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Guidance for Industry

Development of Supplemental Applications for Approved New Animal Drugs

Final Guidance

This final document is intended to provide specific guidance for sponsors of new animal drug applications on the development of supplemental applications for approved new animal drugs.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 99N-2912.

For questions regarding this final document, contact Marilyn N. Martinez, Center for Veterinary Medicine (HFV-130), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7577, e-mail: Mmartin1@cvm.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
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Development of Supplemental Applications for Approved New Animal Drugs

This final guidance represents the agency's current thinking on the information to support the approval of supplements. It does not create or confer any rights for or on any person and does not operate to bind the FDA or public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations.

INTRODUCTION:

On November 21, 1997, the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA) (Pub. L. 105-115) was signed into law. Section 403 of FDAMA concerns the approval of supplemental applications for approved products. Among other things, section 403 requires FDA to issue the following guidance for sponsors (you) of supplemental new animal drug applications (NADAs):

- Guidance that defines supplemental applications that are eligible for priority review status (Section 403(b)(3)).
- Guidance that specifies data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application (Section 403 (b)(2)).

When CVM determines that a product represents an important advance in animal health, the Center may expedite the review of original and supplemental applications. The circumstances in which CVM may make such a determination are outlined in an existing guidance, CVM Program Policy and Procedures Guide 1240.3135, available from CVM.[1] Policy and Procedures Guide 1240.3135 addresses Section 403(b)(3) of FDAMA.

[1] Submit written requests for single copies of the CVM's Program Policy and Procedures Guide 1240.3135 to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855. Send one self-addressed adhesive label to assist the office in processing your requests. Persons with access to the Internet may obtain the guide using the World Wide Web (WWW). For WWW access, connect to CVM at http://www.fda.gov/cvm.

"Final Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs" addresses Section 403(b)(2).

Data Requirements:

A. Background:

Under section 512 (b) (1) (A) of the Federal Food, Drug, and Cosmetic Act (the act), an NADA must include evidence that the drug is safe and effective for use. Section 512(d) (1) of the act requires that you demonstrate safety by "adequate tests" and that you demonstrate effectiveness through "substantial evidence."

In certain situations, the types of changes proposed in supplemental applications do not ordinarily require the submission of safety and/or effectiveness data for approval. Therefore, in these cases, CVM will ordinarily not re-evaluate safety or effectiveness data in the parent application or require the submission of new data. Such supplemental NADAs are designated category I under 21 CFR 514.106 and include the following:

(i) A corporate change that alters the identity or address of the sponsor of the NADA.
(ii) The sale, purchase, or construction of manufacturing facilities.
(iii) The sale or purchase of an NADA.
(iv) A change in container, container style, shape, size or components.
(v) A change in approved labeling (color, style, format, addition, deletion or revision of certain statements, e.g., trade name, storage, expiration dates, etc.).
(vi) A change in promotional material for a prescription drug not exempted by 21 CFR 514.8 (a) (3) (i) and (a) (3) (ii).
(vii) Changes in manufacturing processes that do not alter the method of manufacture or change the final dosage form.
(viii) A change in bulk drug shipments.

(ix) A change in an analytical method or control procedures that do not alter the approved standards.

(x) A change in an expiration date.

(xi) Addition of an alternate manufacturer, repackager, or relabeler of the drug product.

(xii) Addition of an alternate supplier of the new drug substance.

(xiii) A change permitted in advance of approval as listed in 21 CFR 514.8 (d).

(xiv) Changes not requiring prior approval that are listed under 21 CFR 514.8 (a) (5) when submitted as supplemental applications.

For other supplemental NADAs, which are designated category II under 21 CFR 514.106, the types of changes proposed in supplemental applications can affect the safety and/or effectiveness of the new animal drug. Therefore, to approve the supplement, the agency needs sufficient data to determine that the drug meets the requirements of safety and/or effectiveness in section 512 of the act. In some cases, data in the parent application will provide support for the approval without the submission of new data. In other cases, the submission of new data may be requested to meet the requirements of section 512 of the act. Pursuant to 21 CFR 514.106, Category II supplemental NADAs include:

(i) A change in the active ingredient concentration or composition of the final product.

(ii) A change in quality, purity, strength, and identity specifications of the active or inactive ingredients.

(iii) A change in dose (amount of drug administered per dose).

(iv) A change in the treatment regimen (schedule of dosing).

(v) Addition of a new therapeutic claim to the approved uses of the product.

(vi) Addition of a new or revised animal production claim.

(vii) Addition of a new species.

(viii) A change in the prescription or over-the-counter status of a drug product.

(ix) A change in statements regarding side effects, warnings, precautions, and contraindications, except the addition of approved statements to container, package, and promotional labeling, and prescription drug advertising.

(x) A change in the drug withdrawal period prior to slaughter or in the milk discard time.

(xi) A change in the tolerance for drug residues.

(xii) A change in analytical methods for drug residues.

(xiii) A revised method of synthesis or fermentation of the new drug substance.

(xiv) Updating or changes in the manufacturing process of the new drug substance and/or final dosage form (other than a change in equipment that does not alter the method of manufacture of a new animal drug, or a change from one commercial batch size to another without any change in manufacturing procedure), or changes in the methods, facilities, or controls used for the manufacture, processing, packaging, or holding of the new animal drug (other than use of an establishment not covered by the approval that is in effect) that give increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess.

For these category II supplemental NADAs, CVM may accept previously submitted safety or effectiveness data. The remainder of this guidance explains the situations in which reliance on previously submitted data may be acceptable to support not only the safety and effectiveness technical sections, but also the environmental and manufacturing controls technical sections of an application. The guidance also explains when the Center may, under existing statutes or regulations, require you to submit new data.

You should use this guidance as a tool for mapping out a project development strategy and for discussing this strategy with CVM. A meeting with CVM helps ensure that you and CVM agree to the criteria associated with the approval of a supplemental NADA.

B. Applying this Guidance to Project Development Plans:[2]

As with NADAs and abbreviated new animal drug applications, every supplemental NADA must address the technical sections cited in sections 21 CFR 514.1(b) and 514.8(a)(1). Some of the requirements may be satisfied only by the submission of new evidence while other requirements may be satisfied by new or existing information. Some examples are as follows:

- new technical information. For example, a sponsor should submit new information pertaining to the technical section for manufacturing chemistry for a change in the active ingredient concentration of the final product.

- existing information

  1) referencing existing information (through right to reference). For example, a change in the analytical method for drug residues will not usually raise new target animal safety (TAS) or effectiveness concerns. Therefore, you can satisfy the technical sections pertaining to TAS and effectiveness by referencing the data in the relevant technical sections contained within the approved NADA.

  2) referencing information contained within the public domain. For example, you may be able to use data available in a Public Master File (PMF)[3]. Also, you may be able to use data available in published matter. CVM developed a

[2] FDA is currently revising its policy regarding evaluation of the human health impact of microbial effects of antimicrobial new animal drugs intended for use in food-producing animals. When this policy becomes final, if it affects any of the policies in this guidance, the guidance will be revised as necessary.

[3] A Public Master File (PMF) is a file that contains publicly generated or otherwise publicly available data (generally, effectiveness, animal safety, residue chemistry, and environmental assessment) that may be referenced by an NADA sponsor to support an original or supplemental NADA approval. The availability of a PMF is announced in the Federal Register.

guidance document[4] that clarifies circumstances in which published matter may be the basis for approval of a supplemental application.

3) combining new data with previously approved data. For example, you may use a new comparative bioavailability study to bridge to the TAS and effectiveness information contained within the approved NADA.

- a determination that a particular technical section is "Not Applicable". For example, the technical section for human food safety (HFS) would not be germane to supplemental NADAs targeted for companion animal drugs.

You generally will be asked to file a new NADA rather than a supplemental NADA for the following proposed changes:

- a new dosage form
- a new salt form
- a new chemical entity
- a change in the bulk drug substance from racemic mixture to pure stereoisomer

Although these changes result in a new NADA, you may be able to reference data contained within the original application to meet some of the technical section requirements for the new NADA.

CVM recognizes the time and resources associated with planning and executing studies and analyzing data. Therefore, CVM encourages you to consider developing study protocols that not only support your currently proposed product changes but also support anticipated future changes in your product.

[4] This guidance can be found on the CVM home page (www.fda.gov/cvm) as guidance No. 106.

The following tables for each type of Category II supplement list the information requested to support each technical section. The technical sections address separately food and non-food animals, but are consistent across major and minor target animal species. Information requirements associated with these technical sections [see 21 CFR 514.1(b) and 514.8(a)(1)] are coded as follows:

- NA = not applicable. This pertains solely to the human food safety technical section of applications targeted for companion (non-food) animals.
- NEW = new information will generally be needed.
- P = information contained within previously approved applications will generally be adequate to satisfy this technical section.
- NEW/P = depending upon the nature of the supplemental application, new information and/or information contained within previously approved applications may be adequate to satisfy this technical section.

For environmental review, "NEW" indicates that an environmental assessment (EA) is necessary, and "P" indicates that a categorical exclusion is probably appropriate. A "NEW/P" indicates that you will need to provide some type of information to support the determination of whether or not an environmental assessment or a categorical exclusion is appropriate. A categorical exclusion is usually applicable to non-food animal actions. However, for non-food aquatic species (e.g., bait fish and commercial ornamental fish), an EA may be required.

There may be types of supplements in addition to those listed in 21 CFR 514.106 (b)(2) that could require reevaluation of safety or effectiveness data in the parent application. You should contact CVM regarding the data requirements for such supplements.

You should use CVM guidance documents and pertinent regulations for generating your supplemental NADA development plans.[5] These documents include, but are not limited to,

[5] Copies of the Guidelines, Guidance Documents, and "Information for Consumers" flyers are available on the internet at http://www.fda.gov/cvm/ or by contacting:
Food and Drug Administration
Center for Veterinary Medicine

the *Target Animal Safety Guidelines for New Animal Drugs (#33),* the *Guidance for Industry: FDA Approval of New Animal Drugs for Minor Uses and for Minor Species (#61)*, and the guidance *General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals (#3)*. CVM published a final rule regarding substantial evidence necessary to support an NADA on July 28, 1999 (64 FR 40746).

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C. Specific Guidance Based On the List in 21 CFR 514.106 (b)(2)

(i) A change in the active ingredient concentration or composition of the final product.

These changes involve: (1) revision consisting solely of a change in the concentration of the new drug substance [for example, Product A (50 mg/mL) to Product A (100 mg/mL)] or (2) a change in the marketed formulation such as replacing one excipient for another or changing the relative concentrations of the active and inactive ingredients.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	NEW	NEW
Environmental	P	P
Target Animal Safety	NEW/P	NEW/P
Effectiveness	NEW/P	NEW/P
Human Food Safety		
basic toxicology	NEW/P	NA
total residue & metabolism	NEW/P	NA
comparative metabolism	P	NA
residue depletion	NEW/P	NA
methods	P	NA

COMMENTS:

TAS: You should address potential changes in systemic and/or injection site target animal safety when changing the inactive ingredients, composition, or vehicle of a new animal drug product. This may include evaluating product relative bioavailability to determine if the original TAS data are adequate for approval of the supplemental application.

Effectiveness: Generally, you should not need to submit additional study data to support a change in the formulation of an IV solution. For dosage forms other than IV, potential changes in product bioavailability as a result of the formulation changes should be considered, and substantial evidence of effectiveness must be submitted.

HFS: You may need to confirm the appropriateness of the marker residue and withdrawal time, depending upon the magnitude of change in the concentration of the active ingredient. In general, withdrawal time data (cold study) will only be needed if there is a possibility that the rate and/or extent of product absorption has changed as a result of the proposed modification.

A review of the revised formulation may be needed to determine if the proposed excipients present a toxicological concern.

ii) A change in quality, purity, strength, and identity specifications of the active or inactive ingredients.

These changes involve product release specifications rather than changes in product formulation. For example, if a product has a label concentration of 100 mg/mL of oxytetracycline, the release specification may allow a variance of ± 10%. A modification of the magnitude of this variance is considered a 21 CFR 514.106(b)(2)(ii) change.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	NEW	NEW
Environmental	P	P
Target Animal Safety	NEW/P	P
Effectiveness	NEW/P	P
Human Food Safety		
basic toxicology	NEW/P	NA
total residue & metabolism	NEW/P	NA
comparative metabolism	NEW/P	NA
residue depletion	NEW/P	NA
methods	NEW/P	NA

COMMENTS:

The need for additional target animal safety, effectiveness, or human safety studies will depend on the magnitude of change in product specification.

(iii) A change in dose (amount of drug administered at one time).

Dose is the quantity of drug administered at one time, such as a specified amount of medication. By contrast, dosage is the size, frequency and number of doses (Dorlands Illustrated Medical Dictionary, 28th edition, 1994; WB Saunders, Philadelphia). This category applies to supplemental NADAs for which changes in dose are not accompanied by changes in the label indication or dosing schedule.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW/P	NEW/P
Effectiveness	NEW/P	NEW/P
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	NEW/P	NA
comparative metabolism	NEW/P	NA
residue depletion	NEW/P	NA
methods	P	NA

COMMENTS:

TAS: Generally, you should submit additional target animal safety data only if the supplemental NADA is for an increase in dose. For certain drugs, a decrease in dose may present TAS concerns which should be addressed in the supplemental NADA.

For therapeutic drugs, you may support TAS with the submission of new data, information from published literature or by comparing the blood level profiles of the proposed dose and the maximum dose evaluated in the previously approved application for the marketed product. For production drugs, you may need to submit TAS data, even if the proposed change is for a decrease in dose. This concern is based largely on the potential dose selectivity of certain physiological responses. For example, not all hormones are selectively inhibited at the same drug concentration. Consequently, low drug doses may result in a hormonal imbalance such that certain adverse effects occur at low doses which do not occur at higher drug doses when all hormone systems are inhibited.

Effectiveness: You should address the rationale for proposing either an increase or decrease in dose. Effectiveness of the proposed dose must be demonstrated through substantial evidence (21 CFR 514.4), which may be satisfied by bridging back to the approved NADA.

HFS: You generally should submit residue depletion data only when the proposed dose is higher than that already approved for the label indications. If the proposed supplemental NADA is for a change in dose that may result in nonlinear drug kinetics, the marker residue, target tissue, or tolerance may change. In this case, additional metabolism data for the target animal species may also be needed. If the marker residue, target tissue, or tolerance changes with the increased dose, you should re-evaluate the appropriateness of your approved analytical method.

(iv) A change in the treatment regimen (schedule of dosing)

This type of Category II supplement applies when there is no change in product indication and no change in the warnings or contraindication statements on the product label.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW	NEW
Effectiveness	NEW	NEW
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	NEW/P	NA
comparative metabolism	P	NA
residue depletion	NEW	NA
methods	NEW/P	NA

COMMENTS:

TAS: TAS may be addressed through pharmacokinetic bridging studies or published literature.

Effectiveness: Effectiveness must be demonstrated by substantial evidence (21 CFR 514.4), which may be satisfied by bridging back to the approved NADA.

HFS: In general, you should only need to submit residue depletion data to address human food safety. However, if the proposed change in dosing presents a risk of altered drug metabolism (resulting in substantially higher steady state drug concentrations), changes in the marker residue, target tissue, or the tolerance may also occur. Consequently, when the drug is known to be associated with enzyme induction saturable pharmacokinetic processes and/or if there is a risk of saturated kinetic processes due to an elevation in steady state drug concentrations, additional metabolism data in the target animal species may be necessary. Accordingly, if the marker residue, target tissue, or tolerance changes with the increase in dosing, the appropriateness of the approved analytical method may need to be reconsidered.

EA: If the schedule of dosing changes to increase the amount of drug introduced into the environment for a treatment, then an EA may be needed.

(v) Addition of a new therapeutic claim to the approved uses of the product.

This category II supplement applies to a change in product indication that may or may not be associated with a change in total daily dose or frequency of administration. It does NOT include the addition of a new target animal species.

New Indication with the *Same* Total Daily Dose and Frequency of Administration

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW/P	NEW/P
Effectiveness	NEW	NEW
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	P	NA
methods	P	NA

COMMENTS:

TAS: You may need to submit additional target animal safety data if the new indication is for a disease characterized by an altered metabolic state.

Effectiveness*:* Substantial evidence of effectiveness will be needed. (21 CFR 514.4)

New Indication with a *Different* Frequency of Administration and/or Total Daily Dose

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW/P	NEW/P
Effectiveness	NEW	NEW
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	NEW/P	NA
comparative metabolism	P	NA
residue depletion	NEW	NA
methods	NEW/P	NA

COMMENTS:

TAS:

CHANGE IN TOTAL DAILY DOSE, SAME FREQUENCY OF ADMINISTRATION
(E.g., change from 1 mg twice a day to 2 mg twice a day)

You should address target animal safety data if the supplemental NADA is for an increase in dose. TAS may be supported by information from published literature or by comparing the blood level profiles of the proposed dose and the maximum dose evaluated in the previously approved application for the marketed product. For certain drugs [as explained in section (iii)], a decrease in dose may present TAS concerns which should be addressed in the supplemental NADA.

SAME TOTAL DAILY DOSE, CHANGE IN FREQUENCY OF ADMINISTRATION
(E.g., change from 1 mg twice a day to 2 mg once a day)

You may support the TAS associated with these changes by conducting new TAS studies, by referencing data contained in the approved NADA, or by referencing data contained within the published literature.

HFS:

CHANGE IN TOTAL DAILY DOSE, SAME FREQUENCY OF ADMINISTRATION OR CHANGE IN FREQUENCY OF ADMINISTRATION

You should generally submit residue depletion data when your supplement is for a higher total daily dose. If the proposed increase in total daily dose has the potential to saturate drug metabolic processes, additional metabolism data in the target animal species may be needed. If the marker residue, target tissue, or tolerance changes with the increase in total daily dose, the analytical method may need to be reevaluated.

(vi) Addition of a new or revised animal production claim.

Technical section requirements same as detailed in part (v).

(vii) Addition of a new species.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW	NEW
Effectiveness	NEW	NEW
Human Food Safety		
basic toxicology	NEW/P	NA
total residue & metabolism	NEW	NA
comparative metabolism	NEW	NA
residue depletion	NEW	NA
methods	NEW	NA

COMMENTS:

You must submit TAS and effectiveness data when the supplemental application is for the addition of a new target animal species (21 USC 360b(d)(1)). For major food-producing animals, your application should include data on total residues and metabolism in the target animal species, comparative metabolism data, residue depletion data, and the development of an appropriate analytical method. Your submission should include a basic toxicology package if your previous approval(s) did not include a food animal claim.

With regard to minor food animal species, the range of potential minor species and CVM's ability to extrapolate to existing data is highly case-specific. Therefore, you should refer to the CVM Guidance on the FDA Approval of New Animal Drugs for Minor Uses and for Minor Species for additional information on this topic, and consult with CVM to define the specific data requirements associated with your proposed supplement.

(viii) A change in the prescription or over-the-counter status of a drug product.[6]

COMMENTS:

The following considerations are based upon the guidance, CVM Policy and Procedures Manual guide number 1240.2220:

1. **CHANGE FROM RX TO OTC USING SAME INDICATIONS, SAME DOSAGE, SAME ROUTE OF ADMINISTRATION, SAME FORMULATION ETC.**

This change is usually initiated by the drug sponsor and approved by the FDA. The general criteria used for consideration include:

- Target animal safety study under actual use conditions showing wide margin of safety for target animal species and the person administering it.
- Nature of drug entity compatible with OTC use, *i.e.*, the drug has low toxicity and has low misuse and abuse potential incidence of reported adverse reactions of a serious and life threatening nature.
- Ability of laypersons to follow label directions.
- Ability of laypersons to recognize disease condition and monitor health status of sick animals and make informed dosage adjustments.
- Lack of evidence of misuse and abuse potential of the drug product.
- A margin of safety.
- Lack of potential human food safety and user safety concerns (generally, this concern will not necessitate the submission of additional human food safety data).

2. **CHANGE FROM OTC TO RX STATUS.**

This change is usually initiated by the FDA based on strong post-approval marketing surveillance evidence showing:

- A high incidence of reported adverse reactions of a serious and life threatening nature.
- An inability of laypersons to follow label directions.
- The inability of laypersons to recognize disease condition and monitor health status of sick animals and make informed dosage adjustments.
- Evidence of misuse and abuse potential of the drug product.
- A narrow margin of safety.
- Potential human food safety and user safety concerns (generally, this concern will not necessitate the submission of additional human food safety data).

[6] In accordance with the recent change in CVM's thinking with regard to the criteria for RX/OTC classification of antimicrobial-containing drug products, sponsors are advised to discuss with CVM issues pertaining to the RX/OTC classification of their antimicrobial-containing products.

(ix) A change in statements regarding side effects, warnings, precautions, and contraindications, except the addition of approved statements to container, package, and promotional labeling, and prescription drug advertising.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	NEW/P	P
Target Animal Safety	NEW	NEW
Effectiveness	P	P
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	P	NA
methods	P	NA

COMMENTS:

Additions: These changes are generally based upon findings from post-approval drug surveillance.

Removal: You must provide TAS information to support a proposal for removing statements pertaining to side effects, warnings, precautions, and contraindications. (21 CFR 514.4)

EA: Changes in side effects, warnings, precautions, etc. could indicate that an unconsidered environmental impact may occur, in which case, new data might be necessary.

(x) A change in the drug withdrawal period prior to slaughter or in the milk discard time.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	NA
Environmental	NEW/P	NA
Target Animal Safety	P	NA
Effectiveness	P	NA
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	NEW/P	NA
methods	P	NA

COMMENTS:

HFS: You may use data from previously submitted studies to calculate the new withdrawal period or milk discard time. However, when the original data do not meet current acceptance criteria, your proposed change in milk discard time or withdrawal period should be accompanied by data generated in a study conducted in accordance with the currently accepted standards (refer to the guidance, *General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals*).

xi) A change in the tolerance for drug residues.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	NA
Environmental	P	NA
Target Animal Safety	P	NA
Effectiveness	P	NA
Human Food Safety		
basic toxicology	NEW/P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	NEW/P	NA
methods	NEW/P	NA

COMMENTS:

HFS: Proposed changes in tolerance are usually a consequence of a re-evaluation of existing toxicology data or of a review of newly available toxicology information. New residue depletion data and analytical methods may be needed if the change constitutes a decrease in the tolerance. However, additional investigations should not be necessary when adjustments in the tissue withdrawal time or milk discard time are based upon a re-evaluation of existing data to correspond with an increase in the tolerance. Application of the revised tolerance for purposes of revising the preslaughter withdrawal period or milk discard time are discussed in (x) above. In limited situations, the tolerance may be revised based on a change in the official analytical method for residues as described in (xii) below. In these cases, you may refer to new or existing toxicology data to support your proposed change.

(xii) A change in analytical methods for drug residues.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	NA
Environmental	P	NA
Target Animal Safety	P	NA
Effectiveness	P	NA
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	P	NA
methods	NEW/P	NA

COMMENTS:

HFS: When proposing a change in the analytical method for drug residues, you should include a study comparing the performance of the new method to the approved official analytical method. Additional toxicology data may be required if the change in analytical method results in a revision to the codified tolerance (see xi above).

(xiii) A revised method of synthesis or fermentation of the new drug substance.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	NEW	NEW
Environmental	P	P
Target Animal Safety	NEW/P	NEW/P
Effectiveness	P	P
Human Food Safety		
basic toxicology	NEW/P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	P	NA
methods	P	NA

COMMENTS:

These changes involve how a drug product is made (*i.e.* route of synthesis, starting materials, components used in the fermentation broth, etc.). However, revisions in the method of synthesis or fermentation of a new drug substance do not ordinarily involve category II changes in the final product specifications.

Generally, approval will be based solely upon chemistry and manufacturing issues. However, if the impurity profile changes as a result of process changes, you may need to reevaluate TAS and human food safety.

(xiv) Updating or changes in the manufacturing process of the new drug substance and/or final dosage form (other than a change in equipment that does not alter the method of manufacture of a new animal drug, or a change from one commercial batch size to another without any change in manufacturing procedure), or changes in the methods, facilities, or controls used for the manufacture, processing, packaging, or holding of the new animal drug (other than use of an establishment not covered by the approval that is in effect) that give increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess.

TECHNICAL SECTION	FOOD ANIMAL	NON-FOOD ANIMAL
Chemistry, Manufacturing Controls	P	P
Environmental	P	P
Target Animal Safety	P	P
Effectiveness	P	P
Human Food Safety		
basic toxicology	P	NA
total residue & metabolism	P	NA
comparative metabolism	P	NA
residue depletion	P	NA
methods	P	NA

COMMENTS:

21 CFR 514.8(d)(3) requires that you submit a supplemental application for changes in the manufacturing process that give increased assurance that the drug will have the characteristics of identify, purity, strength, and quality which it purports or is represented to possess. It also directs you to implement the change at the earliest possible time.

(FDA is currently revising section 514.8 as required by FDAMA. If necessary, the agency will revise this guidance document to reflect changes in the section.)