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Administrative Applications and the Phased Review Process

Guidance for Industry

This version of the guidance replaces the version made available in May 2015. This document has been revised to update contact information and correct a factual and typographical error.

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. FDA-2002-D-0147 (formerly 02D-0449).

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either https://www.fda.gov/AnimalVeterinary/default.htm or https://www.regulations.gov/.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance defines:

1. the "phased review process" for reviewing application-level information during the investigational period of new animal drug development,

2. an "administrative" new animal drug application (NADA) or abbreviated new animal drug application (ANADA), the content, the procedures a sponsor should follow to submit such an application, and the intended time frame for its review.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. § 321, et seq.) prohibits the introduction into interstate commerce of new animal drugs that are not the subject of an approved new animal drug application (NADA).[1] Further, sections 512(b)(1) and 512(n)(1) of the FD&C Act describes the information that must be submitted as part of an NADA or ANADA, respectively.

The Center for Veterinary Medicine (CVM) encourages sponsors to submit data for review at the most appropriate and productive times in the drug development process. Rather than submitting all data for review as part of a complete application, we have found that the submission of data supporting discrete technical sections during the investigational phase of the new animal drug is the most appropriate and productive. This "phased review" of data submissions has created

[1] To be legally marketed, a new animal drug must be the subject of either an approved application under Section 512(b) of the FD&C Act, a conditional approval under section 571 of the FD&C Act, or an index listing under section 572 of the FD&C Act.

efficiencies for CVM and the animal pharmaceutical industry. These increased efficiencies have facilitated the approval of both pioneer and generic new animal drugs.

This guidance defines what an administrative (A)NADA is, defines and describes the phased review process, and briefly discusses how sponsors should submit an administrative (A)NADA and the time frame for review.

III. DEFINITIONS

The "phased review" of data submissions is a process a sponsor may voluntarily use to complete any or all of the technical sections (see section V for a complete list of required technical sections) required for approval of a new animal drug before submitting an application. The "phased review" process occurs during the investigational phase of the animal drug development process. Specifically, it is when a sponsor submits data and information in support of the various technical sections to their investigational file (i.e., investigational new animal drug (INAD) file for pioneer animal drug products or generic investigational new animal drug (JINAD) file for generic animal drug products) for CVM review and acceptance.

An "administrative (A)NADA" is an original or supplemental new animal drug application (NADA) or abbreviated new animal drug application (ANADA) submitted after all technical sections necessary to fulfill the requirements for the approval of the new animal drug under 21 CFR 514.1 have been reviewed by CVM and CVM has issued a technical section complete letter for each of the required technical sections. The administrative (A)NADA is the culmination of the completion of the phased review process work.

IV. THE PHASED REVIEW PROCESS

The use of the phased review process to review data supporting a technical section of a pioneer or generic new animal drug application is a voluntary program.[2] A sponsor may submit a phased review data submission containing all or part of the data or information needed to address the requirements of one technical section of the application for review during the investigation of the animal drug. There are multiple ways to navigate the phased review process (e.g., technical sections submitted at the same time or submissions that contain data for a portion of the technical section); therefore, CVM recommends sponsors use the presubmission conference process to discuss specific details regarding the content and timing of each technical section. The requirements under 21 CFR 514.1 equally apply to all applications whether data were submitted for phased review or not. The option to phase the review of data submissions applies to all original and supplemental applications and can be exercised up to the point at which the sponsor submits the application.

[2] In deciding whether to seek approval of a new animal drug by taking advantage of the phased review of data submissions or by submitting all data at one time within the application, a sponsor should consider all advantages and disadvantages of each mechanism for approval before submitting data for CVM's review. For example, a sponsor should consider whether seeking approval of a new animal drug under phased review will affect the extension of a patent term. See the discussion in section VIII of this guidance.

If a sponsor exercises the option to use the phased review process:

- Each phased review submission should contain information and data relating to only one technical section. Sponsors should include all relevant draft labeling and all pertinent information they have at the time they submit each technical section. This facilitates FDA's review of the labeling technical section and CVM's preparation of the Freedom of Information (FOI) Summary.

- Sponsors are encouraged to contact their ONADE project manager regarding what information and data should be submitted together and how to make a submission. Alternatively, if the sponsor does not have an ONADE project manager, contact the appropriate review division to discuss informational requirements.

- Each phased review submission should be submitted during the investigation of the new animal drug and filed in the appropriate (J)INAD file established by CVM for the new animal drug.

- The phased review submission to CVM may be made in paper or electronically using the eSubmitter tool. CVM encourages sponsors to use the eSubmitter electronic submission tool. The use of the eSubmitter tool may confer certain review timeline advantages to certain sponsors. The eSubmitter tool provides sponsors with immediate electronic receipt confirmation, immediate electronic transmission of CVM's response, and includes templates for the various types of submissions to help sponsors ensure they include all necessary information. Sponsors are encouraged to visit https://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/UserFees/default.htm for current eligibility and requirements information contained in the current Goals Letters for the user fee programs.

- If there are changes in the product development plan during the phased review process (e.g., indication, dosage, duration of use) or sponsors become aware of any issues that may impact the status of a technical section or the application, sponsors should contact their ONADE project manager for an NADA or the Division of Generic Animal Drugs for an ANADA. CVM will make a decision on the impact this information has on the technical section or application.

To avoid potential delay in the review of phased review data submissions related to the various technical sections, these submissions should be directed to the appropriate review division as provided in the following table.

Technical Sections	**Review Divisions**
Effectiveness, Target Animal Safety (including user safety), Labeling, and All Other Information	Based on the intended uses for the new animal drug, either to: Division of Therapeutic Drugs for Non-Food Animals, Division of Production Drugs, or Division of Therapeutic Drugs for Food Animals
Bioequivalence, Patent and Marketing Exclusivity, and Labeling	Division of Generic Animal Drugs
Chemistry, Manufacturing, and Controls	Division of Manufacturing Technologies
Human Food Safety (Toxicology, Residue Chemistry, and Microbial Food Safety)	Division of Human Food Safety
Environmental Impact	Division of Scientific Support

The review division will notify the sponsor in writing of its conclusions on acceptance or non-acceptance of the data submitted relevant to a technical section. If the review division finds the data for the technical section to be complete and the requirements for the technical section to be met, the division will issue a technical section complete letter. A final decision on the approval of an application will be made when the administrative (A)NADA is submitted and CVM evaluates whether all the data for all technical sections, when viewed as a whole, continue to support approval.

Any person intending to file an application for a new animal drug approval, i.e., an (A)NADA, or a request for an investigational exemption under section 512(j) of the FD&C Act is encouraged to request one or more presubmission conferences with CVM early in the drug development process and before making such submission. One purpose of such a meeting would be to reach an agreement acceptable to CVM regarding the submissions or investigations necessary to meet the requirements for an approval (see 21 CFR 514.1).

Coordinating the submission of technical sections remains the responsibility of the drug sponsor. There are obvious and varying degrees of interdependence among the technical sections, e.g., concerns about target animal safety may place boundaries on the dose(s) evaluated in drug effectiveness studies. Because these interdependencies may exist, individual drugs under development may benefit from particular and unique timings and orderings for the submission of technical sections. Therefore, CVM encourages sponsors to use the presubmission conference process to discuss these details.

Before submission of the (A)NADA (whether administrative in nature or not), the sponsor is responsible for ensuring all necessary technical sections are complete, compatible, and support the approval of the same drug product. If the sponsor chooses to progress from a phased review

approach to the filing of the (A)NADA, and this does not result in an approval, subsequent submissions for the application must be made to the (A)NADA and not to the (J)INAD.

V. DESCRIPTIONS OF THE TECHNICAL SECTIONS

A. For pioneer applications

There are seven technical sections for an NADA: Chemistry, Manufacturing, and Controls; Effectiveness; Target Animal Safety; Human Food Safety; Environmental Impact; Labeling; and All Other Information. Discussions with the appropriate review divisions will be necessary to determine which technical sections are required to support a specific approval. Each of the technical sections is described in detail in 21 CFR 514.1. A brief synopsis of each is presented below.

1. Chemistry, Manufacturing, and Controls

This section contains complete information regarding the manufacture of the new animal drug active ingredient and the new animal drug product. It includes information on personnel, facilities, components and composition, manufacturing procedures, analytical specifications and methods, control procedures, stability, containers and closures, Good Manufacturing Practice (GMP) compliance, and many other aspects of the chemistry and manufacturing processes (21 CFR 514.1(b)(4) and (5)).

2. Effectiveness

This section contains full reports of all studies that show whether or not the new animal drug is effective for its intended use (21 CFR 514.1(b)(8)(i)). This section includes studies conducted by or on behalf of the sponsor or available to the sponsor by right of reference. References and authorizations, if appropriate, to other applications or documents containing information regarding effectiveness of the new animal drug should also be included in this section of the application. Section 512(d)(1)(E) of the FD& C Act (21 USC § 360b(d)(1)(E)) provides that CVM must refuse to approve an NADA unless the sponsor demonstrates by substantial evidence 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 proposed labeling. This section includes any additional pertinent information that is known about the effectiveness of the drug at the time the technical section is submitted.

3. Target Animal Safety

This section contains full reports of all studies required by FDA to demonstrate whether or not the new animal drug is safe to the target species (21 CFR 514.1(b)(8)(i)). All studies should include those studies conducted by or on behalf of the sponsor or that are available to the sponsor by right of reference. References and authorizations, if appropriate, to other applications or documents containing

information regarding safety of the new animal drug should also be included in this section of the application. This section also contains any studies or references relevant to the safety of humans that administer or may come into direct contact with the new animal drug (user safety). This section includes any additional pertinent information that is known about the target animal safety of the drug at the time the technical section is submitted.

4. Human Food Safety

This section is submitted only for applications for new animal drugs intended for use in species that are used for human food (food-producing animals). This section includes a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of the drug will be safe (21 CFR 514.1(b)(7)). This section should also contain any data relating to residue toxicology (including the impact of residues of antimicrobials on human intestinal microflora), residue chemistry, and, if the new animal drug is an antimicrobial, microbial food safety. This section includes any additional pertinent information that is known about the human food safety of the drug at the time the technical section is submitted.

5. Environmental Impact

This section (21 CFR 514.1(b)(14)) contains either an environmental assessment (EA) under 21 CFR 25.40, or a request for categorical exclusion under 21 CFR 25.30 or 25.33. Under 21 CFR 25.15(a), a claim of categorical exclusion must include a statement of compliance with the categorical exclusion criteria and must state that to the sponsor's knowledge, no extraordinary circumstances exist. "Environmental Impact Considerations" and directions for preparing an EA can be found in 21 CFR Part 25.

6. Labeling

This section (21 CFR 514.1(b)(3)) includes facsimile or final copies of container labels, package inserts, and all other labeling components that will be associated with the product. For medicated feeds, copies of representative labeling for the Type B and Type C medicated feeds, often referred to as "Blue Bird" labeling, and a veterinary feed directive form, if required, should also be included. Facsimile labeling is nearly final labeling that adequately reproduces the package size (actual or to scale); graphics; pictures; type size, font, and color of text; and, the substance of the text to demonstrate to the reviewing division that the final printed labeling will be in compliance with applicable regulations.

7. All Other Information (AOI)

This section includes all other information, not included in any of the effectiveness, target animal safety, and/or human food safety technical sections, that is pertinent to an evaluation of the safety or effectiveness of the new animal drug for which approval is sought (21 CFR 514.1(b)(8)(iv)). All other information includes, but is not limited to, any information derived from other marketing (domestic or foreign) and favorable and unfavorable reports in the scientific literature. If there is no additional information that has not been previously submitted, the sponsor's AOI technical section should contain a statement to that effect.

B. For generic applications

There are six technical sections for an ANADA: Bioequivalence; Patent and Marketing Exclusivity; Chemistry, Manufacturing, and Controls; Human Food Safety; Environmental Impact; and Labeling. Discussions with the appropriate review divisions will be necessary to determine which technical sections are required to support a specific approval. The descriptions for the technical sections for an ANADA are the same as those identified above for an NADA with the following exceptions.

1. Bioequivalence

This section contains full reports of all studies that show the generic new animal drug is bioequivalent to the reference listed new animal drug or all information submitted in support of a waiver from the requirement to demonstrate in-vivo bioequivalence. All studies should include those studies conducted by, or on behalf of, the sponsor or available to the sponsor by right of reference.

2. Human Food Safety

In the instances where human food safety information is required, the division responsible for the evaluation of this information will advise the sponsor as to the requirements that must be met.

3. Patent and Marketing Exclusivity

This section includes the appropriate patent certification or statement (see 21 CFR 314.94(a)(12)). It also contains an appropriate statement with regard to the current marketing exclusivity status of the reference listed new animal drug.

VI. SUBMITTING AN ADMINISTRATIVE (A)NADA

When a sponsor has received technical section complete letters for all of the technical sections required to support approval of a new animal drug, the sponsor may file an administrative (A)NADA. It is the responsibility of the sponsor to ensure that all technical sections of an

application are complete and support the approval of the new animal drug application. In those instances in which a collective review of the technical sections of the administrative NADA raises questions about the safety or effectiveness of the new animal drug, CVM will refuse to approve the application under section 512(d)(1) of the FD&C Act. Likewise, when a collective review of the technical sections of the administrative ANADA raises significant questions about any requirement for approval of the ANADA, CVM will refuse to approve the application under section 512(c)(2)(A) of the FD&C Act. CVM encourages sponsors to use presubmission conferences during their drug development and review process to minimize those occasions on which a review division may identify problems after the administrative (A)NADA has been submitted.

An administrative (A)NADA can be submitted in paper or electronic format. A paper submission of an administrative (A)NADA should include a cover letter, signed FDA Form 356V, a table of contents, summary, a copy of each technical section complete letter, and complete facsimile or final printed labeling. Address the cover letter for the application to the division director responsible for the evaluation of effectiveness or in the case of generics, the division responsible for the evaluation of bioequivalence. Clearly identify at the top of the letter that the submission is an "administrative (A)NADA." If this is a paper submission, send it to CVM's Document Control Unit. If the submission is electronic, send it to CVM using the eSubmitter tool and it will contain the equivalent information identified above once the submission process in eSubmitter is complete.

It is important to note the AOI technical section expires 90 days after the date of the AOI technical section complete letter. Therefore, a sponsor needs to submit their administrative NADA within 90 days of that date.

VII. TIME FRAME FOR REVIEW

Section 512(c)(1) of the FD&C Act requires FDA to approve or not approve an application within 180 days, or within such additional period as FDA and the sponsor may agree upon, after the filing of an application. The FD&C Act does not specify the order or timing for submission of data in support of an application. If the data are submitted as part of the phased review process, CVM intends to consider the application filed when it receives the administrative application because it is at this point that the agency should have all the elements required by 21 CFR 514.1.

A. Administrative NADA

If an application is identified as an administrative NADA, CVM will assign the application a 60-day review time frame (or such other review time frame as contained in the current user fee Goals Letter). The application will be forwarded to the director of the division responsible for the evaluation of effectiveness who will review the NADA to determine if it meets the definition of an administrative NADA. If the application does not meet the definition, CVM intends to assign it the statutory 180-day time frame (or such other review time frame as identified in the current user fee Goals Letter) and notify the sponsor. CVM intends to evaluate all NADAs within 30 days of receipt to

determine whether any of the grounds to refuse to file the application under 21 CFR 514.110 apply.

The division responsible for the evaluation of effectiveness will review the information submitted as part of an administrative NADA to ensure that all the information necessary to make an approval decision has been provided, is complete, and is consistent when all the technical sections are considered together.

B. Administrative ANADA

If an application is identified as an administrative ANADA, CVM will assign the application a 90-day review time frame (or such other review time frame as identified in the current user fee Goals Letter). The application will be forwarded to the director of the Division of Generic Animal Drugs who will review the ANADA to determine if it meets the definition of an administrative ANADA. If the application does not meet the definition, CVM intends to assign it the statutory 180-day time frame (or such other review time frame as identified in the current user fee Goals Letter) and notify the sponsor. CVM intends to evaluate all ANADAs within 30 days of receipt to determine whether any of the grounds to refuse to file the application under 21 CFR 514.110 apply.

The Division of Generic Animal Drugs will review the information submitted as part of an administrative ANADA to ensure that all the information necessary to make an approval decision has been provided, is complete, and is consistent when all the technical sections are considered together.

VIII. PATENT TERM RESTORATION ISSUES

Under U.S. patent law (35 U.S.C. § 156(a)), the term of a patent for a new animal drug or its method of use may be extended if it meets certain criteria, one of which is that it was subject to a regulatory review period before its commercial marketing or use. While there are other important criteria that must be met, a full discussion of the issues relating to patent term extension is beyond the scope of this guidance.

In summary, however, the regulatory review period is divided into two time periods. The first period (sometimes called the investigational period) begins when the sponsor submits a request to CVM to establish an INAD file, or when a major health or environmental effects test is initiated, and ends when an NADA is submitted. The second period (the approval period) begins with submission of the NADA and ends when the application is approved (35 U.S.C. § 156(g)(4)(B)).[3] Subject to certain important limitations, a patent may be extended for a time roughly equal to the second time period plus one half the first time period (35 U.S.C. § 156(c)(2)). Because FDA intends that the time it takes to approve an application that qualifies as an administrative NADA usually will be shorter than the time it takes to approve a non-administrative or traditional NADA, a new animal drug that was the subject of an administrative

[3] See Wyeth Holdings Corp. v. Sebelius, 603 F.3d 1291, 1299 (Fed. Cir. 2010) (holding that "an application" is "initially submitted" with respect to the approval phase under 35 U.S.C. § 156(g) when a sponsor submits an administrative NADA to the agency).

NADA is likely, in most cases, to receive a shorter patent term extension than it would have received had it been the subject of the non-administrative ("traditional") NADA review and approval process.