#191

Guidance for Industry

Changes to Approved NADAs – New NADAs vs. Category II Supplemental NADAs

DRAFT GUIDANCE

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Additional copies of this draft guidance document can be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/cvm.

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Guidance for Industry
Changes to Approved NADAs – New NADAs vs. Category II Supplemental NADAs[1]

This draft guidance, when finalized, will represent the agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors who wish to apply for approval of changes to approved new animal drugs that require FDA to reevaluate safety and/or effectiveness data. The guidance explains how the Office of New Animal Drug Evaluation (ONADE) categorizes possible changes to approved new animal drugs that require reevaluation of safety and/or effectiveness data and explains which administrative vehicle — a new original new animal drug application (new NADA) or a Category II supplemental application to the original new animal drug application (Category II supplemental NADA) — a sponsor should use when applying for approval of these changes.[2] The goal of this guidance is to create greater consistency in how such applications are handled by sponsors and by ONADE.

FDA's guidance documents, including this guidance, 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] This guidance was prepared by the Office of New Animal Drug Evaluation in the Center for Veterinary Medicine at the Food and Drug Administration.

[2] This guidance does not apply to applications for *conditional approvals* under section 571 of the Federal Food, Drug, and Cosmetic Act (FFDCA). Section 571 was added to the FFDCA when the statute was amended by The Minor Use and Minor Species Act of 2004.

II. BACKGROUND

In the past, applications for changes to approved new animal drugs may have been handled inconsistently by sponsors and the Agency. For example, in some instances, a sponsor may have filed an application for a specific change as a new NADA; in other instances an application for a similar change was filed as a supplemental NADA. Inconsistency in handling such applications has been confusing for sponsors and for ONADE, particularly when reviewing and referencing the history of specific NADAs. This guidance is intended to improve consistency in the way applications for changes are handled. For these reasons, we believe that consistent handling of these types of applications also will help maintain clarity in the administrative record, which is an important part of protecting the public health.

For purposes of this guidance, a *new animal drug* is defined as any drug intended for use in animals other than humans, the composition of which is such that such drug is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling of the drug (21 U.S.C. § 321(v); 21 CFR 510.3(g)(1)). A new animal drug as referenced in this document consists of the final dosage form as given to the animal. Before a new NADA can be approved by FDA, the submitted study data, which are reviewed by the Agency, must demonstrate that the new animal drug is safe and effective for use (21 U.S.C. § 360b(d)(1); 21 CFR 514.1(b)(8)).

When proposing a change to an approved new animal drug that may affect the safety and/or effectiveness of the drug, such changes generally must be submitted to FDA either as a new NADA or a supplemental application to the original NADA. Category II supplemental NADAs are the type of supplement that is used to propose changes that may require a reevaluation of certain safety or effectiveness data in the parent application. Specific changes meeting the requirements for a Category II supplemental NADA are described in 21 CFR 514.106(b)(2). This guidance provides examples and makes specific recommendations about when a change to an approved NADA that requires FDA to review safety and/or effectiveness data should be submitted as a new NADA and when such a change should be submitted as a Category II supplemental NADA. In addition, the guidance addresses how to handle submissions relating to certain types of proposed changes at the investigational stage.

Other guidances are relevant to this discussion. For example, CVM's guidance for industry #82, *Development of Supplemental Applications for Approved New Animal Drugs*, provides limited guidance on how to determine when changes to approved new animal drugs should be submitted as a Category I or Category II supplemental NADA (based on 21 CFR 514.106) or as a new NADA. Guidance #82 primarily outlines the general information that should be included in each technical section when submitting a supplemental NADA. The CVM guidance #83, *Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA* also may be of interest.

This guidance makes recommendations that apply only to changes to approved new animal drugs that require the review of safety and/or effectiveness data. This guidance expands upon CVM's guidance #82 and more clearly defines which changes in approved new animal drugs will result in a new NADA or a Category II supplemental NADA. Furthermore, this guidance also addresses appropriate submissions at the investigational stage. The recommendations in this guidance apply to any study (e.g., dose characterization, dose confirmation, target animal safety, palatability, residue, toxicology) submitted to FDA to fulfill effectiveness and/or safety technical sections for new animal drugs. Except for some noted exceptions, the recommendations generally are similar to those in CVM's guidance #82.[3]

Specifically, this guidance and its appendices discuss the following:

- When to submit an individual change to an approved NADA as a new NADA or as a Category II supplement to the original application, assuming nothing else about the new animal drug product is changed.
- When multiple concurrent changes to an approved NADA should be submitted as one or separate applications, and whether each of these applications should be a new NADA or a Category II supplemental NADA.
- How to handle submissions at the investigational stages of development (i.e., submissions to investigational new animal drug files (INADs)) relating to proposed changes in approved new animal drugs.
- Definitions for various dosage forms and routes of administration for new animal drugs, as well as information about the species and classes of major food animals.

III. DEFINITIONS

For purposes of this guidance, the following definitions apply:

Active Pharmaceutical Ingredient (API) is the substance or mixture of substances in a drug product that is intended to furnish the direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body. For the purposes of this document, the terms *active ingredient* and *API* are considered synonymous.

Dosage form is the pharmaceutical product type, or physical form, of an API as produced or given to the animal (Appendix I). A **new dosage form** contains the same API as included in an existing new animal drug previously approved by FDA but as a different pharmaceutical

[3] The recommendations in this guidance are consistent with the guidance *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, issued by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), which addresses how sponsors should handle differences in human drugs and biologics when submitting an original application and when wishing to make changes to an approved product.

product type (see guidance #74, *Stability Testing of New Veterinary Dosage Forms*, VICH guidance *GL4*). Dosage forms are distinct from routes of administration (Appendix II).

A **new animal drug** is defined, in part, as any drug intended for use in animals other than man, the composition of which is such that such drug is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling of the drug (21 U.S.C § 321(v); 21 CFR 510.3(g)(1)). All such drugs are called *new* animal drugs. A new animal drug as referenced in this document consists of the final dosage form as given to the animal.

In addition, we note that:

A **Category I supplemental NADA** ordinarily does not require a reevaluation of any of the safety or effectiveness data in the parent application (21 CFR 514.106(b)(1)).

A **Category II supplemental NADA** may require a reevaluation of certain safety or effectiveness data in the parent application (21 CFR 514.106(b)(2)).

IV. NEW NADA OR CATEGORY II SUPPLEMENTAL NADA — WHICH IS BEST?

In the following sections, we discuss when you should submit a new NADA and when you should submit a Category II supplemental NADA if you are requesting changes to an approved new animal drug that require review of safety and/or effectiveness data. We also discuss how to handle these types of changes at the investigational stage (i.e., INAD submissions). In addition, with regard to requests for multiple concurrent changes to an approved new animal drug, we offer examples to help determine whether such changes should be submitted as a single application or multiple applications, and how to handle these requests at the investigational stage. Before discussing specific cases, we note the following important considerations:

1. When you submit a new NADA or Category II supplemental NADA, you must own or have a *right of reference*[4] to the data that support the application. If a sponsor does not own or have a right of reference to data supporting an application, CVM will find the application to be deficient or incomplete. If you transfer ownership or lose the right of reference, you should consider the possible effect on pending, and future, submissions and applications. If you withdraw an approved NADA, you may no longer reference the data in that application (21 CFR 514.115(d)).
2. The sponsor's decision about whether to file a new NADA versus a Category II supplemental NADA ordinarily will not alter CVM's decisions as to what specific safety and/or effectiveness data will be needed to support the approval of an

[4] 21 CFR 514.1(a)

Table 1 summarizes whether a new NADA or a Category II supplemental NADA would be appropriate for specific changes to an approved new animal drug that require review of safety and/or effectiveness data. The subsequent sections of this document provide details on handling each specific change.

Table 1. Summary of when to file a new NADA or a Category II supplemental NADA.

Proposed Change to Your Approved New Animal Drug	**Submit as:**		**Or Contact ONADE for Recommendations**
	New NADA	**Cat. II Supplemental NADA**	
New API	X		
New Dosage Form	X		
Variation of Previously Approved Dosage Form		X	
New Major Route of Administration	X		
Variation of Previously Approved Major Route of Administration		X	
Add Species/Class		X	
Add/Change Dose		X	
Change Dosing Schedule		X	
Add Indications/Claims		X	
Change Rx/OTC Status		X	
Replace, Add, Delete, or Change Concentration of Inactive Ingredient			X
Change Concentration of Active Ingredients			X
Multiple Changes			X

A. New Active Pharmaceutical Ingredient (API) — Submit as New NADA

If you are submitting a change that will create a new active pharmaceutical ingredient (API), we recommend you submit a new NADA. As noted previously, a *new animal drug* is any drug intended for use in animals other than man, the composition of which is such that such drug is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling of the drug (21 U.S.C § 321(v); 21 CFR 510.3(g)(1)). Changes to the API drug molecule, as well as a change to the salt, ester, or enantiomer/racemic mixture of an existing API drug molecule, are considered to be a change in the API, which is a basis for the "newness" of an animal drug (21 CFR

510.3(i)(1)). In such cases, a new NADA should be submitted, not a Category II supplemental NADA.[5, 6]

Similarly, a new combination of two or more active ingredients for use in animals should be submitted as a new NADA, not a Category II supplemental NADA.

During the investigational phase of development, sponsors of new animal drugs should establish separate investigational new animal drug files (INADs) for new animal drugs containing different APIs.

B. New Dosage Form — Submit as New NADA

New dosage forms of the same API typically result in delivery of the drug by a different route of administration or a different delivery system, which is another basis for the "newness" of an animal drug (21 CFR 510.3(i)(6)). Thus, your application for a different dosage form of an API for which you have already received approval for use in animals should be submitted as a new NADA, not a Category II supplemental NADA. Although a Category II supplemental NADA does provide for a "change in the…composition of the final product" and a "change in the treatment regimen (schedule of dosing)" (21 CFR 514.106(b)(2)(i) and (iv), respectively), CVM considers these situations to pertain to changes in composition that ***do not*** alter the dosage form of the new animal drug.

Special considerations may be appropriate for new animal drugs approved as medicated articles and feeds (21 CFR part 558). An application may be submitted for a new physical form of a Type A medicated article (e.g., liquid formulation versus dry formulation). If it is determined that the new physical form and inactive ingredient composition do not significantly affect the safety and effectiveness of the API (similar to some changes in inactive ingredients in other new animal drugs as described in Section IV. I), the application should be submitted as a Category II supplemental NADA. However, if changes in the physical form and inactive ingredient composition significantly affect safety and/or effectiveness of the API compared to the previously approved Type A medicated article, the application should be submitted as a new NADA, not a Category II supplemental NADA (see Section IV.I). Consult with ONADE to determine whether the application should be submitted as a new NADA or a Category II supplemental NADA. It may be necessary for

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[5] In its October 17, 1990, policy letter regarding the implementation of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), CVM stated that a product that contains a different salt or ester form of the same drug in the finished new animal drug product is considered to contain a different active ingredient.

[6] The CVM draft guidance #185, *Target Animal Safety for Veterinary Pharmaceutical Products*, Veterinary International Conference on Harmonisation (VICH) GL 43, (5/17/07), indicates: "Margin of safety studies are generally recommended for new salts of the pharmacologically active substance or formulations of an IVPP [Investigational Veterinary Pharmaceutical Product]. Exceptions should be justified, for example, on the basis of known toxicology and target animal safety profiles for the pharmacologically active substance, widespread clinical use of existing products, and/or where the systemic or local exposure (as applicable) of the new product is proven to be equivalent to or less than that of the existing product."

CVM to review safety and effectiveness information relevant to the proposed change during the investigational (INAD) process to determine the appropriate administrative vehicle.

Applications for new Medicated Type B and C feeds derived from the same approved Type A Medicated Article should be submitted as Category II supplemental NADAs to the affected Type A Medicated Article NADA.

To improve clarity of the administrative record, sponsors of new animal drugs containing the same API should establish a separate INAD for each dosage form of the new animal drug.

Appendix I provides the names and definitions of dosage forms of currently approved new animal drugs (21 CFR parts 520, 522, 524, 526, 529, and 558), including medicated articles and feeds. Dosage forms are distinguished from routes of administration (Appendix II, see below). In general, if you intend to add a dosage form or change the dosage form of your approved API to any other dosage form listed in the far left column of the table in Appendix I, the application should be submitted as an NADA. There are *variations* of specific dosage forms (second column). If you intend to add or change from one variation to another within the same dosage form of an approved API (e.g., from capsule to coated capsule), the application should be submitted as a Category II supplemental NADA.

Appendix I is not intended to include all possible dosage forms of new animal drugs. Contact ONADE[7] on how to handle applications for dosage forms not listed.

C. New Major Route of Administration — Submit as New NADA

CVM considers adding or changing to a different major route of administration to be a change to "the newness of a dosage, or method or duration of administration or application…" (21 CFR 510.3(i)(6)). Thus, your application for approval of a different major route of administration for a new animal drug for which you have previously received approval should be submitted as a new NADA, not a Category II supplemental NADA.

To improve clarity of the administrative record, sponsors of a new animal drug should establish separate INADs for different major routes of administration of the drug product.

Appendix II describes some major routes of administration for new animal drugs. In general, if you intend to add or change a major route of administration of your approved new animal drug to any other major route of administration specified in Appendix II, you should submit the application as a new NADA. There are variations within some major routes of administration, such as *Intramuscular* and *Subcutaneous* within *Injection*. An application to add or change a variation within a major route of administration of a new animal drug for

[7] Typically you should contact the reviewer assigned to the approved new animal drug and/or that reviewer's Team Leader from the Target Animal Division in ONADE, i.e., the Division of Therapeutic Drugs for Non-Food Animals, Division of Production Drugs, or the Division of Therapeutic Drugs for Food Animals.

which you have already received approval within that major route should be submitted as a Category II supplemental NADA, not a new NADA.

Appendix II is not intended to include all routes of administration for new animal drugs. Contact ONADE on how to handle applications for routes of administration of new animal drugs not listed.

D. Adding Species/Classes of Animals — Submit as a Category II Supplemental NADA

The regulations regarding Category II supplemental applications provide for the addition of a new species (21 CFR 514.106(b)(2)(vii)). Thus, your application for approval of the use of a new animal drug in a new species or class of animals should be submitted as a Category II supplemental NADA, not a new NADA.

Sponsors should consult with ONADE as to whether it would increase administrative clarity to establish separate INADs for each species and class of animals being investigated for treatment with a specific new animal drug. General recommendations are as follows:

- Major food animals

Appendix III defines specific classes of cattle, swine, chickens, and turkeys consistent with longstanding FDA practice as well as current animal industry standards. Because Target Animal Divisions within ONADE may group or separate specific classes of species differently, you should contact the applicable Target Animal Division to determine when separate INADs are appropriate for different classes or groups of classes of major food animals. For example, if a new animal drug is being investigated for use only in specific classes within a major species of food animal, separate INADs should be established for each species and class. If the new animal drug is being investigated for use in all classes within a species, separate INADs for each species, but not class within species, should be adequate. New animal drugs may be intended for intermediate groupings of cattle species due to physiological differences, such as beef versus dairy cattle, and/or lactating versus nonlactating cattle. Thus, for example, if a new animal drug is intended for use in beef cattle, one INAD may be established for this group. Similarly, one INAD may be used for new animal drugs intended for use in a grouping of beef and nonlactating dairy cattle.

- Companion animals

Classes or breeds of companion animals generally are not distinguished in new animal drug indications. Thus, unless a new animal drug is intended for use in a specific class (e.g., kitten versus mature cat) or breed of companion animal, separate INADs for each species (e.g., cat, dog, horse), but not class or breed within species, should be adequate.

- Minor species

In general, a separate INAD should be established for each minor species of animals being investigated for treatment with a specific new animal drug. For aquaculture, it is recommended that separate INADs be established for finfish, crustaceans, and mollusks. Separate life stages, including eggs, may be included within a single INAD.

E. Adding or Changing Doses — Submit as a Category II Supplemental NADA

As provided for in 21 CFR 514.106(b)(2)(iii), your application for approval of the use of a new animal drug at a dose different from your previous approval should be submitted as a Category II supplemental NADA, not a new NADA. A single INAD may also be used for different doses of the same new animal drug product intended for use in the same species for the same indication.

F. Changing Dosing Schedule — Submit as a Category II Supplemental NADA

Your application for approval of the use of a new animal drug with a dosing schedule different from your previous approval should be submitted as a Category II supplemental NADA, as provided for in 21 CFR 514.106(b)(2)(iv), not a new NADA.

Examples of changing the dosing schedule include the following:

- Original approval was for giving 2 tablets a day, 12 hours apart; change would allow 2 tablets to be given once a day at the same time.
- Original approval was for an injectable sustained release suspension to be given every 14 days; change would allow injections every 10 days.
- Original approval was for the drug to be given for a limited amount of time, such as the first 7 days postsurgery; change would allow the drug to be given for the life of the animal.

Consult with ONADE as to whether it would increase administrative clarity to establish separate INADs for different dosing schedules of a specific new animal drug.

G. Adding Indications/Claims — Submit as a Category II Supplemental NADA

The Category II supplemental application regulations provide for additions of therapeutic and production claims (21 CFR 514.106(b)(2)(v) and (vi)). Thus, your application for approval of the use of a new animal drug for additional indications should be submitted as a Category II supplemental NADA, not a new NADA.

To increase administrative clarity for both CVM reviewers and new animal drug sponsors, sponsors should at least establish a separate INAD for therapeutic claims in food animals, a separate INAD for therapeutic claims in nonfood animals, and a separate INAD for animal production claims. Contact ONADE for claims handled within the same Target Animal Division to determine which claims may be included in the same INAD and which should be in separate INADs.

H. Changing (Rx or OTC) Status — Submit as a Category II Supplemental NADA

Category II supplemental applications include changes from prescription or over-the-counter (OTC) status (21 CFR 514.106(b)(2)(viii)). Thus, your application for approval of such a change in the status of your previously approved new animal drug should be submitted as a Category II supplemental NADA, not a new NADA.

I. Replacing, Adding, Deleting, or Changing Concentrations of Inactive Ingredients

Replacing, adding, deleting, or changing the concentration of inactive ingredients from that found in an approved new animal drug may result in a new animal drug composition that is not generally recognized as safe and effective. Such a change may be considered a new animal drug (21 U.S.C. § 321(v); 21 CFR 510.3(g)(1)). However, the Category II supplemental application regulations also provide for changes in "composition of the final product" and changes in "quality, purity, strength, and identity specifications of the active or inactive ingredients" (21 CFR 514.106(b)(2)(i) and (ii)). Furthermore, these regulations provide for changes in active ingredient concentration (21 CFR 514.106(b)(2)(i)), which will usually occur with a concurrent change in the concentration of inactive ingredients (see Section IV.J of this document). Therefore, as discussed below, the nature of the changes to the inactive ingredient composition of a new animal drug product will determine whether it is submitted as a new NADA or a Category II supplemental application.

CVM recognizes that many changes to the inactive ingredient composition of a new animal drug product do not significantly affect the safety and effectiveness of the API. In such situations, a new NADA would not be warranted. For example, the deletion or reduction of an ingredient intended to affect only the color of a product can be reported in an annual report (21 CFR 514.8(b)(4)(ii)(B)).[8] In some situations, additional safety and/or effectiveness data may need to be submitted to CVM for a new formulation. For these types of changes to the inactive ingredient composition that require review of safety and/or effectiveness data due to such changes in drug delivery and/or distribution of the API, an application should be submitted as a Category II supplemental NADA.

[8] Additionally, changes consistent with guidance #83, *Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA*, may be submitted as Category I or Category II supplemental NADAs.

However, some changes in inactive ingredient composition of a previously approved new animal drug may significantly affect the safety and/or effectiveness of the formulation compared to the previously approved formulation. In such situations, your application for an API formulation in which inactive ingredients have been replaced, added, deleted, or their concentration changed from the new animal drug for which they have already received approval should be submitted as a new NADA, not a Category II supplemental NADA.

Because of the potential difficulty in determining the significance of replacing, adding, deleting, or changing the concentration of inactive ingredients of your previously approved new animal drug, consult with ONADE to determine whether the application should be submitted as a new NADA, a Category II supplemental NADA, or another appropriate administrative vehicle.[9] The reason for the proposed change may be considered during the review process. It may be necessary for CVM to review safety and effectiveness information relevant to the proposed change during the investigational (INAD) process to determine whether the application should be a new NADA, Category II supplemental NADA, or another appropriate administrative vehicle (see e.g., 21 CFR 514.8).

Consult with ONADE to determine whether separate INADs should be established for APIs with different inactive ingredient compositions. During the early stages of development of a new animal drug formulation, it may be acceptable to use one INAD until a specific formulation is selected for further investigation.

J. Changing Concentrations of Active Ingredients

The Category II supplemental application regulations provide for changes in active ingredient concentration in addition to changes in the composition of the final product (21 CFR 514.106(b)(2)(i)). A change in the concentration of an active ingredient is necessarily accompanied by a change in the concentration of one or more inactive ingredients, and/or by a change to the ratio of active ingredients if two or more active ingredients are used in the formulation. These secondary changes may or may not significantly affect the function of the API or the safety and/or effectiveness of the new formulation compared to the previously-approved formulation. Therefore, the nature and degree to which the proposed changes to the *inactive ingredients* affect the function of the API(s) or safety of the new formulation should be used to determine whether an application to change the active ingredient concentration should be submitted as a new NADA or a Category II supplemental NADA. Refer to the section in this document on "Replacing, Adding, Deleting, or Changing Concentrations of Inactive Ingredients" for guidance.

Sponsors should consult with ONADE to determine whether separate INADs should be established for new animal drug formulations with different concentrations of active ingredients.

[9] For example, as a category I supplemental NADA or in an annual report.

K. Multiple Changes

You can request multiple concurrent changes to an approved new animal drug. For changes that require FDA to reevaluate safety and/or effectiveness data, ONADE will consider whether the requested changes are *related* to each other and, therefore, should be submitted in a single application (new NADA or Category II supplemental NADA). If the concurrent requested changes are not related to each other and could be filed individually as *stand-alone* submissions, they should be submitted as separate applications (new NADA(s) and/or Category II supplemental NADA(s)). The decision as to whether an application should be submitted as a new NADA or Category II supplemental NADA should be based on how the ***specific*** changes within the application are usually handled if submitted individually.

In deciding whether multiple requested changes to an approved new animal drug should be submitted in a single or multiple application(s), ONADE will consider the relationship between the proposed changes, e.g., whether one change is necessary to allow the other change. If the proposed changes are unrelated (i.e., one change is not necessary to allow approval of the other change), separate safety and/or effectiveness data sets typically will be needed for each change, and each change should usually be submitted in separate applications. For example:

> **Example 1.** In this example, assume a sponsor requests to expand usage of their approved new animal drug in an additional species for the same indication, and the safe and effective dose for the additional species is different from the dose originally approved for the first species. In this case, the request is for two concurrent changes from the original approval: a new species and a new dose for that species. These requests are related and cannot stand alone because a new dose is necessary to gain approval in the new species, and the same safety and effectiveness data set will support the two concurrent changes. Thus, the request for these two related changes from the original approval (species and dose for that species) should be submitted in the same application.
>
> **Example 2.** In this example, assume a sponsor requests approval of a new dosage form of their approved new animal drug and that the new dosage form has different inactive ingredients and is safe and effective at a different dose of the API than the approved dosage form. In this case, the request is for three changes from the original approval: a new dosage form, changes in inactive ingredients, and a new dose. These requests are related and cannot stand alone because a new dose and different inactive ingredients are necessary to gain approval of the new dosage form, and the same safety and effectiveness data set will support the three concurrent changes. Thus the sponsor's request for these three related changes from the original approval (dosage form, inactive ingredients, and dose) should be submitted in the same application.

Example 3. In this example, assume a sponsor wishes to expand the approved dose range for an already approved product (original dosage form) as well as gain approval of a new dosage form of the API (with changes in inactive ingredients and dose necessary to allow approval of the new dosage form). In this scenario, the request for the change in dose range for the original dosage form is unrelated to, and can stand alone from, the request for a new dosage form (and associated changes in inactive ingredients and dose). Separate safety and/or effectiveness data sets would be necessary to gain approval of the expanded dose range for the original dosage form versus the new dosage form. Thus, the request for the expanded dose range for the original dosage form should be submitted in a separate application from the request for approval of the new dosage form (and associated changes in inactive ingredients and dose).

Example 4. In this example, assume a sponsor has an approved new animal drug to treat a specific disease in dogs. The sponsor wishes to expand the approved dose range for dogs, as well as gain approval of use of the drug to treat the same disease in cats. The requested change in the dog approval is unrelated to, and can stand alone from, the request for the cat approval. Separate safety and effectiveness data sets would be necessary to gain approval of the expanded dose range for dogs versus gaining approval for use in cats. Thus, the request for expanding the approved dose range for dogs should be submitted in a separate application from the request for approval in cats.

Example 5. In this example, assume a sponsor who has an approved new animal drug for increased rate of weight gain in pasture cattle wishes to add a claim of increased carcass leanness in pasture cattle plus gain approval of the increased rate of weight gain and carcass leanness claims in cattle fed in confinement for slaughter. The requested change for pasture cattle is unrelated to, and can stand alone from, the request for approval in cattle fed in confinement for slaughter. The requested new claim for pasture cattle would require separate safety and/or effectiveness data from the request for cattle fed in confinement for slaughter. Thus, the request for adding the carcass leanness claim for pasture cattle should be submitted in a separate application from the request for approval of the increased rate of weight gain and carcass leanness claims in cattle fed in confinement.

Once a determination is made as to whether multiple proposed changes may be submitted as one or separate applications, contact ONADE if you need help deciding whether each application should be submitted as a new NADA or a Category II supplemental NADA. In general, if any one of the changes proposed within an application could, on its own, be submitted as a new NADA, the application should be submitted as a new NADA, not a supplemental NADA. In summary, using the previous examples:

Example 1. A request to approve a new animal drug for use in an additional species at a different dose than for the original approval should be submitted as a single Category II supplemental NADA.

Example 2. A request to approve a new dosage form of a new animal drug with necessary changes in inactive ingredients and dose from the approved dosage form should be submitted as a single new NADA.

Example 3. A request for additional doses of an approved dosage form should be submitted as a Category II supplement to the original NADA, whereas the request for the new dosage form should be submitted as a new NADA.

Example 4. The request to expand the approved dose range for an approved new animal drug in dogs should be submitted as a Category II supplement to the original NADA; the request to gain approval of use of the drug to treat the same disease in cats should be submitted as a separate Category II supplemental NADA.

Example 5. The request to add a production claim in pasture cattle should be submitted as a Category II supplement to the original NADA; the request for production claims in cattle fed in confinement for slaughter should be submitted as a separate Category II supplemental NADA.

An exception may apply for multiple requested changes such as described in Examples 4 and 5 where:

1) Essentially the same product applies to each request;
2) All safety, effectiveness, and chemistry, manufacturing and control information for each request has been reviewed under one or more INADs;
3) Technical section complete letters have been issued by ONADE for each of these technical sections for each request under one or more INADs;
4) All requests would be reviewed by the same Target Animal Division in ONADE; and
5) You plan to submit an administrative NADA (or administrative Category II supplemental NADA, if appropriate)[10].

If these criteria are met, you may be able to submit multiple requests as one administrative NADA or one administrative Category II supplemental NADA. Consult with ONADE if you believe your requests meet these criteria and you wish to submit your requests as one administrative NADA or one administrative Category II supplemental NADA.

You should also consult with ONADE as to whether it would increase administrative clarity to establish one or more separate INAD(s) for investigation of multiple proposed changes to an approved new animal drug. In general, changes that should be submitted as a new NADA should be investigated under a separate INAD.

[10] See CVM draft guidance #132, *The Administrative New Animal Drug Application Process (11/6/02).*

V. CONCLUSIONS

By applying the recommendations in this guidance, we believe that applications for changes to approved new animal drugs will be handled in a more consistent manner. This in turn will improve the clarity of the administrative record for new animal drug applications. You are encouraged to contact ONADE with any further questions regarding the most appropriate administrative vehicle for proposed changes to approved new animal drugs.

APPENDIX I. EXAMPLES OF DOSAGE FORMS OF NEW ANIMAL DRUGS

DOSAGE FORM[1]	VARIATIONS[2]	DEFINITION
Block		A solid dosage form usually in the shape of a square or rectangle that animals consume voluntarily; but not a Type C Medicated Feed.
Capsule	Capsule	A dosage form in which the drug is enclosed within either a hard or soft soluble container or shell made from a suitable form of gelatin.
	Capsule, Coated	A capsule with an additional designated coating.
Cream		A semisolid dosage form where the drug is dissolved or dispersed in a base, usually consisting of emulsions of oil and water, where water is the main ingredient.
Culture		Microorganisms or living tissue cells in special media conducive to their growth.
Emulsion		A liquid dosage form with a two-phase system in which one liquid is dispersed throughout another liquid in the form of small droplets.
Gel		A semisolid dosage form consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid; usually water-based and thickened without oil or fat.
Liquid		A liquid dosage form consisting of a pure neat chemical in its liquid state (an intermediate state entered as matter goes from solid to gas). Do not use this term to describe solutions.
Ointment		A semisolid dosage form, usually consisting of emulsions of oil and water, where oil is the main ingredient; intended for topical application.
Packing		A solid dosage form consisting of a material covered by or impregnated with a drug, that is inserted into a body cavity or between the tooth enamel and the gingival margin.
Particulates	Crumbles	A solid dosage form consisting of small irregularly shaped fragments or particles; but not a Type C Medicated Feed.
	Granule	A solid dosage form consisting of particles or grains smaller and more uniform than crumbles; but not a Type C Medicated Feed.
Paste		A semisolid dosage form that is a fatty, viscous, or mucilaginous base, or a mixture of starch and petrolatum.
Pellet		A solid dosage form in a small mass consisting of highly purified drug with or without excipients, made by compression and molding; but not a Type C Medicated Feed.

DOSAGE FORM[1]	VARIATIONS[2]	DEFINITION
Powder		A solid dosage form consisting of an intimate mixture of dry, finely divided drugs and/or chemicals.
Powder, Aerosol		A powder product packaged under pressure and released upon activation of an appropriate valve system.
Solid Matrix		A solid dosage form in a special shape (e.g., ring, cylinder, cartridge, etc.) and embedded with the drug. It is typically placed in a body cavity or under the skin, where the medication is released for localized or systemic effects.
Solution	Solution	A liquid dosage form in which the drug is dissolved in a solvent or mixture of mutually miscible solvents; but not a Type C Medicated Feed.
	Solution, Concentrate	A solution in which the concentration of drug is increased by the evaporation of nonactive ingredients. The concentrated solution is diluted with appropriate vehicles before the drug is administered.
	Powder, for Solution	A powder product, which upon the addition of suitable vehicles, yields a solution.
Sponge		A solid dosage form in which the drug is embedded in an absorbent pad of natural or synthetic materials.
Spray		A liquid dosage form in which the drug is minutely dispersed by a jet of air or steam.
Spray, Aerosol		A spray which utilizes a compressed gas as the propellant to provide the force necessary to expel the product as a wet spray.
Suspension	Suspension	A liquid dosage form that consists of solid particles dispersed throughout a liquid phase, in which the particles are not soluble.
	Suspension, Concentrate	A suspension in which the concentration of drug is increased by the evaporation of nonactive ingredients. The concentrated suspension is diluted with appropriate vehicles before the drug is administered.
	Powder, for Suspension	A powder product, which upon the addition of suitable vehicles, yields a suspension.
Suspension, Extended Release		A suspension formulated to allow a reduction in dosing frequency.
Syrup		A liquid dosage form consisting of a solution with high concentrations of sucrose or other sugars.
Tablet	Tablet	A solid dosage form containing a mixture of the drug and diluents that are granulated and compressed.
	Bolus	A large tablet.
	Tablet, Coated	A tablet that is covered with a designated coating.
	Tablet, Flavored	A tablet that contains compounds intended to improve palatability.
Tablet, Chewable		A tablet that is formulated to be chewed.

DOSAGE FORM[1]	VARIATIONS[2]	DEFINITION
Tablet, Effervescent		A tablet that contains mixtures of acids (e.g., citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water; it is intended to be dissolved or dispersed in water before administration.
Tablet, Sustained Release	Tablet, Sustained Release	A tablet formulated to allow continued release of the drug over time.
	Bolus, Sustained Release	A bolus formulated to allow continued release of the drug over time.
Medicated Article/Feed[3]	Type A Medicated Article	Intended solely for use in the manufacture of another Type A Medicated Article or a Type B or Type C Medicated Feed. It consists of a new animal drug(s), with or without carrier (e.g., calcium carbonate, rice hull, corn, gluten) with or without inactive ingredients, as defined in 21 CFR 558.3(b)(2).
	Type B Medicated Feed	Intended solely for the manufacture of other Medicated Feeds (Type B or Type C). It contains a substantial quantity of nutrients including vitamins and/or minerals and/or other nutritional ingredients in an amount not less than 25 percent of the weight. It is manufactured by diluting a Type A Medicated Article or another Type B Medicated Feed, and meets the additional requirements defined in 21 CFR 558.3(b)(3).
	Type C Medicated Feed	Intended as the complete feed for the animal or may be fed *top dressed* (added on top of usual ration) on or offered *free-choice* (e.g., supplement) in conjunction with other animal feed. It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A Medicated Article or a Type B Medicated Feed. A Type C Medicated Feed may be further diluted to produce another Type C Medicated Feed, as defined in 21 CFR 558.3(b)(4). A dosage form that meets this definition may be considered a Type C Medicated Feed even if it is provided in the physical form of blocks, crumbles, granules, pellets, or other dosage forms described above.

[1] When changing from one dosage form to another in this column, the application should be submitted as a new NADA.

[2] When changing from one variation to another within the same dosage form of an approved new animal drug, the application should be submitted as a Category II supplemental NADA.

[3] See Section IV.B. regarding Medicated Articles/Feeds.

APPENDIX II. EXAMPLES OF ROUTES OF ADMINISTRATION FOR NEW ANIMAL DRUGS

MAJOR ROUTE[1]	DESCRIPTION	VARIATIONS[2]	CFR REFERENCE
Oral	Through the mouth.	Bolus delivery: solid drug product delivered into the gastrointestinal tract usually by use of a balling gun.	21 CFR 558 (Animal Feeds); 21 CFR 520 (Oral)
		In Feed	
		Drench: delivery of liquid into the mouth	
		In Drinking Water	
		By Intubation: by tube inserted through the mouth or nose into the gastrointestinal tract.	
Injection	Placing a non-formed (liquid or semisolid) drug product into a tissue or body cavity through a needle.	Intramuscular: in a muscle.	21 CFR 522
		Intravenous: in a vein.	
		Subcutaneous: directly under the skin.	
		Intraarterial: in an artery.	
		Intraarticular: in a joint.	
		Intraperitoneal: in the peritoneal cavity.	
		Intradermal: in the dermis of the skin.	
		Intrarumenal: in the rumen.	
		Subconjunctival: under the conjunctiva.	
Implantation	Placing a formed (solid) drug product into a tissue or body cavity.		21 CFR 522
Topical	Directly to a particular area of the external body surface; affects only the area to which it is applied (in contrast to *transdermal*); includes otic administration.		21 CFR 524
Transdermal	On or into the skin resulting in a systemic action (in contrast to *topical*).		21 CFR 524
Transbuccal	Across the oral mucous membrane resulting in systemic action.		21 CFR 524
Intramammary	Into the mammary gland, including mammary infusion into a quarter through the teat canal.		21 CFR 526

MAJOR ROUTE[1]	**DESCRIPTION**	**VARIATIONS**[2]	**CFR REFERENCE**
Nasal	Into or through the nose, localized to the nasal passages.		21 CFR 529
Inhalant	Through the respiratory system.		21 CFR 529
Ophthalmic	To the eye.		21 CFR 524
Rectal	Into the rectum.		21 CFR 529
Intravaginal	Into the vagina.		21 CFR 529
Intrauterine	Into the uterus.		21 CFR 529
Aquatic Exposure	Immersion therapy administered to aquatic animals via bath treatment (exposure).	External-Systemic: absorbed through the skin, gills, etc., and intended action is systemic.	21 CFR 529
		External-Topical: direct contact with the external surfaces of skin, gills, etc., and intended action is local.	
In ovo	Into a fertilized egg (poultry) before laid by the female.		
Egg Dip	Submerged and/or coated with the drug.		21 CFR 529

[1] When changing from one major route of administration to another in this column, the application should be submitted as a new NADA.

[2] When changing from one variation to another within the same major route of administration of an approved new animal drug, the application should be submitted as a Category II supplemental NADA.

APPENDIX III. SPECIES AND CLASSES OF MAJOR FOOD ANIMALS

SPECIES	CLASS		DEFINITION
Cattle	Beef Cattle (cattle intended for meat production)	Suckling Calves	Immature, pre-ruminant cattle (including *dairy breeds* intended for meat production), maintained with and dependent upon their dam for nourishment. Veal calves are not considered suckling calves.
		Pasture Cattle (stocker, feeder, slaughter, and sometimes replacement beef heifers)	Weaned cattle (including dairy breeds) maintained on pasture and receiving the majority of their diet from grazing. The term *pasture cattle* is intended to refer to cattle considered to be stockers, feeders and/or slaughter cattle. Therefore, parenthetical reference to *stocker, feeder, or slaughter cattle* is typically included in labeling. *Stockers* refers to weaned calves grazing pasture to enhance growth prior to finishing and slaughter; they are usually younger, weigh less, and are of lower condition (finish) than "feeders." *Feeders* refers to weaned calves grazing pasture and of sufficient weight and maturity to be placed on high-energy rations for finishing; they are generally older, weigh more, and carry more condition (finish) than stockers. *Slaughter* refers to cattle grazing pasture and suitable for slaughter. Sex differentiation (e.g., heifers, steers and/or bulls) should be indicated on product labeling. *Replacement beef heifers* may be added to the Pasture Cattle class if the drug has been shown to have no negative impact on reproduction in female cattle during the period from weaning until first calving and the female cattle are intended for reproduction to produce calves intended for meat production.
		Cattle Fed in Confinement for Slaughter:	Cattle (including dairy breeds) confined in group pens and fed a high-energy diet *ad libitum* until slaughter. Sex differentiation (heifers, steers, and/or bulls intended for slaughter) should be indicated on product labeling.
		Growing Cattle on Pasture or in Dry Lot (stocker and feeder)	Weaned cattle (including dairy breeds) maintained on pasture or in a dry lot, receiving the majority of their diet from forage.
		Lactating Beef Cows	Lactating beef breed female cattle nursing calves intended for meat production; their milk is not intended for human consumption.
		Non-Lactating (Dry) Beef Cows	Female beef breed cattle that had previously nursed calves intended for meat production, but which are not currently producing milk.

SPECIES	CLASS		DEFINITION
		Replacement Beef Bulls	Intact male beef breed cattle intended for reproductive purposes.
	Veal Calves		Immature cattle (including dairy breeds) lacking a functional rumen and intended for meat production. They are recognized as a separate class from suckling calves because of their handling, housing, and proximity to slaughter.
	Dairy Cattle (cattle intended for production of milk for human food)	Dairy Calves	Female or male dairy breed cattle being fed a ration that includes milk or liquid milk replacer and which are not intended for veal production.
		Replacement Dairy Heifers	Female dairy breed cattle from weaning until first calving.
		Lactating Dairy Cows	Female dairy breed cattle that are producing milk.
		Non-Lactating (Dry) Dairy Cows	Female dairy breed cattle that had previously lactated, but which are not currently producing milk.
		Replacement Dairy Bulls	Intact male dairy breed cattle intended for reproductive purposes.
Swine	Boars		Intact, sexually mature, male pigs intended for breeding purposes; generally not intended for slaughter in the U.S.
	Barrows		Castrated male pigs intended for slaughter.
	Gilts		Female pigs intended for slaughter or breeding purposes; have not yet farrowed a litter.
	Replacement Gilts		Breeding female pigs that have not yet farrowed a litter; usually weigh 220 to 300 lb (100 to 135 kg).
	Sows		Female pigs that have had at least one litter.
	Nursing pigs		Pigs from birth until weaning and still nursing.
	Starter or Nursery Pigs		Boars, barrows and gilts from approximately 2 to 4 weeks of age and approximately 50 to 60 lb (23 to 27 kg).
	Growing Pigs		Barrows and gilts from approximately 50 to 60 lb (23 to 27 kg) to 120 to 150 lb (55 to 68 kg).
	Finishing Pigs		Barrows and gilts from approximately 120 to 150 lb (55 to 68 kg) to market weight for slaughter.
Chickens	Egg		From *in ovo* until hatching.
	Chicks		Chickens from day of hatch until they are able to survive in ambient temperature (no longer brooded).

SPECIES	CLASS	DEFINITION
	Broiler Chickens (or fryers or frying chickens)	Meat-type chickens normally grown to a market age of 35 to 49 days and market weights between approximately 4 and 7 lb (1.80 and 3.2 kg).
	Roasters (or roasting chickens)	Meat-type chickens grown to market weights between approximately 6 and 9 lb (2.7 and 4.1 kg).
	Replacement Chickens	Chickens intended to become meat-type chickens, laying hens, or breeding chickens.
	Breeding Chickens	Sexually mature male and female chickens of any type intended for the production of fertile eggs; the eggs are not intended for human consumption.
Turkeys	Egg	From *in ovo* until hatching.
	Laying Hens (or layers)	Hens that produce eggs for human consumption.
	Poults	Turkeys from day of hatch until they are able to survive in ambient temperature (no longer brooded).
	Growing Turkeys	Turkeys grown for meat purposes to a market age of approximately 17 (female) or 22 (male) weeks; may be further divided into heavy or light turkey strains.
	Finishing Turkeys	Turkeys intended for meat production during the last 2 to 4 weeks of growth.
	Replacement Turkeys	Turkeys intended to become either growing turkeys or breeding turkeys.
	Breeding Turkeys	Sexually mature male or female turkeys intended to produce fertile eggs; their eggs are not intended for human food use.