Center for Veterinary Medicine Second eSubmitter Webinar, Afternoon Break-out Session Target Animal Review Divisions 1, Webinar for Demonstration of the 60- and 180-day Animal Drug Availability Act Combination Submissions
August 22, 2018

I. Introduction

Hello and welcome to the CVM eSubmitter webinar training for the submission of a New Animal Drug Application (NADA) for an Animal Drug Availability Act or ADAA combination.

This webinar will address both the 180-day traditional NADA and the new for ADUFA IV, 60-day NADA for those proposed combinations that have gone through phased review under an Investigational New Animal Drug file (INAD). For more information on ADAA combinations that qualify for a shortened 60-day review period, we direct you to the webinar covering that topic now available on CVM's training website. First, we will begin with the traditional 180-day NADA template. These are submissions that have not undergone a complete phased review process under an INAD, although some work may have been done under the INAD.

First you will click on "Create New Submission". However, for the purposes of this demonstration, I have already filled out the template and will be walking you through it. So, I will click on "Open Existing Submission".

II. CVM ONADE Submissions Tab

A. Screen 1.0 Document Information

On the first screen you will select your document type from the drop-down menu. In this scenario, you will select "New Animal Drug Application" or document type N. Because you are opening a new NADA you will answer the question, "Is this submission for a currently established file or application with "No". Because of this response, the text box beneath the question is grayed out. The Document Number will be assigned to you upon submission of this request.

Next, using the right arrow you will advance through the remainder of the screens on this tab.

B. Screen 2.0 Firm Information

For more information on filling out each of these screens, I direct you to the "How to Use the eSubmitter Tool" webinar for additional instructions. Once these have been completely filled out, you can advance to the next tab.

III. Submission Type Selection (NADA) Tab

A. Screen 6.0 Submission Type Code/Amendment Information I

On this screen, you will select from the drop-down menu the NADA Submission Type. In this case, because we selected "No' to the question on the first screen, there is only one option, "Original NADA" or submission type A; likewise, these is only one option for the second drop-down menu. Next, you will select the review division to which you are submitting. All ADAA combinations, regardless of the proposed indications (e.g., therapeutic indications only, a combination of therapeutic and production indications, or production indications only) all are reviewed by HFV-120, the Division of Production Drugs. Again, because of the submission type, the following

question, which would be used to indicate an amendment to a current pending submission, is grayed out.

Then, click the right arrow to advance to the next screen.

IV. Original NADA (N/A/OT) Tab

As you can see here on the left, there is a lot of information that can potentially be submitted as part of an original or traditional NADA. However, because this webinar is specific for ADAA combinations, the requirements for approval are not as comprehensive as those for approval of a new single-drug product.

A. Screen 1.0 General Information

1. At the top of the first screen, you will click on the button with the green plus sign to attach your User Fee cover sheet.
2. For the first question, "Is this application requesting approval or a combination that meets the criteria outlined in the Animal Drug Availability Act, as amended?", you will respond, "Yes".
3. Please answer "no" to the second question, as we will cover NADAs for qualifying 60-day review under ADUFA IV at the end of this webinar.
4. This is not an administrative NADA, so please select "No" to the next question.
5. For the next question, you will always answer "Yes". Animal Drug Availability Act combinations rely on the original safety and effectiveness data contained in the single-drug approvals and their respective NADAs, which must be referenced in this submission.
6. The next question asks if there are patent information to be submitted which claims the drug or the use of such drug. If you select "yes", this will activate screen 1.2 for you to provide additional information. If you do not have a patent for the drug product, you will select "no" and then check the box at the right of the screen to attest that there is no such patent that claims the drug or the use of the drug in the manner prescribed. For our demonstration purposes today, I will select "yes" so that we can preview that screen.
7. At the bottom of the screen, please provide in the text box, a brief description of the application. For example, I have provided the following sample text, "This submission is for the approval of a new ADAA combination using drug 1 Type A medicated article and drug 2 Type A medicated article for the proposed indication in the target species and class.

You will then use the right arrow again to advance to the next screen.

B. Screen 1.1 Referenced Applications and Files

1. Here you will provide information regarding the various associated files that contain information to support approval of this combination. Although 60-day combinations require phased-review through an INAD and 180-day combinations do not, it is not uncommon for sponsors to have an INAD for 180-day combinations. Presubmission conferences, review of labeling, and

other components of the development plan may be conducted under an INAD, even if you do not intend to submit each technical section for review under the INAD.

A common occurrence for these types of applications is for a sponsor to have conducted a presubmission conference and to have received a memorandum of conference stating that the proposed combination meets the qualifications for review under the Animal Drug Availability Act, and as such, the requirements for Target Animal Safety and Effectiveness have been satisfied. If this scenario, you would click "new", provide the file type, INAD, the number of the file, and then check the appropriate boxes for the technical sections for which the MOC or other documents in the file will address. In the text box beneath, you will provide details that relate to the referenced technical sections, such as the submission identifier, the date of the submission, et cetera.

2. Because the INAD belongs to you, you will answer "yes" to the next question.

3. In addition, you will need to click "new", an add information for each of the NADAs for the single-drug approvals that are part of the proposed combination. Once you have selected the NADA file type and input the number, you select the boxes for all four major technical sections. There's no need to provide details about this application further on this screen.

4. The last question asks if you own the referenced application file. If you do, no additional information is needed. However, if one of, or more, of the Type A medicated articles proposed in your combination are not owned by your firm, you must select "no" and then provide a right of reference provided to you from the sponsor or owner of the NADA for the Type A medicated article that you do not own. Without this right of reference, CVM cannot refer to the data the safety and effectiveness data, contained within the NADA to support your combination. As a result, we will not be able to review your application and your combination application will not be approvable.

   Once you have input the information for all of the type A medicated articles, you may proceed to the next screen.

C. Screen 1.2 Patent Information

Here, if you answered in the affirmative that there is a patent applicable to your drug product, you will click "new" and then provide the patent number, the expiration date, as well as the patent type.

D. Screen 2.0 Product Description

Next we move to the product description screen. You will start by clicking "new" to provide information specific to your product. First, you will respond appropriately if your drug product has a USP monograph or not, and then provide the product established name. The established name is the names of the individual Type A medicated articles as shown here: drug 1 Type A medicated article and drug 2 Type A

medicated article, and so on and so forth for as many proposed Type A medicated articles that are in your combination. Next you will input the associated proprietary names for each of the Type A medicated articles.

For the Dosage Form, select "Medicated Article/Feed".

The Dosage Form Variation is "Type C Medicated Feed"

The Route of Administration is "Oral"

The Route of Administration Variant is either "In Feed" or "In Drinking Water".

And then you will select the Common Animal Name, Class, and Sub-Class, if applicable, as appropriate for your proposed combination.

Lastly, select "yes" or "no" if the drug was formally granted a MUMS designation for the proposed indication.

E. Technical Sections

As you proceed to the next screen for the technical sections, you will identify which technical sections you are submitting to support the NADA. All of the technical sections must be complete before approval of your combination. If you are submitting only partial information, anticipate that you will either be required to submit additional information as an amendment or you will need to reactivate your application upon receiving an incomplete letter from CVM. For today's demonstration, we will assume that all technical sections will be addressed in a single submission.

Please respond appropriately if the combination is an application is for conditional approval, and then we will advance to the next screen.

1. Screen 3.1 Target Animal Safety

   Proposed combinations that qualify for review as ADAA combinations do not require additional target animal safety data or studies. Please attach the TS complete letter or appropriate MOC on this screen if you have such information.

2. Screen 3.2 Effectiveness

   Likewise with effectiveness, as with target animal safety, proposed combinations that qualify for review under the Animal Drug Availability Act do not require additional effectiveness data or studies. You should attach the technical section complete letter or appropriate MOC, as applicable, on this screen.

3. Screen 3.3 Chemistry, Manufacturing, and Controls

   For Chemistry, Manufacturing, and Controls, under the ADAA, CVM has historically not required submission of a CMC technical section and has considered CMC to be fully addressed by reference to the approved applications for the individual Type A medicated articles. This was a policy decision, as ADAA does not actually modify or reduce the CMC requirements for approval. CVM has recently re-evaluated the science behind that policy and

determined that, going forward, a CMC technical section will be required for ADAA feed-use combinations. The CMC requirements for approval include data to support homogeneity, non-segregation, and stability of the combination feed and a demonstration that each drug does not interfere with the FDA-approved feed assay method for each other drug in the combination.

Where separately approved Type A medicated articles are combined in dry medicated feeds, the requirements for homogeneity, non-segregation, and stability of the combination feed may typically be addressed through references to the existing data in the approved applications for the individual Type A medicated articles, with the rationale that addition of a small amount of another Type A medicated article is not likely to impact those properties in the feed. Additional data would be required for combination liquid feeds or free-choice feeds.

CVM strongly recommends sponsors request a presubmission conference under the INAD, prior to submission of the NADA, to discuss the specific requirements to be met for approval of their proposed ADAA feed-use combinations.

For further information on completing the CMC section of the NADA eSubmitter template, please view the webinar for how to complete a P-MC submission (i.e., a data submission for the CMC technical section under the INAD). That template and this section of the NADA template are the same.

4. Screen 3.4 Environmental Impact

Next we move to environmental impact. Typically, ADAA combination drug applications will qualify for a categorical exclusion under 21 CFR 25.33(a)(2), which is for combination of previously approved animal drugs. As with the CMC requirements, CVM strongly recommends sponsors request a presubmission conference under the INAD to discuss which categorical exclusion citation is most appropriate for your proposed combination. If you received confirmation during a presubmission conference that your proposed combination qualifies for a categorical exclusion, you will respond to the following sections as follows.

a. Select a claim of categorical exclusion.
b. Select the first option, that the proposed action does not increase the use of the animal drug.
c. Then, on the third screen, you will select the second option, that the drug product is a combination of previously approved animal drugs.
d. In the text box below, you will provide the indication, including the dosage, species, duration, frequency of use, etc. as would appear on the product labeling.
e. And, lastly, you will answer the following question to the best of your knowledge, if there any extraordinary circumstances that may have a significant effect on the quality of the human environment.

If you need further information on how to fill out this portion of the template, please view the P/NV webinar from this series or contact the Leader of the Environmental Safety Team.

5. Screen 3.5 Human Food Safety

   Next, for human food safety; with respect to the human food safety evaluation for these types of combination new animal drug applications, the Agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs in the combination interferes with the methods of analysis of another active ingredient or drug in the combination [section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act].

   As with the previous two sections, CVM strongly recommends sponsors request a presubmission conference under the INAD, prior to submission of the NADA, to discuss the specific requirements to be met for approval of their proposed ADAA feed-use combination.

   If you have additional questions when preparing a submission, please contact your PM for more information.

6. Screen 3.6 Labeling

   The next technical section addresses labeling. Because most labeling for a 180-day application will not be reviewed under the INAD, often times you will not have a technical section complete letter, as a result. If you do, please select "yes" and attach that document accordingly. If you do not, you will need to identify the type of labeling that you are submitting.

   Because Blue Bird labels are considered "representative labeling", you will select "Facsimile Labeling".

   And then respond, "yes" that this drug is used in a medicated animal feed.

   a. Screen 3.6.1

      On this screen you will identify the types of labeling included in the submission.

      (1) If your combination includes an antimicrobial drug of human importance as described in Guidance for Industry #209 and #213, you are required to include a veterinary feed directive with your application.

          CVM requests that you include the approved VFD for the Type A medicated article and a copy of the proposed draft VFD for the combination.

(2) CVM also encourages sponsors to include the approved Type A medicated article labels for the individual drugs used in the combination.

(3) If your product will utilize a Type B (or intermediate) label, please check that box.

(4) Additionally, you will need to provide Type C labeling for all proposed ADAA combinations and indications.

(5) And, if your product also requires a shipping label, you will need to check this box to provide copies for CVM review.

b. Screen 3.6.2

Based on your responses to the previous screen, you will have different options to attach different types of labeling. For this example, because I selected VFD, Type A, and Type C labeling, I am now prompted to attach those labeling pieces here by clicking on the box with the green plus sign under each section.

Once you have done this, you may proceed to the next screen.

7. Screen 3.7

For All Other Information you will provide a reference to the Drug Experience Report or DER for each of the Type A medicated articles used in the combination. In addition, if you have any pilot studies or investigative work using the combination, you should provide this information to CVM review if it has not previously been submitted. Please do so, again, by attaching the documents using the button with the green plus sign.

8. Screen 5.0

Lastly, on screen 5, if there are additional comments you would like to provide to CVM regarding this submission, you may enter text in the box or attach a PDF with your comments on this screen.

This concludes our walk-through demonstration of the 180-day NADA for an Animal Drug Availability Act combination. Next I will demonstrate in the template for the 60-day qualifying ADAA combinations.

V. Qualifying 60-day ADAA Combinations

Again, this portion of the webinar will discuss the differences in completing the NADA template for those combinations that qualify for review under the shortened 60-day timeline as approved under ADUFA IV. Again, I direct you to the webinar regarding those eligibility requirements for more information.

Here, we will pick up on Tab 3, Screen 1, as the information on the first 2 tabs is the same as was discussed in the earlier section of this webinar.

A. Screen 1.0 General Information

1. As before, you will attach your User Fee Cover Sheet and answer "yes" to the first question.
2. Because this is a 60-day qualifying combination, you will select "yes" to the second question.
3. Although this submission has the same timeline as an administrative NADA because labeling may be evaluated during this submission timeline, this is not considered an administrative NADA. So, please select "no".
4. As with before, this submission does reference other documents. In this case, it must reference an INAD under which the phased review was completed as well as the individual NADAs for each of the Type A medicated articles used in the combination.
5. Please then answer the questions regarding the patent and provide a description of the application.

B. Screen 1.1 Referenced Applications and Files

Like before, you will click "new" to add information for all of the applicable application files and types that have supportive information. In this case, the one difference is that the INAD should contain information for all four of the major technical sections. In addition, please provide the submission details here, such as the submission identifiers for memorandums of conference for presubmission conferences or technical section complete letters for P or data submissions.

And, as before, for any NADA you do not own, you must attach a right of reference.

C. Screen 1.3 60 Day ADAA Qualification

Next, and new to this template, is a qualification screen with six prompts to evaluate the six major requirements for qualification for review under the 60-day timeline.

The first question simply affirms that the application meets the basic criteria for review as an ADAA combination.

The second affirms that a presubmission conference was held and prompts you to provide the number of the Z submission.

The AOI technical section must, only, for the purposes of this submission, be experiencing the drug experience report. If there was additional all other information regarding this combination, it must have been submitted to the INAD.

You must affirm that you are attaching all of the appropriate representative Type B and/or C labeling and VFD, if applicable.

You must have confirmed with CVM prior to this submission that the application does qualify for a claim of categorical exclusion and that you do have a right of reference to all of the NADAs you do not own.

Once this screen is completed, if you can answer affirmatively to all questions, then your application for a 60-day review time clock, at least at the beginning of the review period.

D. Screen 2.0 Product Description

On this screen, as before, you will click "new" and provide the information for your proposed drug product.

E. Technical Sections

Again, you will select all of the boxes for the technical sections, as you will be providing references to your technical section complete letters or MOCs to confirm that these requirements have been met.

Then you will answer the question "yes" or "no" if the application is for a conditional approval.

On the following screens, all of the information that you provide should be in the form of a technical section complete letter or MOC. You will need to select "yes" and then attach to the submission the TSC or MOC, as appropriate for both target animal safety, effectiveness, CMC, and environmental impact. Human food safety is also to be answered in the affirmative and attach the technical section complete or MOC.

1. Screen 3.6 Labeling

   However, labeling is slightly different. Because review of the labeling prior to submission to the original NADA is not required, it is acceptable to submit labeling for review in the NADA. If you have received a technical section complete letter, please select "yes" and attach the document. If you have not, you will answer "no", identify again that this is representative labeling, and it's for use in medicated animal feed.

   As before, you will identify the types of labels that you are submitting and attach copies of each of those.

2. Screen 3.7 All Other Information

   If AOI exists beyond what was submitted to the DERs or drug experience reports for the individual Type A medicated articles, it must be reviewed under the INAD and result in a technical section complete letter. However, if no other information exists beyond what is contained in the DERs, you can attach a document with a statement referencing the DERs and a statement that no other AOI exists.

3. Screen 5.0 Comments

   And then, lastly, as before, you have additional comments you would like to provide to CVM regarding this submission, you may enter it in the text box or attach it as a PDF document.

And with that, we conclude this webinar. Thank you for your time.

All right, everyone, that concludes our webinar on ADAA combinations. I don't see any questions in the chat pod, but I would be happy to entertain any of those, or if you would like to come off mute, again I would be happy to address them at this time.

While waiting for any questions to come in, I just want to clarify that I notice that it's always interesting when you pre-record a webinar and then you have to sit and listen to yourself, you catch little things that you might would have worded a little differently or information you might have added. One thing I would want to add is that while it is perfectly allowable for labeling to be reviewed under the NADA and still qualify for a 60-day time review period, we do strongly recommend that sponsors submit that to the INAD as an M submission prior to submitting their NADA. And the reason for that is primarily because if you are coming in on a 60-day path, you want to stay on that path. And if there are significant revisions that are required to your labeling, that could easily result in having to have a major amendment which would then convert the submission from a 60- to a 180-day. So with the 60-day review for an M under the INAD, obviously you are going to be looking at saving yourself some time if you have some concerns that your labeling might not be in close enough to being in an approvable state when you are getting ready to submit that NADA. So, I just want to caution you that as much work as can be done under the INAD, the more likely you are to submit this as a 60-day and be able to stay on that review clock and get an approval within that time frame.