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Chemistry, Manufacturing, and Controls Considerations for Type A Medicated Articles

Guidance for Industry

Draft Guidance

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations to sponsors submitting chemistry, manufacturing, and controls (CMC) information for Type A medicated articles. Type A medicated articles contain new animal drugs and provide for administration of these drugs in animal feed. Type A medicated articles are intended solely for use in the manufacture of another Type A medicated article or in the manufacture of a Type B or Type C medicated feed.[1] Because Type A medicated articles are not directly administered to the animal, there are some issues specific to Type A medicated articles that do not apply to other new animal drug dosage forms. These unique considerations are highlighted in this guidance under the relevant Common Technical Document - Quality (CTD-Q)[2] section headings.

This guidance is applicable to new animal drug applications (NADAs), applications for conditional approval (CNADAs), abbreviated new animal drug applications (ANADAs), investigational new animal drug (INAD) files, and generic investigational new animal drug (JINAD) files. Although the recommendations in this guidance refer to (A)NADAs (ANADAs and NADAs) and (J)INADs (JINADs and INADs), the general principles described may also be applicable to supplemental (A)NADAs.

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.

[1] See 21 CFR 558.3(b)(3) and 21 CFR 558.3(b)(4) for the definitions of Type B and C medicated feeds, respectively, and USP <1152> Animal Drugs for Use in Animal Feeds.

[2] The Common Technical Document is an internationally agreed-upon format for the preparation of drug applications, maintained by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). CTD-Q is the Quality section of the CTD and provides for a harmonized structure and format for presenting CMC information in an application. CVM recognizes and supports use of the CTD-Q for submission of CMC information for animal drug approval.

II. Background

This guidance primarily addresses the CMC information for Type A medicated articles, also referred to as medicated premixes in VICH[3] and other international documents, and does not provide recommendations for medicated feeds made from the Type A medicated articles. Type A medicated articles may be used to manufacture other Type A medicated articles or are added to non-medicated feed to either make a Type B medicated feed, which is then further mixed into a Type C medicated feed, or directly make a Type C medicated feed. Animals are fed Type C medicated feeds. If a drug substance is used to directly manufacture a Type B/C medicated feed, an application is required for the Type B/C medicated feed (21 CFR 558.3(b)(5)), and the application should contain CMC information for the Type B/C medicated feed similar to that typically submitted for the Type A medicated article.

Type A medicated articles are manufactured under 21 CFR 226 Current Good Manufacturing Practice (CGMP) requirements, while medicated feeds are typically manufactured under 21 CFR 225 CGMP requirements. Medicated feed manufactured directly from the drug substance will be subject to 21 CFR 226 CGMP requirements.[4] For competitive exclusion Type A medicated articles, please discuss with CVM to determine additional requirements.

III. Control of Drug Substance (3.2.S.4)

If a U.S. Pharmacopeia (USP) monograph for the drug substance exists, the drug substance used to manufacture the Type A medicated article should be USP grade. The specifications for the drug substance proposed in the application should be based on: (1) the drug substance supplier's specifications; (2) the recommendations in Guidance for Industry (GFI) #176 (VICH GL39), "Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances"[5]; (3) the recommendations in GFI #169, "Drug Substance Chemistry, Manufacturing, and Controls Information"[6]; the recommendations in GFI #216, "Chemistry, Manufacturing, and Controls (CMC) Information – Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use"[7]; and the compendial monograph, if applicable. Other applicable GFIs for drug substances used in the manufacture of Type A medicated articles include GFI #92 (VICH GL10(R)), "Impurities in New Veterinary Drug Substances (Revision),"[8] and GFI #100 (VICH GL18(R2)),

[3] International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (https://www.vichsec.org/en/home.html).

[4] Final Rule: New Animal Drugs for Use in Animal Feeds; Definitions and General Considerations; Revised Procedures Re Medicated Feed Applications (51 FR 7382 at 7383; March 3, 1986).

[5] https://www.fda.gov/media/69909/download (June 2006).

[6] https://www.fda.gov/media/69923/download (August 2010).

[7] https://www.fda.gov/media/79873/download (March 2012).

[8] https://www.fda.gov/media/70365/download (November 2007).

"Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients (Revision 2)."[9]

Particle size controls provide a link between the Type A medicated article batches used to perform homogeneity and segregation studies and the commercial batches. As particle size of the raw materials may impact homogeneity and segregation of the Type A medicated article, particle size should be included in the specifications for all drug substances, unless the drug substance is dissolved during the manufacturing process. CVM generally expects that the drug substance will have a particle size less than 1 mm and that the drug substance specification can control the particle size distribution (i.e., a single limit specifying that all particles are less than 1 mm is insufficient).

IV. Description and Composition (3.2.P.1)

The composition of the Type A medicated article includes all components used in the manufacture of the Type A medicated article, including tracers and any solvents or processing aides, even if removed during the manufacturing process.[10] If alternate formulations with excipients that can be used in place of one another are proposed, each alternate formulation should be supported with studies, such as homogeneity, segregation, and stability of the Type A medicated articles and resulting Type B and C medicated feeds.

Amounts of each excipient should be specified in the composition and a fixed amount is required for all excipients except dust control oil. The amount of carrier may also vary to compensate for allowable variability in potency of a fermentation derived drug substance. If a range is necessary for oil used for dust reduction, both the typical amount and the allowable range should be specified. The range should be the narrowest one that is practical, with the pilot batch(es) manufactured within the range. For very wide ranges, a commitment to provide additional studies may be appropriate to support that Type A medicated articles, and resulting Type B and C medicated feeds, made with compositions at either end of the range remain homogenous, do not segregate, and are stable.

V. Manufacture (3.2.P.3)

A. Add-back (3.2.P.3.3)

The use of add-back, or the addition of the remainders of a previous batch to a subsequent batch, should be clearly defined in the manufacturing batch record, along with any associated controls. A limit for add-back material of not more than 5% of the total batch size is acceptable without additional justification. The length of time add-back can be retained should be specified and add-back should be stored under conditions consistent with the labeled storage conditions for the Type A medicated article. Expiry of a batch of Type A medicated article should be based on the oldest material added to the batch, and a statement regarding the policy for setting expiry should be included in the manufacturing

[9] https://www.fda.gov/media/70410/download (July 2022).

[10] 21 CFR 514.1(b)(4)

process description. Add-back material should only come from batches that meet the quality specifications for release.

B. Batch stacking (3.2.P.3.3)

Batch stacking is a practice unique to Type A medicated articles where consecutive batches are released under a single lot number. The batches may be individually manufactured and packaged but then placed on pallets under one lot number, or the batches may be individually manufactured and then combined in the packaging equipment, but the individual batches are not physically mixed together in a blender to produce a larger, homogeneous batch. The practice is acceptable with the appropriate controls in place to ensure the quality of each batch, including the maximum number of batches that can be included in one stacked batch lot. Each of the individual batches manufactured should be tested for release. In the case where individual batches are allowed to co-mingle in the packaging equipment, if any individual batch is found to be out of specification, the entire lot should be treated as out of specification. Expiry of the lot should be determined based on the oldest individual batch. The number of batches placed on stability is calculated based on the number of individual batches manufactured and not the number of stacked batch lots.

VI. Control of Excipients (3.2.P.4)

The excipients in the Type A medicated article should at a minimum be feed grade,[11] and specifications should be based on the manufacturer's certificate of analysis (COA) with a justification for omitting any tests that are not relevant for the excipient's function in the Type A medicated article. If the excipient is listed in the Association of American Feed Control Officials (AAFCO) Official Publication manual, the tests listed there should be included in the specification and a justification should be provided for any tests that are omitted. For excipients that AAFCO indicates should meet additional requirements in the CFR, such as mineral oil where AAFCO cites 21 CFR 573.680, those requirements should also be included in the specification.

Particle size controls should be included in the specification for all dry excipients, unless they are dissolved during the manufacturing process, as discussed in the Control of Drug Substance section above. If excipient suppliers are changed post-approval, new Type A medicated article homogeneity and segregation studies may be required to support the change in supplier unless the particle sizes of the excipient from both suppliers are equivalent.

VII. Control of Type A Medicated Article (3.2.P.5)

Release specifications for Type A medicated articles should follow the recommendations in GFI #176 (VICH GL39) and should include identification, assay, impurities, loss on drying, and residual solvents, at a minimum. If a USP monograph for the Type A medicated article exists,

[11] Even if a NF monograph exists, there is no requirement that Type A medicated article excipients meet the NF monograph.

the monograph specifications are considered minimal requirements (see section 501(b) of the Federal Food, Drug, and Cosmetic Act).

Generic Type A medicated articles should meet the assay limits codified in 21 CFR §558.4(d).

If the manufacturing process alters the particle sizes of the drug substance or excipients, e.g., granulation, a particle size specification should be included as part of testing as a critical quality attribute (CQA) of the finished Type A medicated article.

If a tracer is present, the Type A medicated article specification should include appropriate tests to support the use of that tracer.[12]

VIII. Container Closure System (3.2.P.7)

A description of each component of the packaging material should be provided, including a description of how the bag is closed (e.g., sewn, heat sealed, or glued). The product contact surface of the container closure should meet USP <661> Plastic Packaging Systems and Their Materials of Construction (including all sub-chapters) requirements if applicable, in addition to the appropriate requirements for indirect food additives if applicable (21 CFR parts 175 (Adhesives and Coatings), 176 (Paper and Paperboard), 177 (Polymers) and 178 (Adjuvants, Production Aids, and Sanitizers)).

IX. Stability (3.2.P.8)

Stability studies should be conducted as described in GFI #91 (VICH GL8), "Stability Testing for Medicated Premixes."[13] In order to use the stability studies to support an excursion statement on the label (e.g., "Excursions permitted up to 40°C."), the Type A medicated article should remain within specifications at that temperature for the duration of the accelerated stability study.

Scaled-down containers for samples placed on stability are allowed, but they should be representative of the commercial packing in the type of packaging, the product contact surface, and the method of closure.

Additional studies on the Type A medicated article are appropriate based on the form (dry, liquid) of the Type A medicated article.

A. Freeze-thaw studies

Stability of Type A liquid medicated articles should be demonstrated following a freeze-thaw study as described in GFI #5, "Drug Stability Guidelines."[14]

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[12] See GFI #258, "Use of Tracers in Animal Food, Type A Medicated Articles, and Medicated Feeds," (https://www.fda.gov/media/156527/download) (October 2022).

[13] https://www.fda.gov/media/70356/download (March 2000).

[14] https://www.fda.gov/media/69957/download (December 2008).

B. Photostability studies

Photostability of Type A medicated articles, both liquid and dry, should be demonstrated as described in GFI #75 (VICH GL5), "Stability Testing: Photostability Testing of New Veterinary Drug Substances and Medicinal Products."[15] If the Type A medicated article is susceptible to UV degradation, or in lieu of performing a photostability study, a statement should be included on the Type A medicated article label to protect the product from light.

X. Homogeneity Studies (3.2.R)

Homogeneity studies demonstrate that the manufacturing process is capable of producing a uniform final packaged product. Homogeneity studies should be conducted to support original approvals, as well as for post-approval changes to the Type A medicated article manufacturing site, manufacturing equipment, manufacturing processes, or formulation, or to the manufacturing site for the drug substance used in the Type A medicated article.

Blender uniformity may be assessed in addition to packaged product homogeneity but is not required for filing the Type A medicated article application. If included in the file/application, the number of samples collected and the sample locations within the blender should be indicated, as well as the acceptance criteria for the study.

A. Study Design

The pilot/registration batch(es) are packaged and samples are taken from bags at equal intervals across the batch, typically consisting of 10 bags total, including the first and last saleable bag.

1. When Type A medicated article assay limits are 90 – 110%

   CVM recommends that Type A medicated articles be tested using the principles described in the Content Uniformity test in USP <905> Uniformity of Dosage Units. The Content Uniformity test calls for the collection of 30 samples per batch. For Content Uniformity testing of Type A medicated articles, USP <905> procedures can be adapted by taking 3 samples from each of the 10 bags described above. In the first round of testing, one homogeneity sample from each bag should be tested, for a total of 10 samples. If a second round of testing is necessary, the remaining 20 homogeneity samples should be tested. Sample quantities should be equal to or less than the amount of Type A medicated article that would be used in the manufacture of 1 ton of the least concentrated Type C medicated feed. For new and existing Type A medicated articles with assay limits of 90 – 110% of label claim (i.e., permissible analytical variability (PAV)=10 and assay limits centered around 100%), the Content Uniformity test can be performed as described in USP <905>.

[15] https://www.fda.gov/media/70262/download (September 1999).

2. When Type A medicated article assay limits are not 90 – 110%

   For Type A medicated articles with assay limits centered on a value other than 100% or with a PAV other than 10, it is recommended that the Content Uniformity test be implemented as indicated in USP <905> (with the use of the T value as necessary).

3. As an alternative, sponsors have the option to continue to perform their homogeneity assessment according to CVM's historical method, which requires the collection of 10 samples across a batch of packaged Type A medicated article, including the first and last saleable bags, and the testing of each sample for assay.

B. Acceptance criteria

1. If using the Content Uniformity test, the acceptance criteria stated in USP <905> should be followed. Namely, the calculated acceptance value for the first 10 samples assayed should be less than or equal to L1. If the calculated acceptance value for the first 10 samples assayed is greater than L1, then the next 20 samples should be assayed, and the calculated acceptance value for the 30 samples should be less than or equal to L1 and no individual assay result may exceed the specified range in USP <905>.

2. If the historical approach is being used, the %CV for the 10 homogeneity samples per batch should not exceed 5% and all individual assay results should fall within the Type A medicated article assay limits. Any individual out of specification assay results should be investigated.

XI. Segregation Studies (3.2.R)

Segregation studies simulate actual transport conditions of the final packaged product to demonstrate that the drug substance will not concentrate in one portion of the product or container during transport.

A. Study Design

Testing one bag per pilot/registration batch is acceptable. Testing may be performed either by transporting a bag for at least 50 miles or by placing a bag on a shaker for a sufficient amount of time to simulate transport for 50 miles; the bag should be maintained in the upright position throughout the study. Samples should be collected pre- and post-transport from the top, middle, and bottom of the bag. The segregation sample size should be the same as the sample size used for the homogeneity assessment. In addition, the same batch(es) of Type A medicated article should be assessed for both the homogeneity and segregation studies.

B. Acceptance Criteria

As part of the homogeneity testing, a mean and a standard deviation for each batch tested is determined.[16] Each mean and standard deviation can be used in the assessment of segregation during transport for the same batch used for homogeneity studies. A two-tier system may be used to allow for the least testing necessary to demonstrate that there is no segregation occurring during shipping.

Tier 1: If the post-transport assay results fall within the Mean ± (2 x standard deviation) then the data support that segregation does not occur during shipping.

Tier 2: If any of the post-transport assay results fall outside of the Mean ± (2 x standard deviation), then the pre-transport segregation samples should be assayed and the percent change pre- and post-transport at each sampling location (top, middle, bottom) should be calculated. If any of the percent change values pre- and post-transport are greater than 5%, appropriate action should be taken to determine if the product is segregating during shipping.

XII. CMC-Related Label Statements

The content of the Type A medicated article label is dependent on information submitted in the CMC technical section. If draft labeling has not been submitted in a General Correspondence (G) submission or Labeling (M) technical section received concurrent with the CMC technical section, the proposed wording of any CMC-related information that will appear on the labeling should be submitted in the CMC technical section.

- A storage statement including a numeric temperature or temperature range supported by the long-term stability data should be present on the label. Excursion statements should be supported by accelerated stability data that remain within specification for the duration of the study.

- A statement to "protect from light" may be appropriate based on the outcome of the photostability study performed according to GFI #75 (VICH GL5).

- Mixing directions for using the Type A medicated article to make the Type C medicated feed and the Type B medicated feed, if applicable, should be present on the Type A medicated article label.[17] The Type B, if present, and Type C medicated feed concentrations should correspond to or be within the range of the medicated feeds

[16] The mean and standard deviation used for the segregation analysis is the mean and standard deviation calculated for 10 samples during the homogeneity assessment. If the homogeneity assessment is conducted using the Content Uniformity test as prescribed in USP <905> and the data do not meet the L1 criterion with 10 samples, the segregation data should be assessed using the mean and standard deviation of the 30 samples unless the standard deviation of the 30 samples exceeds 6.25, in which case 6.25, the maximum allowable standard deviation for 10 samples to meet L1, should be used.

[17] Approval of a Type B medicated feed is optional for a pioneer sponsor. For a generic sponsor, approval of a Type B medicated feed is determined by whether the reference listed new animal drug has an approved Type B medicated feed.

manufactured for homogeneity, segregation, and stability studies provided in the CMC technical section.

- If the amount of Type A medicated article used to manufacture one ton of medicated feed is less than 5 lbs, the Type A medicated article should be mixed with a small amount of feed to create an intermediate pre-blend before being mixed into the full amount of the feed used to manufacture the medicated feed. The instructions for making the intermediate pre-blend should be included on the Type A medicated article label. The intermediate pre-blend is not considered a Type B medicated feed.