass assay, if appropriate.

POTENCY TEST

Animal-Based Procedure The Request for Revision should include a procedure to assess the vaccine's potency or safety. It also should include the animals' species, number, sex, and weight range, and indicate how the study animals are assigned to different control and experimental groups. The Request for Revision should include the dose range used in the procedure, which should bracket the vaccine dose expected to protect 50% of the animals when challenged with the virulent microorganism. The Request for Revision should indicate the statistical treatment of the results in terms of linearity and dilution parallelism and should calculate the standard limits for the specific vaccine.

In-vitro Antigen Content The Request for Revision should include an ELISA or RIA procedure for the In Vitro Antigen Content. When commercially available kits are used, they should be qualified for suitability using an in-house, US, USP, or WHO standard.

SPECIFIC TESTS

Specific tests, in addition to the ones described above, may be included to better describe and control the purity, quality, and potency of a vaccine. Reference should be made to appropriate General Chapters, where applicable. If the procedure is not included in a General Chapter, the Request for Revision should include complete validation data (see General Chapter *Validation of Compendial Methods* <1225>).

INJECTIONS

Sterility Test An injectable vaccine should comply with the test for General Chapter *Sterility Tests* <71>, when required by the license. When a Sterility test is not included for an injectable vaccine, the Sponsor should provide the rationale for its omission in the Request for Revision. The Request for Revision should indicate if the membrane filtration method (preferred method) or the direct transfer method is used. The direct transfer method is used if the membrane filtration method is not applicable.

Bacterial Endotoxins Test or Pyrogen Test The Request for Revision should include the procedure to be used for the Bacterial Endotoxins test (see General Chapter *Bacterial Endotoxins Test* <85>), when required. Different procedures may use different limits, depending upon the product type. The limit is expressed per dose and is calculated based upon the dose injected per kg of body weight. When the Bacterial Endotoxins test cannot be validated or the regulatory requirement indicates otherwise, a procedure to test for pyrogens should be employed (see General Chapter *Pyrogen Test* <151>).

Container–Closure Test The Request for Revision should document that the Container–Closure test demonstrates integrity (see General Chapter *Sterility Tests* <71>).

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Particulate Matter Test Injections must meet the limits set forth under General Chapter *Particulate Matter in Injections* <788>.