

Preservatives in Biologics Manufacture

Overview

The purpose of this chapter is to outline the policy of the Center for Veterinary Biologics regarding preservative use in veterinary biologics. Applicable regulations and guidance are found in:

- 9CFR 114.10
- 9CFR 112.2(a)(10)
- 9CFR 113.100(f)
- 9 CFR 113.200(f)
- VS Memorandum 800.206

Background

The regulations consider any antibiotic to be a preservative, and the CVB includes in this definition antibiotics added to the production media or at any subsequent stage of the manufacturing process. 9CFR 114.10 specifies the maximum permissible amounts and combinations of antibiotics authorized for use as preservatives in veterinary biological products. The maximum allowable concentrations of antibiotics listed are expected to inhibit growth of common susceptible bacterial contaminants, and a definite genetic determinant for resistance would be necessary for survival at these concentrations. These levels are also below a therapeutic dose for the animal receiving a dose of the biological product.

Antibiotics used in virus seed stock purification are not restricted as to the kind or amounts, provided carryover into the final product is controlled and specified in the Outline of Production. The CVB considers carryover to be controlled if the antibiotics used in seed stock purification are added to the seed stock culture in concentrations no greater than generally accepted inhibitory levels for susceptible contaminants and/or the resultant culture media is decanted.

One permitted combination includes penicillin and streptomycin. Penicillin and streptomycin are commonly used in combination to minimize contamination in the laboratory. Penicillin interferes with bacterial cell wall synthesis while streptomycin inhibits bacterial protein synthesis. Through these different mechanisms of action, the combination of the two antibiotics acts against a broad spectrum of bacteria.

Another permitted combination includes either amphotericin B **or** nystatin with one of the other antibiotics listed. Amphotericin B and nystatin are both antifungal agents that affect membrane permeability. Allowing one of these agents to be used with the other permitted antibiotics generates a preservative that is effective against a broader spectrum of organisms, but allowing both to be used in the same product would be of little benefit. Amphotericin B or nystatin may also be used with a combination of polymyxin B and neomycin, or with the penicillin/streptomycin combination. Polymyxin B (a cationic polypeptide) and neomycin (an

aminoglycoside) have different mechanisms of action so allowing this combination provides for the creation of a broad spectrum preservative.

Requests for antibiotic combinations not listed in 9CFR

A request to use an antibiotic or antibiotic combination not specified in 9 CFR 114.10(b) or (c) as a preservative may be considered under certain conditions. A request for use should include the reason why the antibiotic or antibiotic combination is needed, a risk assessment, the expected levels of the antibiotic in the final product, and data indicating the residual antibiotic level in tissues of animals to which the product is administered.

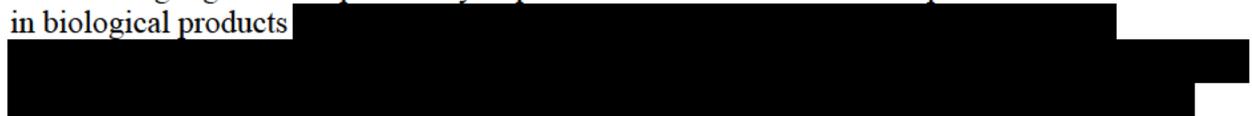
Declaration of preservatives in Outline of Production and/or Labeling

Antibiotics used in the manufacturing process, not restricted to those added expressly as preservatives, and not removed and/or diluted, should be listed on product labeling and in Section VI of the Outline of Production. If a preservative is added at batching/serial assembly, the identity and actual concentration added should be specified in Section IV.B. It is not acceptable merely to cite 9 CFR 114.10 or to include open-ended ranges (e.g., <30 U/mL).

If residual amounts of antibiotics may be present in the final product due to upstream processes (e.g. growing organisms in media containing antibiotics), Section IV.B.2 of the Outline should indicate which antibiotics may be present in residual amounts, and the stage(s) at which the antibiotics were added should be identified. It is not necessary to estimate the concentration of residual antibiotics in the final product, provided that there is no material risk that this level exceeds the maximum amounts codified in 9 CFR 114.10.

Exceptions to including antibiotics on the label may be granted if sufficient data are submitted to indicate that processing reduces the amount of antibiotics present in the final product below detectable levels. Granted exceptions should be included in Section IV.B of the Outline of Production by stating that although the antibiotic is used during the manufacturing process, the concentration in the final product is below the limits of detection and therefore the antibiotic is not mentioned as a preservative in this section, or on the label, as approved on (date of letter approving exception), (CVB Mail Log number, if known).

Our labeling regulations specifically require the disclosure of antibiotic preservatives contained in biological products



For diagnostic test kits, the preservatives should be listed in the product insert, but do not need to be listed on the carton label if there is insufficient space.