#285

Manufacture of Batches in Support of Original NADAs, ANADAs, and CNADAs

Guidance for Industry

Draft Guidance

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U.S. Department of Health and Human Services
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Draft Guidance for Industry

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I. Introduction

The information included in this document is intended to provide recommendations for the primary batches[1] of drug product manufactured to support the approval or conditional approval of new animal drug products. This guidance is applicable to all original new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs), and their associated investigational new animal drug files (INADs) and generic investigational new animal drug files (JINADs), respectively, as well as applications for conditional approval of new animal drugs (CNADAs).

This guidance does not apply to Intentional Genomic Alterations (IGA) in animals or Animal Cells, Tissues, and Cell- and Tissue-Based Products (ACTP).

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. Background

New animal drugs cannot be legally marketed unless they are the subject of an approved NADA, ANADA, or CNADA.[2] The required information to be submitted for these original applications is outlined in the FD&C Act sections 512(b)(1), 512(n)(1), and 571 and 21 CFR 514.1. The Chemistry, Manufacturing, and Controls (CMC) technical section is one portion of the original (A)NADA or CNADA and must contain full information regarding the manufacture of the new animal drug substance and new animal drug product.

[1] For the purpose of this guidance, primary batches are defined as drug product batches manufactured and used for the registration and approval of the drug product with the FDA.

[2] A new animal drug must be the subject of either an approved application under section 512(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a conditional approval under section 571 of the FD&C Act, or an index listing under section 572 of the FD&C Act.

Animal drug manufacturing processes must be robust and able to produce drug product batches of consistent identity, strength, quality, and purity.[3] Primary batches of drug product are manufactured as part of the original (A)NADA (and associated (J)INAD files) or CNADA (and associated INAD files). Data from these batches are used to establish that the manufacturing, sampling, and control processes described in the CMC portion of the application will consistently provide a quality, stable drug product that, within a batch and on a batch-to-batch basis, does not vary beyond the established specification(s). Additionally, they are used in studies to establish that the drug product is safe and effective (or in the case of an ANADA, bioequivalent to the reference listed new animal drug). As such, the primary batches demonstrate that the applicant can consistently manufacture batches of same quality as those used in safety and effectiveness (or bioequivalence) studies.

Reference is made throughout this guidance to International Cooperation on Harmonization of Technical Requirement for Registration of Veterinary Medicinal Products (VICH) stability guidances.[4] Although the VICH stability guidances were developed to provide guidance on the information that should be provided in new animal drug applications to ensure the stability of new drug substances and animal drug products, CVM believes the recommendations should also be applied to ANADAs.

III. Selection of Batches

A minimum of three primary batches of drug product should be manufactured under current good manufacturing practice (CGMP)[5,6,7] in support of the approval of all original (A)NADAs and CNADAs. These batches should be of the same formulation and packaged in the same container closure system as intended for marketing. For animal drugs intended for a minor use or a minor species (MUMS animal drugs), contact the Office of New Animal Drug Evaluation's Division of Manufacturing Technologies (DMT) to discuss the appropriate number of batches to support approval.

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[3] 21 CFR 514.1(b)(5)

[4] VICH guidances that address stability for new drug substances and animal drug products include: Guidance for Industry (GFI) #73 (VICH GL3(R)), "Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)," (November 2007); GFI #74 (VICH GL4), "Stability Testing of New Veterinary Dosage Forms," (September 1999); GFI #75 (VICH GL5), "Stability Testing: Photostability Testing of New Veterinary Drug Substances and Medicinal Products," (September 1999); GFI #91 (VICH GL8), "Stability Testing for Medicated Premixes,"(March 2000); GFI #99 (VICH GL17), "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products," (March 2001); GFI #198 (VICH GL45), "Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products," (July 2015); and GFI #219 (VICH GL51), "Statistical Evaluation of Stability Data," (May 2014).

[5] 21 CFR part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

[6] 21 CFR part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals

[7] 21 CFR part 226 – Current Good Manufacturing Practice for Type A Medicated Articles

In some cases, and with appropriate justification, bracketing can be used in the selection of the primary batches manufactured and placed on stability. Bracketing is the strategy of only manufacturing batches on the extremes of certain design factors of the marketed product (e.g., strength, container size, and/or fill).[8] In cases where the drug product application includes a single product formulation with multiple fill sizes and/or multiple container sizes, each batch may be split into multiple fill or container sizes. If the application includes multiple drug product strengths (where the amounts of drug substance and excipients are proportional across strengths), the manufacture of three batches each of the lowest and highest strength may be acceptable. CVM does not recommend using a bracketing approach for new biotechnological or biological animal drug products of different strengths. Applicants should consider submitting a protocol with the proposed bracketing approach or requesting a meeting to discuss with DMT.

We recognize the impact the recommendations of this section of the guidance may have on products currently in development, particularly for generic animal drugs. FDA anticipates that sponsors of generic animal drugs products in development should be able to utilize these recommendations in support of approval within 1 year from the date of publication of the final version of this guidance.

IV. Drug Substance Source

CVM recommends that the primary batches of drug product be manufactured using a single source of drug substance that is the same as that intended for commercial production. Additional sources of the drug substance should be proposed in supplemental applications, rather than in the original application.

As possible, the primary batches of drug product used to support approval of the application should be manufactured using two or more different batches of drug substance from the same source.

V. Drug Product Manufacture

The primary batches of drug product can be manufactured at pilot scale (no less than 10% of the largest proposed commercial scale batch size). The primary batches should be manufactured under CGMP using the same or comparable process, controls, and equipment (similar operating and design principles) as intended for commercial batches, with reasonable allowances made for process scale. CVM recommends that the primary batches be manufactured at the same manufacturing site proposed for commercial production.

Executed batch records for the primary batches should be included in the CMC technical section, along with a blank master batch record for the intended commercial batch size(s).

[8] GFI #198 (VICH GL45), "Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products," (July 2015).

Batch release and stability data[9,10] should be provided for the primary batches. A minimum of 6 months stability data (at both long-term and accelerated storage conditions) should be included in the CMC technical section for the primary batches. Three months stability data can be provided at the time of submission, with additional stability data submitted through the amendment process while the pending original application is in the review queue (up to 30 days before the ADUFA / AGDUFA due date for the submission).

The primary batches of drug product reported in the CMC technical section should be used in any necessary target animal safety or effectiveness studies, bioequivalence studies, and human food safety studies. Applicants should contact CVM to discuss situations in which the CMC primary batches may be different than those used to support these studies. If additional batches of drug product are needed, the batches should be of the same formulation and be manufactured using the same drug substance source and manufacturing process as used for the primary batches. CMC information for these additional batches (batch records, release data, stability data, etc.) should also be provided in the application.

VI. Considerations for Changes in Drug Substance Source or Drug Product Manufacturing Site after Manufacture of Primary Batches

CVM recommends that the primary batches be manufactured at the same site and using the same drug substance source as that intended for commercial production. However, CVM recognizes that it may be necessary to change the drug substance source or the commercial drug product manufacturing site prior to approval of the original application. In these situations (e.g., site closures, deficient CGMP status after manufacture of the primary batches), the applicant should request a meeting with DMT to discuss potential paths forward.

The applicant should assess the risk of the proposed change to product quality and the impact on the information in the application. While the information necessary may differ depending on the reasons for the changes, as well as the complexity of the proposed drug product, some general points to consider include:

- All drug substance suppliers and manufacturing sites should be manufacturing in compliance with CGMP at the time of the applicable drug substance[11] or drug product batch manufacture. Drug substance sources and drug product manufacturing sites intended for use in the manufacture of commercial batches must be in compliance with CGMP at the time of application approval.

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[9] GFI #73 (VICH GL3(R)), "Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision)," (November 2007). Further guidance on new dosage forms, medicated premixes, and on biotechnological/biological products can be found in GFI #74 (VICH GL4), "Stability Testing of New Veterinary Dosage Forms," (September 1999); GFI #91 (VICH GL8), "Stability Testing for Medicated Premixes," (March 2000); and GFI #99 (VICH GL17), "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products," (March 2001), respectively.

[10] Stability data should be obtained in accordance with GFI #5, "Drug Stability Guidelines," (December 2008).

[11] ICH Q7, "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," (April 2018).

- For most animal drug products, no less than one pilot scale batch of drug product should be manufactured under CGMP at the new commercial facility and/or using the new drug substance supplier's material. It may also be necessary to manufacture additional batches of drug product (2 – 3 total) depending on the acceptability of the primary batches manufactured prior to the change. The manufacture of additional batches at the new facility and/or using the new supplier's material may not be needed for some true solutions.

- In cases where the drug substance source has changed, the critical quality attributes (e.g., impurity profile, polymorphism, particle size) of the drug substance from each source should be shown to be comparable (e.g., batch analysis, specifications).

- In cases where the drug product manufacturing site has changed, the applicant should demonstrate that the raw materials, equipment, and manufacturing processes used at the two sites do not differ significantly.

- Executed and blank master batch records, release data, and stability data should be provided in the application for the batch(es) manufactured after the change, as well as for the three primary batches manufactured at the original site or with the original drug substance source. Applicants should demonstrate that the quality of drug product manufactured before and after the applicable changes is comparable.

- Comparative dissolution data, and/or additional bridging data (which might include clinical studies), may be necessary to support the new drug substance source or new drug product manufacturing site.