Animal and Plant Health Inspection Service

Veterinary Services

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Antimicrobial Resistance Policy

Document Number: CVB-SOP-5114 **Revision:** 01

Previous Number:

Vault: CVB-Released

Section/Area: CVB-SOP-PEL-REV

Effective Date: 11 Jan 2021

Notes:

Antimicrobial Resistance Policy

Mention of trademark or proprietary product does not constitute a guarantee or warranty of the product by USDA and does not imply its approval to the exclusion of other products that may be suitable.

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1. Purpose

The spread of antimicrobial resistance (AMR) has become a major public health problem, and responsible actions are required to mitigate any potential contributors to the problem. Effective vaccines are rightfully considered a tool to help address AMR, but future vaccines must be designed to minimize the risk of environmental spread of AMR genes. This document outlines the Center for Veterinary Biologics policy regarding the presence of AMR genes in veterinary biological products. This policy would not apply to diagnostics except for those administered to animals (e.g. tuberculin).

2. Scope

All products which are known to contain, or could conceivably contain, AMR genes capable of environmental spread will be analyzed by the CVB to determine what, if any, AMR genes are present. In general, the CVB will not allow products containing AMR genes capable of environmental spread to be used as future Master Seeds (MSs) for non-inactivated products. CVB recommends that firms screen potential seeds for AMR genes and eliminate cultures which pose a threat of spreading resistance from consideration as master seed candidates. Master Sequences (MSQ) or MSs used to produce bacterial or nucleic acid based products prepared with inactivation or other steps that are highly likely to inactivate any DNA or RNA which may encode antibiotic resistance will continue to be allowed with restrictions requiring the mitigation steps. At this time, the CVB is not applying this policy to the potential use of MS/MSQ candidates demonstrating resistance to common disinfectants or antiviral drugs. However, firms still need to consider the potential for and impact of environmental spread of antiviral and disinfectant resistance in their risk analysis and environmental impact for all non-inactivated Master Seeds.

The CVB will also apply this policy to commercially available plasmids or nucleic acid based molecular biology tools used in veterinary biologics and present in final product. CVB recommends that licensees and permittees use other available selection methods, rather than AMR, to improve the likelihood that a final product is licensable.

3. Policy

3.1 Methods

For this policy, the CVB is currently focusing on the presence of AMR genes, particularly those capable of vertical and horizontal transfer, regardless of the occurrence of an AMR phenotype. In contrast, the CVB is less concerned about point mutations conferring an AMR phenotype. Since phenotype-based tests are based on clinical breakpoints without identifying the genetic basis for resistance, this type of test is not well-suited for characterization of MS/MSQ, but might be useful for providing supplemental information. The CVB evaluation of antibiotic resistance genes will be done by next generation sequencing and screening of genetic data against a catalog of known resistance genes using the AMRFinder tool. In brief, the CVB will test for AMR genes utilizing next-generation sequencing of the MS/MSQ genome. The sequence data

will be analyzed using the National Center for Biotechnology Information (NCBI) tools and databases. The AMRFinder tool will use BLASTX to search a hierarchy of gene families with predetermined cutoffs. The CVB recognizes that databases evolve with time and that decision makers use the best data available at the time of testing.
Specific guidance on CVB methods can be found in CVB-PRO-5104 (Bacterial Identity Testing by Whole Genome Sequencing) and CVB-PRO-5105 (Antimicrobial Resistance Genotype Detection). There may be multiple routes to replicate this sequence-based testing, whether internally or via an external laboratory. One possible option to obtain identical fee-for-service testing is via the USDA National Veterinary Services Laboratories (NVSL) at www.aphis.usda.gov/nvsl.
In order to include this information early in the MS/MSQ process, relevant Summary Information Format (SIF) documents will be updated to include a section on AMR.

3.2 Categorical Exclusion

It is expected that various molecular biology methods might be utilized to remove AMR genes from MS/MSQ candidates. If the product is a conventional live biologic, and the only change to the candidate MS is the removal of the AMR genes, the CVB will apply an immediate categorical exclusion so that a Federal Register Notice due to NEPA will not be required. This will be applied to new MSs as well as existing approved MSs as indicated below.

3.3 Exceptions

If there are extenuating circumstances, the CVB might consider using a risk based approach to accept AMR positive MS/MSQ candidates. The risk evaluation would include consideration of potentially extenuating circumstances in the following areas:

3.3.1. Likelihood of spread based on location of gene [redacted]

3.3.2. Current prevalence of the AMR resistance gene in the environment.

3.3.3. Medical importance of antibiotic in animal and human medicine (e.g. hygromycin would be more likely to be allowed as an exception as compared to colistin). An exception is unlikely to be given for an antibiotic listed by the World Health Organization as being medically important to humans.

3.3.4. Copy numbers of the gene involved (e.g. attempts to purify final product which leave only minute levels of AMR genes would be more likely to be considered for an exception as compared to a crude, non-purified preparation.)

3.3.5. Likelihood of spread based on proposed use as a veterinary biologic product (e.g. parenteral administration of a product to dogs with cancer would represent a much lower risk of environmental spread than water administration of a product to fish in ponds.)

3.3.6. Availability of a suitable alternative. Lack of any suitable alternative will strengthen the case for an exception to the policy.

3.3.7. Public health review.

3.4 Existing Approved Master Seeds

A firm's request, to expand the use of currently approved MSs/MSQ harboring AMR genes into new products, will be subject to the same policy outlined above. The CVB will consider exercising regulatory flexibility, where appropriate, when a currently licensed product is modified to remove one or more AMR genes. The CVB will evaluate proposals to transition or modify MSs/MSQs with AMR to ensure scientifically sound decisions. Manufacturers of previously licensed non-inactivated bacterial vaccines have been informed, by the CVB, of the antimicrobial resistance status of the MSs/MSQs. The CVB is encouraging manufacturers to transition away from the use of currently licensed MSs/MSqs containing AMR genes capable of environmental spread.