OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

STERILITY AND PYROGEN REQUIREMENTS OF INJECTABLE DRUG PRODUCTS

I. PURPOSE

This guide describes CVM's policy regarding sterility and pyrogenicity requirements of veterinary injectable drug products. All injectable veterinary drug products are sterile except euthanasia products and natural and synthetic steroid hormonal ear implants intended for use in bovine and ovine species. Pyrogen levels in sterile, injectable veterinary drug products are within established limits.

II. BACKGROUND

Based in part on the United States Pharmacopeia (USP) requirements and historical perspective, it is CVM's position that sterility is an expected quality of injectable drug products by virtue of their intended use. Therefore, injectable drug products purport to be sterile and are subject to the following:

1. the USP, which requires injectable drugs to be sterile;
2. Section 501 (b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) which states that a drug is adulterated if it purports to be or is represented as a drug which is recognized by an official compendium and its quality falls below the standards set forth in the official compendium;
3. Section 501 (c) of the FD&C Act, which states a drug is adulterated if it is not a compendial drug and its quality falls below that which it purports to possess;
4. Section 501 (a) (2) (B) of the FD&C Act, which states that a drug is adulterated if it does not meet current good manufacturing practice to assure that such drug meets the requirements of the Act;
5. 21 CFR 211.113 which requires validation of sterilization processes for drugs purporting to be sterile; and
6. 21 CFR 514.1 (b) (5) (vii) (b) which requires documentation for the sterilization processes for drugs purporting to be sterile to be provided in drug applications.

With the following exceptions, CVM has historically required that veterinary injectable products be sterile and pyrogen free. The injectable drug products that have been exempted from sterility requirements in the past are euthanasia products, bovine and ovine ear implants, and intra-mammary products.

The reasons for exempting euthanasia products from these requirements are obvious. Natural and synthetic steroid hormonal bovine and ovine ear implants have been exempted from the sterility and pyrogen requirements because (1) some ear implants were already on the market as non-sterile products before CVM came into being, (2) bovine and ovine ears are not used as human food, (3) the products for sheep are considered to be minor use, and (4) technology for sterile manufacture of these drugs either did not exist at the time these drugs were developed or was impractical.

In the past, when intra-mammary products were not required to be sterile they were required to be pathogen free. Demonstration that a product is pathogen free requires extensive microbiological testing which is often difficult and unreliable due to the composition of mastitis products. The CVM now believes that these products should be sterile because: (1) any viable organism (in addition to pathogens) when placed in an advantageous medium can cause problems, (2) the sterile manufacture of these drugs is economically feasible using current technology, and (3) this is consistent with our efforts to achieve harmonization with European requirements since these products are required to be sterile in Europe.

CVM believes that euthanasia products and the ear implants which are exempted from the sterility and pyrogen requirements for injectable veterinary drugs must be labeled as non-sterile. The reasons are (1) unless otherwise informed, users perceive that all injectable drugs are sterile, (2) there have been problems with ear infections associated with the use of these products some of which might have been due to lack of sterility rather than implantation technique, (3) some products have been coated with antibiotics to aid in preventing infections possibly caused by the non-sterile products, and (4) using current technology these drugs could be manufactured to be sterile. The Center is hesitant to impose the sterility and pyrogenicity requirements on these products because of the impact these requirements might have on products that are already approved. However, the labeling of these products as being nonsterile would inform the user that these products are manufactured by a non-sterilizing process.

III. POLICY

It is CVM policy that (1) all injectable drug products (including intra-mammary products) be sterile except euthanasia products and the ear implants for bovine and ovine species, and that (2) pyrogen levels in sterile veterinary drugs should not exceed established limits. Approved products (including intramammary) that fail to meet the requirements for sterility and pyrogens will be labeled as being "manufactured by a non-sterilizing process". The labeling requirement is effective at the time of the next label printing after the date of this Notice.

Sterile veterinary drug products should be manufactured using validated processes that assure sterility and pyrogen levels that are within established limits. CVM will review the sterilization processes used to produce each drug product to determine if they provide assurance that the final product will be sterile and that pyrogens will be within established limits.

The USP has recognized the Limulus Amebocyte Lysate (LAL) method as the official method for assaying drug products for lipopolysaccharides produced by gram-negative microorganisms (bacterial endotoxins). The rabbit pyrogen test may be used only if a product is incompatible with the LAL test. CVM endorses this position. However, during the development of a product and the manufacturing process validation (the first 3

commercial batches manufactured), the product should be assayed by both the LAL test and the rabbit pyrogen test. This is because there is the possibility of the presence of pyrogenic materials in the product that are not lipopolysaccharides. Testing the first three (3) commercial batches would demonstrate if pyrogen contamination other than lipopolysaccharides is present in the final drug product. After the first three (3) commercial lots, provided the rabbit pyrogen testing is negative, the LAL test should be utilized for release testing.

CVM's policy is that euthanasia products and the bovine and ovine ear implants manufactured by a process other than a validated sterilization process are labeled as "manufactured by a non-sterilizing process." The labeling requirement is effective at the time of the next label printing after the date of this Notice.

CVM believes that products produced in accordance with the controls associated with sterile processes will have enhanced quality. Nonetheless, CVM does recognize that there may be instances where our expectations regarding the manufacture of a sterile injectable drug product may not be feasible. In these instances, the effects of microbial contamination on the efficacy and safety of the product must be addressed as well as the issues associated with the inability of manufacturing a sterile drug product. The information necessary to support the inability to manufacture a sterile injectable drug product and the information to support the safety and efficacy of a non-sterile injectable product may be extensive. A sponsor proposing to take this alternate route should discuss these issues with CVM early in the drug product development process. CVM will work with sponsors in exploring options to collect acceptable information and data to address our manufacturing, safety and efficacy concerns. If this information is developed, a sponsor may apply for an exemption from the sterility requirements. CVM will make a decision based on the documentation provided to support the exemption. When an exemption from the sterility requirements is granted by CVM, we will determine other appropriate controls and specifications to assure the quality of the non-sterile drug product. For example, these controls and specifications could include bioburden testing and limits, and pathogen testing, etc. A sponsor proposing an exemption to the sterility requirement should be aware that alternate standards may be as difficult to meet as the sterility requirements. Any injectable product manufactured by a non-sterilizing process that receives an exemption from the sterility requirements will also be expected to be labeled as being "manufactured by a non-sterilizing process".

IV. REFERENCES

CVM Policy Letter dated June 29, 1995.

V. VERSION HISTORY

April 25, 2000 – Original version.

June 21, 2022 – Updated to create a word version and format in the proper template.

August 5, 2022 – Corrected to include a mistakenly omitted portion of the text.

February 6, 2024 – Quality management review completed. No substantive updates needed. The document was put into the office's current template and format.