

Adjuvants and Excipients

The Food Safety and Inspection Service (FSIS) transferred the official responsibility to evaluate adjuvants and excipients used in Veterinary Biologics back to the Animal and Plant Health Inspection Service (APHIS) in 2006. Center for Veterinary Biologics ([CVB Notice 06-13](#)) provides details regarding this transfer. FSIS had been providing chemical, toxicological, and pathologic evaluations of new adjuvants/excipients, but APHIS now has the scientific resources necessary to conduct these evaluations. Resuming adjuvant reviews eliminates a step in the approval process that industry must follow and requires contact only with APHIS.

All new product licensing packages should include a thorough description and the composition of any adjuvants. [Veterinary Services Memorandum 800.51](#) provides guidance regarding appropriate data that should be submitted for adjuvants. In general, **all** new product license applications should contain the following information:

1. Generic name of adjuvant (and Trade Name if applicable)
2. Chemical composition of adjuvant (list all ingredients and proportions).
3. Amount of completed/total adjuvant per dose of product
4. Dose volume of product
5. Animal species in which the product is to be used
6. Route of administration (and specific anatomical site, if designated)
7. Information regarding source, grade, quality of tests performed (if any) on each lot
8. Slaughter withdrawal period proposed [at least 21 days is required as per 9 CFR 112.2(a)(8)]
9. Other products for which the adjuvant/excipient has been approved (if applicable)

Initial Reviewer Evaluation

Reviewers should compare the additive description and composition with historic data regarding adjuvants and excipients on file at the CVB. A spreadsheet containing approved adjuvants is available to facilitate review of historic data (see adjuvant spreadsheet). The spreadsheet contains information regarding adjuvants and miscellaneous additives that have been approved for use by the CVB. Please note that not all of the products that these approved additives are to be used in are currently licensed. Some products are in the pre-license stage. Some products listed have been licensed but may not be currently manufactured. The adjuvant spreadsheet may not contain all of the adjuvants approved by the CVB. It is simply meant to be used as a tool for reviewers to use when reviewing adjuvant submissions. Reviewers are encouraged to contact the Adjuvant Coordinated Review Team (CRT) chair [REDACTED] if revisions or updates to this spreadsheet are identified. Additional data regarding previously approved adjuvants are filed in the adjuvant folder for each firm, located in the file room. [REDACTED]

[REDACTED]

Additional data and evaluation may be required for previously approved adjuvants that are to be included in products in unique ways. The reviewer should consult with the Adjuvant CRT if any questions arise regarding adjuvants. The purpose of the Adjuvant CRT is to generate useful and timely information for the reviewer in order to facilitate scientific review of adjuvants. In order to achieve this purpose, goals of the Adjuvant CRT include:

1. The CRT will strive to provide a response to adjuvant-related questions within 4 weeks of initial consultation.
2. The pathologist on the adjuvant CRT is also available for specific questions related to pathology at any time. [REDACTED]

3. [REDACTED]

The reviewer should consult the Adjuvant CRT prior to approval of new adjuvants, or to approval of previously approved adjuvants to be used at increased levels, in different routes of administration, or with different withdrawal periods. Results of an injection site study in the host animal may be required to complete evaluation of the adjuvant.

Considerations for an injection site study

The following guidelines should be considered when reviewing an injection site study:

1. A protocol should be submitted by the firm prior to conducting the study to ensure the study design is adequate. The proposed dates of conducting the study should be included to allow observation by CVB personnel if deemed necessary.
2. At least 10 animals of the minimum age should be included for adjuvants used in food-producing species other than fish and poultry:
 - a. The firm should compare the injection site of the new adjuvant to a product matched placebo by injecting the new product on one side of the animal, and the placebo on the other side of the animal. In certain instances, a placebo other than a product-matched placebo may be considered. Justification for using other types of placebos should be included in the protocol submitted for review. [REDACTED]

[REDACTED] The injection sites should be examined grossly by a veterinarian or board certified veterinary pathologist. The veterinarian or veterinary pathologist should also collect the tissues to be analyzed histologically. The results of gross pathologic examination should be included in the report. High resolution pictures of any gross pathology should be included.

- c. Histopathology of tissue samples taken from all injection sites should be analyzed by a board certified veterinary pathologist who has no knowledge regarding the products used in the study, and photographs of the histopathologic sections of the injection site should be included in the final report. The same pathologist should evaluate all the slides. The slides should be submitted to the CVB for Adjuvant CRT evaluation if requested. The histological evaluation is conducted to evaluate and ensure that the local inflammatory response is consistent with the expected physiological/immunological response to foreign material in the respective tissue. Observations that are inconsistent with the expected process may require additional evaluation.
 3. At least 10 birds of minimum age of the species the product is to be used in should be included for adjuvants to be used in poultry.
 4. At least 20 fish of minimum age/size of the species the product is to be used in should be included for injection site studies in aquatic species meant for human consumption. The study may be done using the same dose as per label recommendations, or at double the dose recommended on the label.
 - a. Many adjuvants cause some degree of tissue adhesion and pigmentation in the abdominal cavity when administered intraperitoneally. The Speilberg Scoring System, based on the size and density of the adhesion, should be used to analyze data from aquatic species. This scoring system is described in the article, *Experimental studies on the efficacy and side-effects of intraperitoneal vaccination of Atlantic salmon (Salmo salar L.) against furunculosis*, by Midtylyng, et al, in "Fish and Shellfish Immunology (1996) 6, 335-350. The study should be evaluated for degree of tissue pigmentation and adhesion in the abdominal cavity, as well as vaccine residues in the abdominal cavity. Speilberg scores of 3 or less are acceptable. Speilberg scores of 4 or greater are likely to be noticed by laymen during evisceration and may leave damage to the carcass after evisceration.
 - b. Vaccine residues in edible portions of fish present at slaughter are not acceptable.
5. For non-food producing animals like dogs and cats, the results of an acceptable field safety study are adequate to demonstrate safety of the adjuvant. [REDACTED]

Additional information that may be considered as supporting data in an injection site study report include:

1. Summary of any available studies (i.e., peer reviewed publications, relevant internal reports) that contain pathologic assessments of the experimental product when administered to the target species
2. Data showing the time required for the resolution of any injection site reactions
3. For live organisms, a summary of any available data regarding clearance of the organism from the target species
4. Results of safety studies in laboratory animals like mice and guinea pigs

Additional considerations for novel adjuvants/excipients

For new adjuvants that are unique and have not been included in previously approved veterinary biological products, the following information may be required.

1. Toxicological Profile which should include
 - a. Any information relative to the listing of the additives on lists of approved additives (i.e. Generally Regarded as Safe (GRAS), Annex II, Drinking Water Standards, etc.). Provide a copy of the Material Safety Data Sheet (MSDS) or reference the MSDS number for each additive (if available)
 - b. Results of toxicological studies to determine the local and or systemic effects of the additive on laboratory animals.
 - c. Summary of any oral/acute testing of the additives in target and non-target species.
 - d. Summary of any information regarding how additives are metabolized by the target animal
 - e. Information regarding the carcinogenicity of the additives
 - f. Known reactivity of each additive.
 - g. Known pharmacological activity of each additive
2. Human Exposure Profile
 - a. Estimate of the total volume/mass of the additives that will be administered to the target animal under the proposed label indication
 - b. Estimate of the human consumption/exposure to each additive
 - c. Measurements of the levels of residue in tissue at proposed withdrawal period to make sure the levels are not over Food and Drug Administration (FDA) tolerances for food if available
 - d. FDA tolerance established for additive and cite source if available

Exceptions to Slaughter Withdrawal Period Requirements

No slaughter withdrawal statement is needed for a non-injectable (i.e. oral, intranasal, immersion, etc.) product clearly labeled solely for neonatal animals because they do not enter the food chain.

Non-injectable biologics used for food producing animals entering the food chain must have a slaughter withdrawal period of not less than 21 days, as per 9 CFR 112.2(a)(8).

[REDACTED]

CVB Response to Adjuvant Submissions

Based on the data requested, the CVB will make a determination regarding the suitability of the adjuvant. The assessment may be:

1. Withholding period not necessary
2. Minimum withholding period of 21 days is appropriate
3. Longer withholding period is appropriate
4. Additional data required

[REDACTED]