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Guidance for Industry

In-Use Stability Studies and Associated Labeling Statements for Multiple-Dose Injectable Animal Drug Products

Draft Guidance

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Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of in-use stability testing is to establish a period of time during which a multiple-dose drug product may be used while retaining acceptable quality specifications once the container is opened (e.g., after a container has been needle-punctured). For multiple-dose injectable drug products intended for use in humans, there is a volume limit of 30 mL in the multiple-dose container. There is also a 28 day in-use period associated with multiple-dose injectable drug products intended for use in humans unless otherwise labeled, when supported by successful antimicrobial effectiveness testing (AET) per U.S. Pharmacopeial Convention (USP) <51> *Antimicrobial Effectiveness Testing*. Multiple-dose injectable animal drug products have no volume limit and are often packaged in much larger containers. In addition, some animal species weigh less than humans and, thus, individual doses are often smaller than those used in humans. As such, more punctures and a longer in-use period may be applicable to multiple-dose injectable animal drug products compared with their human counterparts. CVM recommends that all multiple-dose injectable animal drug products have an in-use statement on the labeling. This document serves to provide CVM's current thinking on how to formulate in-use statements for multiple-dose injectable animal drug products as well as how to design and carry out in-use stability studies to support these in-use statements.

It should be noted that this current thinking pertains to both generic drug products and pioneer drug products regardless of whether or not the pioneer reference listed new animal drug (RLNAD) currently has an in-use statement on the labeling.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. NUMBER OF PUNCTURES AND NEEDLE GAUGE

The target species and labeled dosage(s) should be considered when determining the number of punctures and needle size to be used for an in-use stability study. If multiple container sizes are available for a single drug product, a single in-use stability study may be used to represent more than one container size if the same stopper is used for all the containers. Care should be taken in these cases, however, to ensure that the needle gauge and number of punctures represents the worst-case scenario for the entire group of containers represented.

A. Needle Gauge

In general, the largest needle gauge normally used in practice, taking into account all intended species, should be used for the in-use stability study. We recommend discussion with the appropriate team within the Office of New Animal Drug Evaluation's Division of Manufacturing Technologies (DMT) if special circumstances exist or questions remain regarding the needle gauge to be used for the in-use stability study. Appendix 1 contains recommended needle sizes for major animal species, and Appendix 2 contains an example calculation of the needle gauge and number of punctures to be used for a worst-case in-use stability study of a multiple-dose injectable animal drug product intended for use in multiple species.

B. Theoretical Maximum Number of Punctures

The theoretical maximum number of punctures should be based on the intended species (typically the smallest) receiving the largest number of doses per container. CVM recommends using this approach for the in-use stability study whenever possible. If the theoretical maximum number of punctures is not used, an in-use statement restricting the maximum number of punctures would be recommended in most cases. In certain cases, a proposal to perform the in-use stability study using less than the theoretical maximum number of punctures can be made if proper justification is provided (e.g., use of multiple-dosing equipment,[1] greater historical use in one indicated species than another in the field, equal use between two or more indicated species in the field). If less than the theoretical maximum number of punctures is proposed, both the DMT and the appropriate Target Animal Division (TAD) will determine if the number of punctures proposed is justified based on a reasonable prediction of actual use. If this is the case, then a labeling statement restricting the maximum number of punctures may not be needed.

III. IN-USE STABILITY STUDY DESIGN

Containers (market container/closure system) of drug product should be punctured and stored at the approved or proposed labeled storage conditions. The length of time that the punctured product containers are stored will directly relate to the in-use statement on the labeling. While CVM sees the total number of punctures being carried out initially as representing the worst-case

[1] See section V. OTHER DOSAGE FORMS/DELIVERY SYSTEMS for additional recommendations if the use of multiple-dosing equipment is proposed.

scenario, CVM will also accept properly justified product puncture intervals that simulate those which occur in practice. Performing the maximum number of punctures and withdrawing product each time the container is punctured would leave little or no drug product in the container for testing. Thus, punctures of the container that do not include withdrawal of drug product are acceptable, but contact between the needle and drug product are recommended for each puncture. The drug product should then be tested at time points determined by the drug sponsor, with the specific tests to be carried out as outlined below.

A. Testing for Chemically Preserved Products

If the drug product contains a chemical preservative system, full stability testing should be monitored at each test interval, with the following considerations:

- Assay of the preservative should be part of the testing parameters, and the minimum preservative assay acceptance criterion should be supported by AET data at the lowest acceptable preservative concentration.
- Sterility Testing and Bacterial Endotoxins Testing are not necessary.

B. Testing for Self-Preserved Products

If the drug product contains no chemical preservative(s) and is designated self-preserving, full stability testing should be monitored at each test interval, with the following considerations:

- AET is recommended at the end of the in-use period.
- Sterility Testing may be substituted for AET. If sterility testing is substituted for AET, at a minimum there should be one-time AET data (or similar microbial challenge study data), to support the exclusion of AET during the in-use stability study.
- Bacterial Endotoxins Testing is not necessary.

C. Use of Aged Product

While CVM does not currently have an expectation that aged drug product be used during in-use stability studies, careful consideration should be given to terminally sterilized products or any other products that have shown or may be suspected to show any adverse trending under normal stability storage conditions. If any of these events are anticipated, early discussion with DMT is recommended, as the use of aged product, at or near expiry, for the in-use stability studies may be recommended.

IV. FORMAT OF IN-USE LABELING STATEMENTS

The in-use statement on the labeling should be supported by acceptable data generated during the in-use stability study, as outlined above.

A. Time Limited

If the in-use stability study is carried out with the theoretical maximum number of punctures (or a smaller number of punctures has been justified based on clinical usage), and the longest timeframe investigated is less than the product expiry, the following in-use statement is recommended for the labeling: "Use within *XX timeframe*[2] of first puncture."

B. Puncture Limited

If the in-use stability study is carried out with less than the theoretical maximum number of punctures, and the longest timeframe investigated is less than the product expiry, the following in-use statement is recommended for the labeling: "Use within *XX timeframe*[2] of first puncture and puncture a maximum of *YY*[2] times."

If the in-use stability study is carried out with less than the theoretical maximum number of punctures, and the longest timeframe investigated is the product expiry, the following in-use statement is recommended for the labeling: "Puncture a maximum of *YY*[2] times."

C. No In-Use Restrictions (Package Insert Statement Only)

If the in-use stability study is carried out with the theoretical maximum number of punctures (or the maximum number of punctures labeling requirement has been waived), and the longest timeframe investigated is the product expiry, then no time-limited or puncture-limited in-use statement is needed for the drug product. However, CVM does recommend the following statement be added to the package insert portion of the labeling: "When used as labeled, there is no limit on the number of punctures throughout the full expiry period."

V. OTHER DOSAGE FORMS/DELIVERY SYSTEMS

Other dosage forms and/or delivery systems will be handled on a case-by-case basis. In these cases, justification should be provided to CVM for the number of punctures and needle gauge proposed for the in-use stability study. If the use of multiple dosing equipment (e.g., automatic dosing device, multiple-dose syringe, draw-off needle) is proposed for a new sterile injectable animal product packaged in a multiple-dose container, the TAD should also be contacted as the use of this equipment may be recommended for the safety and effectiveness field studies. While CVM's basic recommended in-use statement language has been outlined in this document, other dosage forms and delivery systems present the possibility for other language to be proposed and or recommended. In any of these cases, early communication with CVM is recommended so that concurrence on acceptable in-use stability study design and/or labeling language can be obtained.

[2] "XX timeframe" represents the in-use timeframe supported by the in-use stability study and "YY" represents the maximum number of punctures supported by the in-use stability study. For example, "Use within 30 days of first puncture," "Use within 30 days of first puncture and puncture a maximum of 10 times," or "Puncture a maximum of 10 times."

VI. FILING STRATEGY

For any new multiple-dose injectable animal drug products, the supporting in-use stability study data should be included as part of the original Chemistry, Manufacturing, and Controls (CMC) Technical Section submitted during phased review to the investigational new animal drug file (J/INAD)[3] or as the original CMC submission to a traditional new animal drug application (NADA)[4] or abbreviated new animal drug application (ANADA)[5], and an appropriate in-use statement should be included on the proposed labeling.

Due to the historical precedent set by human multi-use injectable products, CVM has not always used in-use statements for multiple-dose injectable animal drug products. Thus, there are many previously approved products that, under CVM's current thinking, should include an in-use statement but currently do not. As major changes (e.g., manufacturing site transfers) or other changes that require labeling changes are submitted to these applications, CVM will request that an in-use statement be added to the labeling.

When in-use stability study information is submitted in a supplement to an approved new animal drug application or abbreviated new animal drug application, the submission classification in most cases will be determined as follows (decisions will be made on a case-by-case basis):

- For in-use stability study data and updated labeling submitted to CVM in addition to a major or moderate change, the filing category is determined by the major or moderate change.

- For any submission containing only in-use stability study data and updated labeling to include a supported in-use statement, the filing category will be "Supplement – Changes Being Effected in 30 Days" (CBE-30).

- If the sponsor has already received approval of in-use stability study data and updated labeling and is extending the in-use period with new data and updated labeling, or the sponsor has previously submitted a proposed in-use stability study to DMT and received protocol concurrence, the filing category will be "Supplement – Changes Being Effected" (Immediate CBE).

VII. REFERENCES

1. USP <51>, *Antimicrobial Effectiveness Testing*[6]
   http://www.usp.org/

2. USP <1>, *Injections*
   http://www.usp.org/

[3] 21 CFR part 511.
[4] 21 CFR part 514.
[5] Section 512 of the Federal Food, Drug, and Cosmetic Act.
[6] U.S. Pharmacopeial Convention.

3. CVM GFI #5: *Drug Stability Guidelines (December 2008)*[7]
   http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM051556.pdf

4. CVM GFI #83: *Chemistry, Manufacturing, and Controls Changes to an Approved NADA/ANADA (May 2007)*
   http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052415.pdf

5. CVM Draft Revised GFI #171: *Waivers from the Requirement to Demonstrate Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles (September 2016)*
   http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052493.pdf

[7] All FDA guidances are available at http:/www.fda.gov/RegulatoryInformation/Guidances/default.htm.

APPENDIX 1. Body Weight/Needle Gauge Recommendations

Animal[1]	**Average body weight (lbs)**	**Average body weight (kg)**	**Largest needle gauge-solution**	**Largest needle gauge-suspension**
Dog	45	20.5	20[2]	20[2]
Cat	10	4.5	20[2]	20[2]
Horse	1000	450	18[3]	18[3]
Cattle	1000	450	16[4]	16[4]
Calf	130	60	18	18
Growing beef steers and heifers on pasture	300-900	135-400	16[4]	16[4]
Replacement dairy heifers	200-1300	90-600	16[4]	16[4]
Beef steers and heifers fed in confinement for slaughter	800-1300	360-600	16[4]	16[4]
Lactating dairy cows	800-1600	360-730	16[4]	16[4]
Swine	260	118	16[4]	16[4]
Nursing piglets	10	4.5	18	18
Nursery pigs	55	25	18	18
Growing pigs	110	50	16	16
Finishing pigs	220	100	16[4]	16[4]
Sows	440	200	16[4]	16[4]
Chickens	6	2.7	20	20
Laying hens	3.7	1.7	20	20
Broiler and Roaster chickens	7.4	3.4	20	20
Turkey	22	10	20	20
Sheep	100	45	18	18

[1] Specific classes of animals, notated with italics in the table, should be used if specified on the labeling or a robust justification is provided to CVM. Otherwise the general category information for each species should be applied.
[2] An 18 gauge needle may be needed to draw up viscous materials and should be considered worst case for higher viscosity solutions or suspensions for use in dogs and cats.
[3] A 16 gauge needle may be needed to draw up viscous materials, especially those that need to be administered quickly, and should be considered worst case in these situations for use in horses.
[4] For highly viscous formulations, a 14 gauge needle should be considered worst case for use in large cattle or swine.

APPENDIX 2. Example Calculation for Worst Case In-Use Stability Study Design

Labeling indicates multiple species: cattle and swine

Product = 80 mL vial (50 mg/mL drug substance concentration), true solution

Dosage information from labeling: 0.5 mg/kg for both cattle and swine

The average weight of cattle is 450 kg:

$$\frac{0.5\text{ mg}}{\text{kg}} \times 450\text{ kg} \times \frac{\text{mL}}{50\text{ mg}} = 4.5\text{ mL dose for cattle}$$

The 4.5 mL dose for cattle would result in 18 punctures. The recommended needle gauge for cattle is 16 gauge.

Average weight of swine for food production is 118 kg:

$$\frac{0.5\text{ mg}}{\text{kg}} \times 118\text{ kg} \times \frac{\text{mL}}{50\text{ mg}} = 1.18\text{ mL dose for swine}$$

The 1.18 mL dose for swine represents the smallest dose for all labeled species. This would result in 68 punctures. The recommended needle gauge for swine is 16 gauge.

Justified needle size: 16 gauge, as this is the largest needle size recommended for all intended species.

Worst Case Study Design:

68 punctures carried out using a 16 gauge needle