CENTER FOR VETERINARY MEDICINE
PROGRAM POLICY AND PROCEDURES MANUAL GUIDE 1243.5780

OFFICE OF NEW ANIMAL DRUG EVALUATION
REVIEWERS' CHAPTER

EXCLUSIVITY WORDING FOR USE IN THE FOLLOWING DOCUMENTS: MEMORANDUM RECOMMENDING APPROVAL AND LETTER TO APPLICANT

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I. PURPOSE

This guide describes acceptable wording to be included in ONADE documents to describe what period of exclusivity, if any, is being granted to an NADA/ANADA under section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act

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Responsible Office: ONADE Quality Assurance Team (HFV-102).
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(FFDCA), as amended by the Animal Drug Availability Act (ADAA). This exclusivity wording should be used in the Memorandum Recommending Approval (MRA), Approval Letter, and Freedom of Information Summary (Agency Conclusions section) in the NADA/ANADA approval package.

This guide provides six examples of paragraphs that may be used in CVM documents to describe whether exclusivity has been granted to new animal drug applications. Criteria to help distinguish the applications for which exclusivity may be granted are provided in each section. To determine which exclusivity language should be used for your particular application, carefully read both the descriptive title of each section of the guide and the criteria.

II. DEFINITIONS (As used in this Guide)

- ***Exclusivity (or Marketing Exclusivity):*** A period of time during which others may not obtain approval for a generic copy of the listed new animal drug product for a use(s) for which exclusivity was granted.

- ***Patent Term Restoration:*** Extends the period of protection by U.S. patent for an animal drug, or for its method of use, that was approved after November 16, 1988, to compensate for the time that was required for investigation and regulatory review of the animal drug prior to its approval. Patent Term Restoration is a separate consideration from marketing exclusivity. The marketing exclusivity period and the patent protection period often overlap, but each is mutually exclusive, or independent.

- ***Substantial evidence:***
  Refer to the Attachment for the definition in the act.

III. EXCLUSIVITY WORDING WHEN THE ORIGINAL NADA IS FOR A DRUG, NO ACTIVE INGREDIENT OF WHICH HAS BEEN APPROVED IN ANY OTHER APPLICATION

If the application meets all of the following criteria, it qualifies for exclusivity:

- The active ingredient has not been approved in another application.
- The application is an original (not a supplemental application).
- The application contains one or more investigations to demonstrate substantial evidence of effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

A. Pertinent Part(s) of the Act:
Original NADAs for new chemical entities qualify for FIVE-year exclusivity.

Refer to Attachment, **FFDCA 512 (c)(2)(F)(i)**.

B. Use this Wording in the MRA and Letter:
Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

IV. EXCLUSIVITY WORDING WHEN AN ORIGINAL NADA INCLUDES AN ACTIVE INGREDIENT THAT HAS BEEN APPROVED IN ANOTHER APPLICATION

If the application meets all of the following criteria, it qualifies for exclusivity:

- The active ingredient has been approved in another application.
- The application is an original (not a supplemental application).
- The application contains one or more investigations to demonstrate substantial evidence of effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

NOTE: An example is a combination approval of previously approved drugs.

A. Pertinent Parts of the Act:

Original NADAs that contain new studies to demonstrate safety or effectiveness qualify for THREE-year exclusivity.

Refer to Attachment, **FFDCA 512(C)(2)(F)(ii)**.

B. Use this Wording in the MRA and Letter:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

NOTE: The reviewer should describe in the MRA the investigations on which the exclusivity decision was based. Keep in mind that applications containing human food safety (HFS) studies conducted to change the tolerance or withdrawal time are not eligible for exclusivity. In most cases, a new study that is part of the substantial evidence of effectiveness or a new animal safety study conducted by or on behalf of the sponsor, not HFS studies, would provide grounds for granting exclusivity.

Or, if the original application does not meet the criteria stated above, use the following language:
This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

V. EXCLUSIVITY WORDING WHEN A SUPPLEMENTAL NADA INCLUDES AN ACTIVE INGREDIENT THAT HAS BEEN APPROVED IN ANOTHER APPLICATION

NOTE: Exclusivity is most frequently granted for supplemental applications that add claims or species.

If the application meets all of the following criteria, it qualifies for exclusivity:

- The active ingredient has been approved in another application.
- The application is a supplemental application (not an original application).
- The application contains one or more investigations to demonstrate substantial evidence of effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

A. Pertinent Part of the Act:
Supplemental NADAs that contain new effectiveness studies, studies of animal safety, or human food safety studies qualify for THREE-year exclusivity.

Refer to Attachment, **FFDCA 512(c)(2)(F)(iii)**.

B. Use this Wording in the MRA and Letter:
Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the

<insert change, i.e., new claim, new species, etc., provided for in the supplemental application> for which this supplement is approved.

NOTE: The reviewer should describe in the MRA the investigations on which the exclusivity decision was based. Keep in mind that applications containing human food safety (HFS) studies conducted to change the tolerance or withdrawal time are not eligible for exclusivity. In most cases, a new study that is part of the substantial evidence of effectiveness or a new animal safety study conducted by or on behalf of the sponsor, not HFS studies, would provide grounds for granting exclusivity.

If a supplemental application does not qualify for exclusivity, use the following language:
This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

VI. EXCLUSIVITY WORDING WHEN THE APPLICATION IS AN ABBREVIATED NEW ANIMAL DRUG APPLICATION

A. Pertinent Parts of the Act:
None.

B. Use this Wording in the MRA and Letter:
Generic applications do not qualify for marketing exclusivity. Thus, no exclusivity wording should be included in the MRA or approval letter. An original Abbreviated New Animal Drug Application (generic) copy of a previously approved active ingredient does not qualify for any exclusivity because, by definition, a generic application does not contain investigations conducted to show substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. Also, ANADAs are approved under section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act, and exclusivity is applicable only to section 512(b)(1) applications. It would be less efficient to include the negative statement that the application does not qualify for exclusivity in the MRA and Letter, so by agreement, the wording is simply left out.

If the application is a supplemental application (providing for a new claim, new species, etc., or other changes from the conditions of approval of the original ANADA), then the criteria and the language provided under Item V (above) apply. In short, a supplement to an ANADA is treated the same as a supplement to an NADA.

VII. EXCLUSIVITY WORDING WHEN THE APPLICATION IS A HYBRID NEW ANIMAL DRUG APPLICATION

NOTE: A "Hybrid" is an application that contains elements of an ANADA and an NADA.

If all of the following criteria are met, the application qualifies for exclusivity:

- The active ingredient has been approved in another application.
- The application is an original hybrid application (not a supplemental application).
- The application contains one or more investigations to demonstrate substantial evidence of effectiveness of the drug involved, any animal safety studies, or human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

A. Pertinent Part of the Act:

The part of the act that pertains to the NADA portion of the hybrid application is pertinent. If the NADA portion of the hybrid application contains animal safety, animal effectiveness, or human food safety studies, the application may qualify for THREE-year exclusivity.

Refer to Attachment, **FFDCA 512(c)(2)(F)(iii)**.

B. Prepare the MRA and Letter as follows:

For the portion of the approval that provides the basis for exclusivity, use the wording in Item V. B. (above) pertaining to a supplemental application.

NOTE: The reviewer should describe in the MRA the investigations on which the exclusivity decision was based. Keep in mind that applications containing Human Food Safety (HFS) studies conducted to change the tolerance or withdrawal time are not eligible for exclusivity. In most cases, only a new study that is part of the substantial evidence of effectiveness or a new animal safety study conducted by or on behalf of the sponsor, not HFS studies, would provide grounds for granting exclusivity.

VIII. EXCLUSIVITY WORDING WHEN THE APPLICATION IS A BIOTECHNOLOGY-DERIVED DRUG PRODUCT

A. Pertinent Part of the Act:

The Generic Animal Drug and Patent Term Restoration Act, section 106, provides that generic applications cannot be submitted for biotechnology-derived drugs.

> **Sec. 106 of the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670): Drugs Primarily Manufactured Using Biotechnology.**
> Notwithstanding section 512(b)(2) of the Federal Food, Drug, and Cosmetic Act, the Secretary of Health and Human Services may not approve an abbreviated application submitted under such section for a new animal drug which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques.

B. Use this Wording in the MRA and Letter:

Under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670), *<Name of Drug Product>* is not eligible for generic copying because it is a drug primarily manufactured using biotechnology.

IX. MISCELLANEOUS NOTES

A. Types of studies that qualify an application for exclusivity include substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies).

Because marketing exclusivity is intended to reward innovation, the investigation must be "required for" approval and "conducted or sponsored" by the applicant for the application to qualify for marketing exclusivity.

The reviewer should ensure that the Memorandum Recommending Approval (MRA, Item 14. Exclusivity) specifies the basis for exclusivity in some detail if exclusivity is granted.

B. An Abbreviated New Animal Drug Application, "generic application," cannot qualify for marketing exclusivity because exclusivity applies only to applications approved under section 512(b)(1) of the act. A generic application is approved under section 512(b)(2).

C. For many supplemental NADA approvals, marketing exclusivity does not apply. Hence, there is no need for exclusivity wording in the MRA or Letter to Applicant. An example of such a supplemental application is the type of application that is described in 21 CFR 5.83 (approved by the Director, Division of Manufacturing Technologies), which does not require the conduct of an effectiveness or safety study that could qualify the application for exclusivity under section 512(c)(2)(F), but may contain stability or other studies that do not qualify. A statement that the approval does not qualify for exclusivity should be included in the MRA and Letter to the Applicant to avoid future misunderstanding.

D. There are other rare situations for which exclusivity may be granted that are not described in sections III through VIII of this guide, for example:

- Five-year exclusivity for first NADA approval in food animal species following waiver of exclusivity in non-food-producing animal species (section 512(c)(2)(F)(v)).

- Three-year exclusivity for an original application for a new chemical entity in non-food animal species when the applicant waives five-year exclusivity (section 512(c)(2)(F)(iv)).

Because these provisions of the act have not previously been used, the pertinent parts of the act are included in the Attachment, but suggested wording for use in the Memorandum Recommending Approval and Letter to Applicant have not been included in this guide. If an application qualifies for exclusion under one of these provisions, the reviewer should consult their Team Leader or the Center Special Resources List, under generic animal drugs, for assistance.

X. REFERENCE

Section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act; as amended by the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670), and by the Animal Drug Availability Act of 1996 (Attachment).

ATTACHMENT
Sections of the Federal Food, Drug, and Cosmetic Act Relevant to Exclusivity

Section 512(c)(2)(F)(i)
If an application submitted under subsection (b)(1) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b)(1), is approved after the date of enactment of this paragraph, no application may be submitted under subsection (b)(2) which refers to the drug for which the subsection (b)(1) application was submitted before the expiration of 5 years from the date of the approval of the application under subsection (b)(1), except that such an application may be submitted under subsection (b)(2) after the expiration of 4 years from the date of the approval of the subsection (b)(1) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (n)(1)(G). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning 48 months after the date of the approval of the subsection (b) application, the 30 month period referred to in subparagraph (D)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

Section 512(c)(2)(F)(ii)
If an application submitted under subsection (b)(1) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under such subsection, is approved after the date of enactment of this paragraph, and if such application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b)(2) for the conditions of approval of such drug in the subsection (b)(1) application effective before the expiration of 3 years from the date of the approval of the application under subsection (b)(1) for such drug.

Section 512(c)(2)(F)(iii)
If a supplement to an application approved under subsection (b)(1) is approved after the date of enactment of this paragraph, and the supplement contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b)(2) for a change approved in the supplement effective before the expiration of 3 years from the date of the approval of the supplement.

Section 512(c)(2)(F)(iv)
An applicant under subsection (b)(1) who comes within the provisions of clause (i) of this subparagraph as a result of an application which seeks approval for a use solely in non-food producing animals, may elect, within 10 days of receiving such approval, to waive clause (i) of this subparagraph, in which event the limitation on approval of applications submitted under subsection (b)(2) set forth in clause (ii) of this subparagraph shall be applicable to the subsection (b)(1) application.

Section 512(c)(2)(F)(v)
If an application (including any supplement to a new animal drug application) submitted under subsection (b)(1) for a new animal drug for a food-producing animal use, which includes an active ingredient (including any ester or salt of the active ingredient) which has been the subject of a waiver under clause (iv) is approved after the date of enactment of this paragraph, and if the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or human food safety studies (other than bioequivalence or residue studies) required for the new approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application (including any supplement to such application) submitted under subsection (b)(2) for the new conditions of approval of such drug in the subsection (b)(1) application effective before the expiration of five years from the date of approval of the application under subsection (b)(1) for such drug. The

provisions of this paragraph shall apply only to the first approval for a food-producing animal use for the same applicant after the waiver under clause (iv).

Section 512(d)(3)
As used in section 512 of the act, the term "substantial evidence" means evidence consisting of one or more adequate and well-controlled investigations, such as

(A) a study in a target species;
(B) a study in laboratory animals;
(C) any field investigation that may be required under section 512 and that meets the requirements of subsection (b)(3) if a presubmission conference is requested by the applicant;
(D) a bioequivalence study; or
(E) an in vitro study

conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.