REVIEW OF 60-DAY ORIGINAL ANIMAL DRUG AVAILABILITY ACT OF 1996 (ADAA) FEED USE COMBINATION NEW ANIMAL DRUG APPLICATIONS (NADAs)

I. PURPOSE

As part of the Animal Drugs User Fee Act (ADUFA) IV reauthorization[1], effective October 1, 2018, the Center for Veterinary Medicine (CVM) agreed to reduce the review timeline from 180 to 60 days for eligible ADAA combination drugs used in or on animal feeds submitted as original new animal drug applications (NADAs) filed under section 512(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). (Note: the process for review of original ADAA feed use combination NADAs within 60 days is currently underway. Anything related to or tied to that process may be revised during the beta test and upon completion of the beta test. Policy and procedure documents will be revised accordingly during and upon completion of the beta test.)

This process differs from the 60-day administrative NADA process, because the review team is not only preparing the approval package for the combination, but is also reviewing the labeling, preparing the complete Freedom of Information (FOI) Summary, and completing a review of the Environmental Impact technical section during the 60-day timeline. Traditionally, the review of this information has either been completed under the phased review process under M, P, and Q submissions made to the investigational new animal drug (INAD) file for the proposed combination, and prior to the receipt of the administrative NADA, or has been submitted for review under a 180-day NADA.

This document describes the evaluation and processing of original ADAA feed use combination NADAs that may qualify for a reduced 60-day review timeline, including the following:

- Determining the eligibility of an original ADAA feed use combination NADA for the 60-day review process;

[1] As captured in 82 FR 49380, dated October 25, 2017. Language from the ADUFA IV reauthorization and draft recommendations that applies to the review of 60-Day ADAA combination original NADA applications are captured in Appendix 1 of this document.

- Determining/identifying the required documents that we need to receive from the sponsor and those we will prepare under the INAD before the original ADAA feed use combination NADA can be submitted;
- Describing the review process for completing the review of an original ADAA feed use combination NADA within the 60-day timeline; and
- Describing how we will handle those original ADAA feed use combination NADAs that initially qualify for a 60-day review timeline, but the timeline is increased to 100 or 180 days, because we find we require additional changes to the application through submission of a minor amendment.

II. ELIGIBILITY OF AN ORIGINAL ADAA FEED USE COMBINATION FOR A 60-DAY REVIEW TIMELINE

An original NADA application for an ADAA feed use combination is eligible for a 60-day review timeline when the following conditions are met and the application, as submitted, is both complete and accurate. These criteria are tightly aligned with the agreed upon language provided in the ADUFA IV reauthorization.

1. The ADAA feed use combination NADA is an original application and receives a submission identifier of A-0000. Reactivations and supplemental applications are not eligible for the 60-day review timeline.
2. The combination is administered in or on animal feed. Combinations administered via drinking water or any other dosage form are not eligible for the 60-day review timeline.
3. Each new animal drug included in the feed use combination has been **previously and separately approved** under section 512(b)(1) of the FD&C Act for the particular uses and conditions of use[2] for which they are intended in the combination. The requirement that the animal drugs be approved under section 512(b)(1) **excludes** generic animal drugs from consideration, as they are approved under section 512(b)(2) of the FD&C Act. It also **excludes** conditionally approved animal drugs, as they are approved subject to section 571 of the FD&C Act.
4. Each new animal drug is different from all other animal drugs in the proposed feed use combination and provides appropriate concurrent use for the intended target animal population.
5. The feed use combination contains no more than one antibacterial.[3]
6. Each active ingredient or new animal drug is intended for at least one use that is different from all other active ingredients or new animal drugs in the feed use

[2] Conditions of use may include, but are not limited to, the indication(s), dose, duration, frequency, and species or classes of species.
[3] 21 CFR 514.4(c)(1)(iii) excludes the classification of ionophores and arsenicals as antibacterials for the purposes of their inclusion in an ADAA combination in animal feed or drinking water.

combination (i.e., each individual drug brings a unique indication to the combination).

7. A presubmission conference (PSC) has been conducted under the INAD that was opened specifically for the ADAA feed use combination to discuss the approval requirements for the combination.

8. Specifically, for Human Food Safety (HFS), either:

    a. No data are needed (no tissue residue non-interference study is required) and this agreement is documented in the memorandum of conference (MOC) for the PSC; or

    b. A justification for not conducting a tissue residue non-interference study has been submitted, reviewed, and found acceptable under an INAD, before the submission of the original ADAA feed use combination application; or

    c. A tissue residue non-interference study has been submitted, reviewed, and found acceptable under an INAD, before the submission of the original ADAA feed use combination application.

9. As part of All Other Information (AOI) submitted to the original ADAA feed use combination NADA, the sponsor references the drug experience reports (DERs) submitted annually for each of the individually approved drugs included in the combination.

10. The original ADAA feed use combination NADA submission includes the following labeling components, as applicable to the combination:

    a. Type B medicated feed representative labeling;

    b. Type C medicated feed representative labeling; and

    c. veterinary feed directive.

11. The original ADAA feed use combination NADA submission includes a claim of categorical exclusion citing 21 CFR 25.33(a)(2) and certification that to the sponsor's knowledge there are no extraordinary circumstances. Extraordinary circumstances per 21 CFR 25.21 have not been previously identified by CVM; therefore, preparation of an environmental assessment (EA) is not required.

12. The original ADAA feed use combination NADA submission includes a copy of the PSC MOC in which the combination was previously discussed. The PSC should confirm which technical sections are satisfied (review of information or data to support a technical section is not required). If the review of information or data is required to support a technical section, that information should have been reviewed under the INAD for the combination (as a P submission) and a technical section complete letter issued.

13. A Right of Reference letter(s) to the NADA(s) not owned by the filing sponsor of the ADAA feed use combination application has been received by the agency, if applicable.

III. SUBMISSIONS TO THE INAD PRIOR TO THE SUBMISSION OF AN ORIGINAL ADAA FEED USE COMBINATION APPLICATION

A. Opening an INAD for the ADAA Feed Use Combination

Once the sponsor has identified a specific combination of drugs, the project manager (PM) will remind the sponsor to open an INAD file[4] to house the documents that will be used to support the approval of the proposed ADAA feed use combination. The INAD will contain the PSC MOC in which agreements are made and copies of the draft FOI Summary sections. This INAD file also may be used to submit any information to complete a technical section (if required) or labeling (if the sponsor chooses to submit labeling ahead of the NADA). While preferable that each proposed combination have its own INAD file, it is acceptable for multiple, related proposed combinations to share a single INAD file (e.g., a proposed four-way drug combination, which the drug sponsor might also intend to pursue approval of the related two- and three-way combinations).

CVM should not provide feedback that could be construed as agreements regarding a specific drug combination until an INAD has been opened and a PSC has been requested to discuss the feed use combination.

B. PSC for the ADAA Feed Use Combination

If a sponsor has not identified a specific combination or opened an INAD for the combination, CVM may only provide general comments regarding eligibility for the 60-day process and approval requirements for ADAA medicated feed use combinations during a PSC for an individual Type A medicated article. CVM may not discuss specific approval requirements for the ADAA medicated feed use combination and/or make agreements unless the specific combination is identified and an INAD has been opened for the combination.

When the sponsor is ready to discuss the ADAA approval requirements for the specific feed use drug combination, they should submit a PSC meeting request to the INAD for the combination. The discussion of the combination(s) may occur in one of the following ways:

- In combination with a PSC for one of the individual Type A medicated articles that is under development[5]; or
- In a separate PSC that only discusses the combination and is unrelated to the discussion of an individual Type A medicated article.

[4] See P&P 1243.4000 on information on opening an INAD file.

[5] For multiple projects (Type A medicated articles and/or combinations) to be discussed and captured under a single PSC, the sponsor must link the files in eSubmitter at the time that the meeting request is submitted, and a clear delineation of each discussion should be made in the associated MOC. If the PSC meeting materials reference multiple projects and the files were not linked at the time of the submission, then the sponsor should request that CVM void the submission and should link the files in eSubmitter when resubmitting the PSC meeting materials. If the sponsor does not link the files, then the PM will request amended meeting materials and specific discussions regarding the unlinked files should occur under a separate, future PSC meeting request.

The PM will invite each of the impacted review units [target animal division (TAD), Division of Human Food Safety (HFS), Environmental Safety Team, and Division of Manufacturing Technologies (DMT)], regardless of whether the sponsor specifically requests their presence, as the consult request will prompt each of the divisions to begin additional review work in preparation for the eventual receipt of a 60-day ADAA feed use combination NADA A-0000.

During the PSC for the specific ADAA feed use combination, CVM will address the approval requirements per ADAA for the specific feed use drug combination. In preparation for the PSC:

1. The TAD reviewer will confirm whether the proposed combination meets requirements outlined in section 512(d)(4)(D) of the FD&C Act, thus confirming that an assessment of the Effectiveness technical section is not needed.

2. The TAD reviewer will confirm that the proposed combination meets requirements outlined in section 512(d)(4)(B) of the FD&C Act, thus confirming that an assessment of the Target Animal Safety technical section is not needed. Alternatively, if the reviewer is aware of existing, well documented safety concerns to the target animal when the proposed drug combination is administered, then the reviewer should determine what target animal safety information or data are needed to support the combination approval.

3. The TAD reviewer will remind the sponsor to check for AOI. If any information is available, it should be submitted to the INAD a minimum of 80 days prior to the submission of the original ADAA feed use combination NADA. If information is submitted for review as part of the NADA, the submission will not qualify for a 60-day review timeline.

4. The Residue Chemistry Team reviewer will determine whether residue chemistry information or data are needed to support the combination approval.

5. The Toxicology Team and Microbial Food Safety Team reviewers will confirm that the proposed combination meets requirements outlined in section 512(d)(4)(A) of the FD&C Act, thus confirming that an assessment of the Toxicology and Microbial Food Safety sections of the HFS technical section are not needed.

6. The DMT reviewer will determine whether further manufacturing information or data are needed for the Chemistry, Manufacturing, and Controls (CMC) technical section to support the combination approval.

7. The Environmental Safety Team reviewer will complete an initial review to determine if the proposed combination(s) will be eligible for a categorical exclusion under 21 CFR 25.33(a)(2), citing no increase in use, for a combination of previously approved animal drugs. The reviewer will also evaluate whether extraordinary circumstance may exist per 21 CFR 25.21 that would require the preparation of an EA for the proposed chemical entities

intended to be included in the combination. This review will be documented as part of the consulting review for the PSC.

During the PSC, eligibility for the 60-day process and approval requirements for the specific ADAA medicated feed use combination should be discussed. Each technical section for the combination use will also be addressed. If additional information or data are needed to support the completion of a technical section, the MOC will document what is required. Alternatively, if a portion of or an entire technical section has been confirmed to require no further assessment, the MOC will document this.

C. P Submissions

If, during the PSC, it is determined that additional information or data are needed to support the completion of a technical section, the sponsor will be instructed to submit information or data to the INAD for the combination as a P submission.

To be eligible for the 60-day review process for an original ADAA feed use combination NADA, the review of all P submissions must have concluded and resulted in a Technical Section Complete letter prior to the sponsor's submission of the ADAA feed use combination original NADA.

D. M Submissions

If AOI beyond a reference to the DERs submitted annually for each of the individually approved drugs included in the combination is identified (i.e., types of information listed in section IV. of P&P 1243.4085), the sponsor must submit this information to the INAD for the combination as an M submission. The sponsor does not need to reference the DERs until the ADAA feed use combination original NADA is submitted. To be eligible for the 60-day review process for an original ADAA feed use combination NADA, the review of this M must have concluded and resulted in a Technical Section Complete letter prior to and within 90 days of the sponsor's submission of the ADAA feed use combination original NADA.

The sponsor may also choose to, but is not required, to submit labeling for the combination to the INAD as an M submission.

E. Preparation of the Draft FOI Summary Sections

Because the process of reviewing a 60-day original ADAA feed use combination NADA differs[6] from the phased review under an INAD, the procedure for preparing the FOI Summary for the 60-day ADAA feed use combination is different. The INAD for an ADAA feed use combination submitted for the 60-day NADA review process will likely not include M submissions that, under the phased review process, normally would signal the need to generate a Q submission to draft a

[6] For an administrative NADA, labeling (and AOI) must be submitted as an M submission under an INAD for review and agreement by CVM (i.e., it is not acceptable to review new labeling under the administrative NADA. For a 60-day original ADAA feed use combination NADA, it is acceptable and expected that the labeling will not be reviewed until the application is submitted. While the sponsor may choose to submit labeling as an M submission under the ADAA feed use combination INAD, they do not have to.

complete FOI Summary. Therefore, portions of the FOI Summary[7] will need to be drafted under separate Q submissions[8] to ensure that the complete FOI summary can be drafted quickly and efficiently once the 60-day original ADAA feed use combination NADA is received.

To facilitate this process, by the date of the ONADE premeeting for the PSC for the ADAA feed use combination, the TAD reviewer and Residue Chemistry Team reviewer will perform the following tasks, respectively:

1. The TAD reviewer will open a Q submission to draft the following sections of the FOI Summary for an ADAA combination based on the information available at that time:

   a. Title page, except for the NADA number,

   b. Section I. General Information,

   c. Section II. Effectiveness,

   d. Section III. Target Animal Safety, and

   e. Section VI. Agency Conclusions.

   The TAD Q submission will also include, as available, the following for each of the single ingredients being proposed for use in the feed use combination: the date of the approval, the submission number under which the approval was completed, the date of the FOI Summary, the date the approval was posted in the FEDERAL REGISTER (formatted as <volume no.> FR <pg no.>, dated <mm/dd/yyyy>), and appropriate CFR citation used to establish effectiveness and target animal safety. This information will aid the TAD reviewer in preparing the approval package documents under the future ADAA feed use combination NADA.

2. If the Residue Chemistry Team reviewer determines that no new information is needed to support the Residue Chemistry section, then the Residue Chemistry reviewer will open a Q submission to draft the Human Food Safety section of the FOI Summary. The Division of HFS will follow their normal process of requesting consulting reviews from the Toxicology and Microbial Food Safety Teams to complete relevant portions of this section.

   If, however, the Residue Chemistry Team reviewer determines that additional information to support the Residue Chemistry section will need to be submitted for review under a P submission to the INAD, then a Q submission will not be opened at this time. Instead, the Division of HFS will follow their normal process of drafting the HFS section of the FOI summary during the review of the P submission.

[7] See P&P 1243.5762 for additional information on preparing an FOI Summary for ADAA combinations.
[8] See P&P 1243.3250 for information on opening a Q submission.

Whether completed under the Q or P submission, the HFS draft FOI Summary will also include, as available, the following for each of the single ingredients being proposed for use in the feed use combination: the date(s) of the approval, the submission number(s) under which the approval was completed, the date(s) of the FOI Summary(ies), the FEDERAL REGISTER citation(s) (formatted as <volume no.> FR <pg no.>, dated <mm/dd/yyyy>), and the appropriate CFR citation(s) used to establish human food safety (i.e., toxicology, residue chemistry, microbial food safety, and analytical method for residues). This information will aid the TAD reviewer in preparing the approval package documents under the future original ADAA feed use combination NADA.

The Q submissions will be opened no later than the date of the CVM premeeting, and the due date will be set to 60 days after the date of the PSC meeting. This timeline ensures that the Q submissions will be complete no later than Day 15[9] of the timeline for the original NADA application if the sponsor submits the application immediately upon receipt of the MOC. Each Q submission will be closed out as a "FNR with Memo" and option for "Draft FOI Summary text" to upload the prepared draft FOI Summary text will be selected. Copies of these draft sections of the FOI Summary should not be provided to the sponsor for comment prior to closing out the Q submissions.

If the original NADA application is received while the Q submissions are still open, the HFS reviewer should close out the Q submission by the due date to ensure that the TAD reviewer has the draft FOI language early during the 60-day review time. The HFS reviewer will notify the TAD reviewer for the NADA when the Q submission is closed out and will attach a courtesy copy of the draft FOI Summary language to the notification email.

The review team may also use key times during the review of the new Type A medicated article (e.g., the end game meeting under the INAD; receipt of the original NADA for the single ingredient) to reassess the original reviews completed under the Z or Q submissions for the ADAA feed use combination to determine whether the original decisions still support the approval of the combination application. If changes have occurred that warrant documentation, then a new review will be prepared. If the changes will impact CVM's ability to approve the ADAA feed use combination (e.g., changes to the conditions of use for one or more of the drugs proposed for use in the combination), then the PM will be notified and will work with the review team to determine the appropriate next steps.

IV. REVIEW OF THE ORIGINAL ADAA FEED USE COMBINATION NADA

A. Initial Processing

1. Initial check for eligibility of the ADAA feed use combination NADA for a 60-day review clock

[9] Day 15 coincides with Day 60 after the MOC (presuming the MOC does not go out earlier than the CVM due date, 45 days after the PSC) is issued and Day 60 of the FOI Summary Q submissions.

Once assigned to the TAD, an initial assessment of the submission will be performed to determine whether it is eligible for the 60-day review clock. If the application does not meet the eligibility criteria, the application will be transitioned to a 180-day review clock (see section V below) and will follow the normal procedures for reviewing a 180-day NADA.

This eligibility check is a separate process from refuse to file (RTF) assessment (as described in P&P 1243.2050) because it is possible that the eligibility requirements for the 60-day review may not be met, but the application can be filed. However, the eligibility check and RTF assessment should be conducted at the same time because of the reduced review timeframe.

a. Verify the application is assigned to the correct TAD. If the application is incorrectly assigned, identify the correct TAD and submit a STARS Correction Request form.

b. Verify that each of the individual drugs proposed for use in the combination has been individually and separately approved under section 512(b)(1) of the FD&C Act for the particular uses and conditions of use for which they are intended in the combination.

c. Verify that the following are included in the eSubmitter report:

    i. A copy of the PSC MOC held under the INAD for the ADAA combination and any Technical Section Complete letters (if applicable) to address the completion of all major technical sections, except for Environmental Impact.

    ii. AOI includes a statement referencing the DERs submitted annually for each of the individually approved drugs included in the combination. AOI also includes either a statement that a search for additional information was performed and no information exists, or that AOI information was submitted and reviewed under the INAD and a copy of the Technical Section complete letter is included in the approval package.

    iii. All proposed labeling components.

    iv. Claim for a categorical exclusion under 21 CFR 25.33(a)(2), no increase in use for a combination of previously approved animal drugs, including a certification that to the sponsor's knowledge no extraordinary circumstances exist that may significantly affect the quality of the human environment (21 CFR 25.21).

    v. If *a*pplicable, a copy(ies) of the Right of Reference letter(s) or the principal submission identification number under which the Right of

Reference letter(s) was submitted to CVM. The reviewer will review the wording of the Right of Reference letter(s) to ensure that the information it references will support the specific drug combination being considered for approval (e.g., is for the drug product included in the combination; reference extends to the dosage and indication intended for use in the combination).

2. Request consulting reviews

   The TAD reviewer will request consulting reviews from the following groups within five days of receipt using the current office policy (P&P 1243.3200):

   a. A scientific reviewer within the TAD to review the labeling components. (Note, a scientific reviewer should be consulted only if they are not the primary reviewer for the submission; for example, if a consumer safety officer (CSO) is the primary reviewer.)

   b. The Feed and Topical Team (HFV-141; for combinations intended for use in terrestrial species) or the Biotherapeutics Team (HFV 144; for combinations intended for use in aquaculture species) to review the labeling components.

   c. The Residue Chemistry Team (HFV-151) to:

      i. Reconfirm any agreements made under the PSC or conclusions made under the phased review process.

      ii. Review the labeling components for information relevant to residue chemistry.

      iii. Confirm that the residue chemistry draft FOI Summary language prepared under the Q or P submission of the associated INAD is still acceptable and reference the appropriate Q or P submission in their consulting review back to the TAD reviewer.

      iv. Confirm, via email with the Toxicology and Microbial Food Safety teams, that the toxicology and microbial food safety draft FOI Summary language prepared under the Q or P submission of the associated INAD is still acceptable.

   d. The Environmental Safety Team (HFV-162) to review the request for a categorical exclusion from the requirement to prepare an EA.

      The environmental safety reviewer will refer to the consulting review completed during the PSC held for the combination. The reviewer will determine whether any additional information has become available since that review was conducted with respect to the existence of extraordinary

circumstances (21 CFR 25.21) and evaluate whether the combination is eligible for a categorical exclusion under 21 CFR 25.33(a)(2).

e. The Medicated Feeds Team (HFV-226) to review the labeling components.

B. Reviewing the A-0000 Submission

If the submission meets the eligibility criteria, is sufficient for review upon receipt, and does not require amending, then the review time is 60 days and the review team should follow the 60-day review timeline (see section IV.B.1 below).

However, if an amendment(s) is needed, the timeline will be extended by 40 days (see section IV.B.2 below) or by 120 days (section IV.B.3 below).

1. 60-day review timeline

a. The TAD reviewer will prepare the approval package per P&P 1243.3800.

i. By Day 8, the TAD reviewer will request the FR notice from OD's Policy and Regulations Staff (HFV-6), and either request from OS&C Marketed Product Information Team (HFV-212) or complete the DER status check.

ii. If the FOI Summary Q submissions are still open under the INAD, the TAD and HFS reviewers for the Q submission will close the submission by Day 15[10] of the review timeline for the 60-day NADA. The HFS reviewer will notify the TAD reviewer once they have closed the Q submission.

iii. By Day 20, the TAD reviewer will have prepared the complete draft FOI Summary.

iv. Review of the draft FR notice and FOI summary will be completed by the TAD's division management by Day 24.

v. By Day 24, the TAD reviewer will email a copy of the complete draft FOI Summary and FR notice to the Division of HFS Division Management for final concurrence. Their concurrence and/or edits for both documents will be emailed to the TAD reviewer by Day 30.

vi. Optional: By Day 24, the TAD reviewer can provide a courtesy copy of the draft FOI Summary to the sponsor for review. If a courtesy copy is provided to the sponsor for review, the sponsor should return the draft FOI Summary with any comments by Day 27.

[10] Day 15 coincides with Day 60 after the MOC is issued and Day 60 of the FOI Summary Q submissions.

b. The consulting reviewers will complete their reviews and return the consults in Appian by Day 30 according to the procedures in P&P 1243.3029.

c. Once the TAD reviewer confirms that all consulting reviews conclude that the labeling and categorical exclusion are acceptable as submitted, they will complete review and finalize the draft approval package by Day 32 and begin routing it through the final approval package review process.

   If any of the consulting reviews conclude that the submission is unacceptable as submitted and an amendment is being considered, the TAD reviewer will follow the process outlined in sections IV.B.2 or 3 below, as applicable.

d. The approval package will be assembled and routed in accordance with 1243.3800 and using the 60-day ADAA combination timeline.

2. Changing the review timeline from 60 days to 100 days (i.e., a 100-day timeline)

The timeline will be extended to 100 days if the need for minor changes are identified during the labeling review. This is an extension of the review clock, not a resetting of the clock to 100 days upon receipt of the amendment.

a. The TAD reviewer will follow the steps outlined in sections IV.B.1.a and b above.

b. If one or more of the reviews concludes that the labeling is unacceptable, but could be fixed with minor changes, the TAD reviewer will prepare the amendment request.[11]

   Minor changes to the labeling components are considered those that the TAD reviewer can easily review without requesting an additional consulting review. For example, a minor change may include misspelled words, rearrangement of sections, or the addition of missing statements on the Blue Bird label(s) that originate from one or more of the individual from the Type A medicated article labels.

c. The TAD reviewer will email the amendment request to the sponsor by Day 40. In addition to the changes needed to the labeling, the amendment request should notify the sponsor that the review clock will be changed from 60 to 100 days.

   The CVM due date in STARS will automatically update to align with the 100-day timeline when the amendment is received. To maintain the 100-

[11] See P&P 1243.3026 for information on amending STARS submissions.

day review timeline, the sponsor must return the amendment by no later than 10 days from the date the amendment request is made; the TAD reviewer and team leader may elect to provide the sponsor less than a 10-day turn around depending on the number of labels being amended.

By Day 60, the TAD reviewer will review the amendment. If the labeling is confirmed to be acceptable as amended, the TAD reviewer will complete review and update and finalize the draft approval package by Day 66. The approval package will be assembled and routed through the final review process in accordance with P&P 1243.3800 and using the 100-day ADAA combination timeline.

If an update to the draft FR notice is needed to incorporate changes made to the labeling, the TAD reviewer will request the revisions from the CVM Policy and Regulations Team (HFV-6) by Day 60; the revised copy will be returned to the TAD reviewer by Day 65.

3. Changing the review timeline from 60 or 100 days to 180 days (i.e., a 180-day timeline)

The timeline will be extended to 180 days if the following situations are encountered:

- Major changes to the labeling, including those that would require additional consulting reviews (e.g., missing entire sections; incorrect calculations to the mixing directions);
- Additional amendments to labeling beyond the first amendment;
- The original amendment to labeling is received more than 10 days after requested;
- An amendment is required for any technical section besides labeling; or
- AOI submission includes information beyond a reference to the DERs submitted annually for each of the individually approved drugs included in the combination.

Note: This is an extension of the review clock, not a resetting of the clock to 180 days upon receipt of the amendment. For information on changing the timeline to 180 days in Appian, see section V. below.

a. The TAD reviewer will follow the steps outlined in sections IV.B.1 and 2 above.

b. If the review team encounters one of the above-listed scenarios, then the review period should be changed to 180 days:

i. For major changes to the labeling: The TAD reviewer will update the review time in Appian from 60 to 180 days by Day 40. The TAD reviewer will also email the amendment request to the sponsor by Day 40.

ii. For additional amendments beyond the first, those amendments received late, or for AOI that needs to be reviewed: The TAD reviewer will update the review time from 100 to 180 days in Appian by Day 70 if additional minor amendments are determined to be needed. The TAD reviewer will email the amendment request to the sponsor by Day 70.

c. If a consulting reviewer needs to review the amendment, the TAD reviewer will request a second consulting review from the appropriate consulting reviewers within 5 days of receiving the amendment request, and by no later than Day 75. The second round of consulting reviews will be returned by Day 130.

d. By Day 140, the TAD reviewer will review the amendment. If the labeling is confirmed to be acceptable as amended, the TAD reviewer will complete their review and finalize the draft approval package by Day 146. The approval package will be assembled and routed through the final review process in accordance with P&P 1243.3800 and using the 180-day ADAA combination timeline.

i. If an update to the draft FR notice is needed to incorporate changes made to the labeling, the TAD reviewer will request the revisions from the CVM Policy and Regulations Team by Day 140; the revised copy should be returned to the TAD reviewer by Day 145.

V. APPIAN PROCESS FOR CHANGING THE REVIEW TIMELINE

If it is determined that the submission is not eligible for a 60-day review (i.e., does not meet the eligibility requirements as listed in section II above; is missing components upon submission; or requires amendments), the TAD reviewer prepares the Review Time Change letter template to inform the Sponsor that the review timeline has been changed. The TAD reviewer should include the TL and DD in the sign-off chain in the Appian Review Time Change workflow. The option to issue correspondence should be selected in Appian and the letter should be uploaded. Completing the Appian workflow updates the review period is in STARS. Refer to the Appian User Guide Internal information redacted. for instructions on completing the Review Time Change.

VI. REFERENCES

CVM Program Policies and Procedure Manual

1243.3026 - Amending STARS Submissions

1243.3029 - Closing Out a Consulting Review for STARS Submissions

1243.2050 - Refuse to File and Refuse to Review

1243.3200 - Routing a Request to Obtain a Review of an INAD, JINAD, ANAD, NADA, or VMF Submission

1243.3250 – Q submissions Agency-Initated Actions

1243.3800 - Preparing and Processing an Approval Package

1243.4000 – Processing a Request to open a (J)INAD File

1243.5762 – Freedom of Information (FOI) Summary for an ADAA Combination New Animal Drug Application

Other References

Review Time Change Letter template

PM Timeline for 60-day ADAA Combination Original Applications

VII. VERSION HISTORY

October 1, 2018- Original version

APPENDIX 1: LANGUAGE FROM THE ADUFA IV REAUTHORIZATION AND DRAFT RECOMMENDATIONS THAT PERTAINS TO THE REDUCTION OF THE REVIEW TIMEFRAME FROM 82 FR 49380, DATED OCTOBER 25, 2017

The Agency will review and act on 90 percent of qualifying ADAA combination medicated feed applications within 60 days after the submission date when all of the following conditions are met:

i. Basic regulatory requirements for an ADAA combination medicated feed application has been met as outlined in 21 CFR 514.4(c)(2)(ii)

ii. A presubmission conference has been conducted and either:

   a. No data (no tissue residue non-interference study is required) are needed and this agreement is documented in the memorandum of conference for the presubmission conference; or

   b. a justification for not conducting a tissue residue non-interference study has been submitted, reviewed, and found acceptable under an INAD, prior to the submission of the ADAA combination medicated feed application; or

   c. a tissue residue non-interference study has been submitted, reviewed and found acceptable under an INAD, prior to the submission of the ADAA combination medicated feed application.

iii. No effectiveness or target animal safety data are required.

iv. No manufacturing data requirements - sponsor can address in meeting assay non-interference, but data submission is not required.

v. All other information is referenced to previous drug experience reports.

vi. Sponsor makes submission and it includes: Representative (Blue Bird) labeling, Veterinary Feed Directive (if applicable).

   i. Includes a request for categorical exclusion from the need to prepare an environmental assessment (EA); i.e., no EA required.

   ii. Reference to presubmission conference.

   iii. Right of reference (if applicable) to NADA(s) not owned by the filing sponsor of the ADAA combination medicated feed application has been received by the Agency.

Review and act on 90 percent of ADAA medicated feed combination applications within 100 days if the application was accepted for the 60-day timeframe and there is a need for minor amendments.

If any of the above conditions cannot be met, the ADAA combination application performance metric will be placed in the original NADA application cohort with a 180-day review timeframe.