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

Guidance for Industry

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2016-D-4437.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either https://www.fda.gov/animal-veterinary or https://www.regulations.gov

U.S. Department of Health and Human Services
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Table of Contents

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Guidance for Industry

This guidance represents 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 time period 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. All multiple-dose injectable animal drug products should 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 the pioneer reference listed new animal drug (RLNAD) currently has an in-use statement on the labeling. CVM considers all in-use statements to be data-driven. Thus, the in-use statements on pioneer and generic drug products may differ as each is based on the chemistry and manufacturing controls data generated for each individual application (see sections 512(d)(1)(C) and 512(c)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act, respectively).

It should also be noted that this document outlines general recommendations from CVM for the design of in-use stability studies and associated labeling statements for multiple-dose injectable animal drug products. Some drug products and their intended use pose unique challenges and will be handled on a case-by-case basis. CVM recommends that the appropriate Target Animal Division (TAD)/Division of Generic Animal Drugs (DGAD) and Division of Manufacturing

Technologies (DMT) be contacted early in the in-use stability study planning process, to ensure that all concerns unique to each drug product are addressed before the study begins and labeled in-use statements are finalized.

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. NEEDLE GAUGE AND NUMBER OF PUNCTURES

All 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/closure 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 identical elastomeric stopper formulations are used for all container/closure systems. In these cases, CVM generally considers the smallest stopper size to be the worst case. Care should be taken to ensure that the needle gauge and number of punctures represents the worst case for the entire group of containers represented.

A. Needle Gauge

In general, the in-use stability study should consider all intended species and routes of administration and use the overall largest needle gauge normally used in practice. If special circumstances exist or questions remain regarding the needle gauge to be used for the in-use stability study, you should discuss this with the appropriate DMT team. Appendix 1 contains recommended needle gauges for major animal species, and Appendices 2 and 3 contain example calculations 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 used for in-use stability studies whenever possible and should be based on the intended species receiving the maximum number of doses per container. If the stopper cannot withstand the theoretical maximum number of punctures, CVM may recommend an in-use statement restricting the maximum number of punctures or the use of multi-dosing equipment,[1] or both.

You may propose, with proper justification (e.g., anticipated or historical clinical/field usage data), to perform the in-use stability study using less than the theoretical maximum number of punctures. If CVM agrees with this proposal, then a labeling statement restricting the maximum number of punctures may not be needed.

[1] See section IV.B. *Puncture Limited* for additional recommendations if the use of multiple-dosing equipment is proposed.

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. CVM views performing all of the punctures at the beginning of the storage period as representing the worst case; however, 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 there should be contact between the needle and drug product for each puncture. The drug product should then be tested at time points of your choosing, and specific tests should 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 should be performed 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 an aged drug product, at or near expiry, 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 (i.e., impurities that increase to near the upper specification limit or API assay that trends downward near the lower specification limit) under normal stability storage conditions. If any of these events are anticipated, early discussion with

DMT is recommended, as the use of an aged drug product 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 fewer number of punctures has been justified as outlined in section II.B. *Theoretical Maximum Number of Punctures* above), 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 a justification, as outlined in section II.B. *Theoretical Maximum Number of Punctures* above, has not been accepted by CVM), 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."

If the in-use study cannot be carried out using the maximum theoretical number of punctures, and a puncture limiting statement is required, the in-use statement should, in most cases, also include language pertaining to the use of multi-dosing equipment (typically for food animal drugs). CVM recognizes the breadth of multi-dosing equipment available to the end-user of animal drug products (e.g., automatic dosing device, multiple-dose syringe, draw-off spike/needle), and as such, suggests the following statement be added to the end of the in-use statement:

"If more than *YY*[2] punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than *ZZ*,[2] discard any product remaining in the vial immediately after use."

[2] "*XX timeframe*" represents the in-use timeframe supported by the in-use stability study, "YY" represents the maximum number of punctures supported by the in-use stability study, and "ZZ" represents the needle gauge used for 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," "Puncture a maximum of 10 times," or "If more than 10 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16-gauge, discard any product remaining in the vial immediately after use."

If the use of multi-dosing equipment is proposed for a new sterile injectable animal product packaged in a multiple-dose container, CVM may recommend using this equipment during target animal safety and field effectiveness studies. CVM recommends that you discuss the use of multi-dosing equipment with the appropriate TAD early in your development process.

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 a labeling statement restricting the maximum number of punctures is not warranted per a justification as outlined in section II.B. *Theoretical Maximum Number of Punctures* above), 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, the following statement should 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. 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 (DMT and the appropriate TAD) is recommended so that concurrence on acceptable in-use stability study design and/or labeling language can be obtained.

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 to the investigational or generic investigational new animal drug application (J/INAD) or the original submission to a traditional new animal drug application (NADA) or abbreviated new animal drug application (ANADA), and an appropriate in-use statement should be included on the proposed labeling. CVM also encourages the submission of an in-use stability study protocol to DMT early in the drug development process, so that concurrence can be obtained before study commencement.

There are some 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, new stopper type) or other changes that require labeling changes are submitted to these applications, you should also generate in-use stability study data and submit the data and updated labeling, including an in-use statement, to that supplement.

When in-use stability study information is submitted in a supplement to an approved NADA or ANADA, 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).

For approved animal drug products that already have an approved in-use statement, if changes are made to the storage temperature or expiry period that would impact the current in-use statement, you should reassess the in-use statement and submit revised labeling to CVM for review as necessary.

VII. REFERENCES

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

2. USP <51>, *Antimicrobial Effectiveness Testing*
   https://www.usp.org/

3. CVM GFI #5, "Drug Stability Guidelines"
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-5-drug-stability-guidelines

4. CVM GFI #83, "Chemistry, Manufacturing, and Controls Changes to an Approved NADA/ANADA"
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-83-chemistry-manufacturing-and-controls-changes-approved-nadaanada

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
Dogs	45	20.5	20 [2]	20 [2]
Cats	10	4.5	20 [2]	20 [2]
Horses	1000	450	18 [3]	18 [3]
Cattle	1000	450	16 [4]	16 [4]
Calves	130	60	18	18
Growing beef steers and heifers on pasture or in drylot/grow yard	300-900	135-400	16 [4]	16 [4]
Replacement dairy heifers	175-1300	80-600	16 [4]	16 [4]
Growing 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	40	18	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 chickens	6.2	2.8	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 number of doses contained in a vial for cattle is calculated as follows:

$$80\text{ mL per vial} \times \frac{1\text{ dose}}{4.5\text{ mL}} = 17.8\text{ doses} = 18\text{ punctures (rounded up)}$$

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 number of doses contained in a vial for swine is calculated as follows:

$$80\text{ mL per vial} \times \frac{1\text{ dose}}{1.18\text{ mL}} = 67.8\text{ doses} = 68\text{ punctures (rounded up)}$$

The 1.18 mL dose for swine represents the smallest dose for all labeled species and 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

APPENDIX 3. Second Example Calculation for Worst Case In-Use Stability Study Design

Labeling indicates multiple species: cattle and horses

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

Dosage information from labeling: 0.5 mg/kg for cattle and 0.25 mg/kg for horses

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 number of doses contained in a vial for cattle is calculated as follows:

$$80\text{ mL per vial} \times \frac{1\text{ dose}}{4.5\text{ mL}} = 17.8\text{ doses} = 18\text{ punctures (rounded up)}$$

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

The average weight of horses is 450 kg:

$$\frac{0.25\text{ mg}}{\text{kg}} \times 450\text{ kg} \times \frac{\text{mL}}{50\text{ mg}} = 2.25\text{ mL dose for horses}$$

The number of doses contained in a vial for horses is calculated as follows:

$$80\text{ mL per vial} \times \frac{1\text{ dose}}{2.25\text{ mL}} = 35.6\text{ doses} = 36\text{ punctures (rounded up)}$$

The 2.25 mL dose for horses represents the smallest dose for all labeled species and would result in 36 punctures. The recommended needle gauge for horses is 18 gauge.

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

Worst Case Study Design:

36 punctures carried out using a 16-gauge needle