REVIEW OF NADA AND ANADA LABELING SUPPLEMENTS

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I. PURPOSE

This document establishes procedures that assure the consistent, timely, and accurate review and processing of labeling supplements described in 21 CFR 514.8(c)(3)(i) and (ii). In general, these supplements are of the kind that either increase or do not decrease the assurance of the safe use of the drug.

II. SCOPE

21 CFR 514.8 describes the types of labeling supplements that are the subject of this document. You should review the relevant parts of the regulation below to determine whether this document applies to the particular supplement you are reviewing:

514.8 Supplements and other changes to an approved application.

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(c) Labeling and other changes to an approved application

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(3) Labeling changes to be placed into effect prior to receipt of a written notice of approval of a supplemental application.

(i) Labeling changes of the following kinds that increase the assurance of drug safety proposed in supplemental applications must be placed into effect immediately:

(A) The addition to package labeling, promotional labeling, or prescription drug advertising of additional warning, contraindication, adverse reaction, and precaution information;

(B) The deletion from package labeling, promotional labeling, or drug advertising of false, misleading, or unsupported intended uses or claims for effectiveness; and

(C) Any other changes as directed by FDA.

(ii) Labeling changes (for example, design and style) that do not decrease safety of drug use proposed in supplemental applications may be placed into effect prior to written notice of approval from FDA of a supplemental application.

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III. ASSIGNING PRIMARY REVIEW RESPONSIBILITIES

Target animal division (TAD) personnel have primary review responsibilities for the review and processing of labeling supplements. For purposes of this document, "target animal division" means the Divisions of Therapeutic Drugs for Non-food Animals, Production Drugs, and Therapeutic Drugs for Food Animals and the Generic Animal Drugs Team. Consumer Safety Officers (CSO) are the TAD personnel that have primary review responsibilities for these supplements. However, they will consult with scientific reviewers and their managers as scientific or process issues warrant.

IV. GENERAL DESCRIPTION OF THE REVIEW PROCESS

TAD personnel review and compare the labeling changes proposed by the sponsor and any other additional labeling changes to the current approved labeling to determine if the changes in labeling are acceptable. If the approved labeling for the supplemented product exists in Volume 0, the review process for these supplements is less complicated and consists primarily of comparing the proposed labeling in the

supplement with that found in Volume 0.[1] If Volume 0 does not exist or if the labeling for the product that is being supplemented is not in Volume 0, then the TAD personnel must first establish exactly what the currently approved labeling for the application and product is before the review of the supplement can begin.

In the generic animal drug supplement review process, TAD personnel must compare the proposed generic labeling with the current approved reference product labeling, as well as the latest approved ANADA labeling. Each of these are found in a Volume 0 or, if one does not exist, the ANADA and NADA jackets.

V. REVIEW OF A SUPPLEMENT WHEN VOLUME 0 EXISTS

A. Determine if the sponsor has addressed any outstanding label changes requested by the Office of Surveillance and Compliance (OSC)

The Division of Surveillance (DS) has developed a spreadsheet containing current OSC requests for labeling changes. Contact them to get more information. The TAD personnel should determine whether the outstanding label change requests, if any, identified in the spreadsheet are incorporated in the labeling for the pending supplement.

B. Perform a comparison of all components of the current approved labeling (Volume 0) and the proposed labeling from the supplement

The TAD personnel will identify the following:

- The differences between the approved and proposed labeling, and
- Any needed changes to the Code of Federal Regulations (CFR) citation for the approval. Use a printed copy of the eCFR citation for this evaluation.[2]

[1] Volume 0 is the reference copy of all components of the currently approved labeling for the application.
[2] The most current copy of the approval regulation is located in the electronic Code of Federal Regulations (eCFR; http://ecfr.gpoaccess.gov).

C. Determine if the supplement can be approved

1. The supplement can be approved

   Proceed to section V.D.

2. The supplement may be amended

   If we cannot approve the supplement as submitted, determine whether the sponsor can amend the application in a timely manner to correct the observed deficiencies.[3] If we can approve the application as amended, proceed to section V.D., otherwise proceed to section V.C.3.

3. The supplement cannot be approved

   If it is not possible to approve this supplement because of unacceptable changes in the labeling either:

   - requested by the sponsor in this supplement, or
   - there are other additional changes to the labeling that have been made since approval,

   then prepare an incomplete letter and the necessary supporting review documentation (e.g., consulting review from scientific reviewers, management, or both) outlining the unacceptable label changes.

D. For supplements that can be approved

The TAD personnel will:

1. Prepare a Memorandum Recommending Approval (MRA) that supports the approval of the supplement.[4] The MRA will:

   a. Document all of the labeling changes requested by the sponsor.

[3] See P&P 1243.3026 for information related to requesting and processing submission amendments.
[4] Use the office template to create the MRA. Instructions for finding and using templates are located on the ONADE Reviewer's Reference Page under Review Aids/Approved Products on the ONADE Templates page.

b. In addition to the changes requested by the sponsor, verify if any of the following specific aspects of the labeling have been changed so that changes to the Center's Database of Approved Animal Drugs can be identified:

   i. Proprietary name,

   ii. Trademark or registration mark (e.g., ™ or ®) associated with the proprietary name,

   iii. Wording of any indication,

   iv. Species of bacteria or parasites named in any indication,

   v. Wording of any caution, precaution, or warning statements,

   vi. Name or address of the sponsor, or

   vii. Patent information, including deleting patent information from labeling,

c. State whether there are any additional changes between the proposed and currently approved labeling, other than those specifically requested by the sponsor (list only substantive changes).

d. State affirmatively that the changes in the labeling requested by the sponsor in this supplement , and any other additional changes the sponsor has made from the approved labeling that were found because of our comparison, are acceptable, and

e. State if there are changes to the labeling the sponsor should make in a future supplement (e.g., addition of any warning or caution statements).

The Team Leader will review the MRA, the outcome of the labeling comparison, and eCFR citation with the TAD personnel to reach concurrence on whether the revised labeling is approvable.

2. Prepare the approval letter

   Use the Labeling Supplement Approval Letter template to prepare a letter granting approval of the supplement.[5]

3. Determine the need for a Freedom of Information (FOI) Summary, FEDERAL REGISTER (FR) Notice, or both.

   a. FOI Summary

      The approval of the supplement needs an FOI Summary only when the supplement has a significant impact on how the drug is used, or requires significant review of data.[6]

   b. FR Notice

      An FR Notice is needed only when a labeling supplement causes a change in the existing CFR citation for the approved drug. When this occurs, send the Regulations and Policy Staff a request to prepare a draft FR Notice.

4. Complete the STARS "Review Summary" field.

   This field should contain information that generally documents our finding and actions regarding the supplement.

5. Appropriate routing procedures

   When the approval package is complete and in final, the following routing procedure should be used to ensure that the approval is executed properly.

[5] Use the office template to create the approval letter. Instructions for finding and using templates are located on the ONADE Reviewer's Reference Page under Review Aids/Approved Products on the ONADE Templates page.
[6] See P&P 1243.5761.

a. For the Divisions of Therapeutic Drugs for Non-food Animals, Production Drugs, and Therapeutic Drugs for Food Animals use the following:

HFV-1XX (TAD Personnel)
HFV-1XX (Team Leader)
HFV-1XX (Division Director)
HFV-107 (QAT) [The QAT will review the FR Notice if present; otherwise, will process as with other approvals.]
HFV-190
HFV-199

b. For the Generic Animal Drug Team use the following:

HFV-104 (GADT Personnel)
HFV-104 (Team Leader)
HFV-107 (QAT) [The QAT will review the FR Notice if present; otherwise, will process as with other approvals.]
HFV-190
HFV-199

6. Send e-mail to the DS where appropriate

If ONADE identifies additional changes to the labeling that should be incorporated into a future supplement, the TAD personnel will send an e-mail to the DS detailing the labeling changes needed in a future supplement immediately before the TAD forwards the final action package to the DCU. For Type A medicated articles and medicated feeds, the TAD personnel will also include the Division of Animal Feeds (DAF) on the email. The TAD will include a copy of the e-mail on yellow paper in Folder B of the approval package.

DS files the e-mail in the Drug Experience Report (DER) records and sends a letter to the sponsor detailing the new changes that CVM wants the sponsor to request in their next supplement. The timeliness in which the sponsor must submit that next supplement will be determined jointly between ONADE and OSC personnel. DS sends this letter within 30 days after receiving the e-mail from the QAT announcing the approval of a supplement. DS files a copy of the letter to the sponsor in the appropriate DER, ANADA or NADA, and on the R:\drive.

7. Annotate the ONADE Final Action Form

   In the "Comments/Instructions to DCU" box, identify from which copy of the submission the copy of the labeling components were removed. Indicate that you are returning obsolete labeling components that are to be destroyed.

VI. REVIEW OF A SUPPLEMENT WHEN VOLUME 0 DOES NOT EXIST

A. Request reviews from OSC personnel

TAD personnel should issue all consulting review requests through STARS within five days of the CVM Received Date.

1. For dosage form products

   a. The TAD personnel are responsible for:

      i. Requesting a consulting review (A1 Package) from DS, and

      ii. Including the appropriate directions in the "Action Requested" section on the DCU Routing Slip:

      For NADAs, include "Please review this supplement to determine if the sponsor has made all of the changes to the labeling that you previously requested in your DER records. Clearly identify in your review any changes the sponsor must incorporate into their labeling before we can approve this supplement and those labeling changes the sponsor can address in a future supplement."

      For ANADAs, include "Please review this supplement to determine if the generic and pioneer sponsors have made all of the changes to the labeling that you previously requested in your DER records. Clearly identify in your review any changes the sponsor must incorporate into their labeling before we can approve this supplement and those labeling changes the sponsor can address in a future supplement."

b. The DS personnel are responsible for:

i. Determining if the sponsor has made all of the changes to the labeling that DS previously requested in the DER records,

ii. Clearly identifying those changes that the sponsor must incorporate into their labeling before we can approve the pending supplement and those labeling changes the sponsor can address in a future supplement,

iii. Completing and returning the paper copy of the consulting review through STARS to the TAD personnel within the assigned consulting review timeframe, and

iv. Sending an electronic copy of the review directly to the TAD personnel when the paper copy is returned.

2. For Type A medicated articles and/or medicated feeds

a. The TAD personnel are responsible for:

i. Requesting a consulting review (A1 Package) from the DAF, and a secondary consulting review (A2 Package) from DS, and

ii. Including the appropriate directions in the "Action Requested" section on the DCU Routing Slip:

For DAF review requests, include "Please review the labeling enclosed with this supplement. Clearly identify in your review any changes the sponsor must incorporate into their labeling before we can approve this supplement and those labeling changes the sponsor can address in a future supplement."

For DS review requests of NADAs, include "Please review this supplement to determine if the sponsor has made all of the changes to the labeling that you previously requested in your DER records."

For DS review requests of ANADAs, include "Please review this supplement to determine if the generic and pioneer sponsors have

made all of the changes to the labeling that you previously requested in your DER records."

b. The DS personnel are responsible for:

i. Determining if the sponsor has made all of the changes to the labeling that DS previously requested in the DER records,

ii. Completing and returning the paper copy of the consulting review through STARS to the DAF personnel within the assigned consulting review timeframe, and

iii. Sending an electronic copy of the review directly to the DAF personnel when the paper copy is returned.

c. The DAF personnel are responsible for:

i. Clearly identifying those changes that the sponsor must incorporate into their labeling before we can approve the pending supplement and those labeling changes the sponsor can address in a future supplement,

ii. If any OSC review differences exist, leading (and documenting) the discussion resolving those differences so that the DAF consulting review presents a unified OSC review position to ONADE,

iii. Completing their consulting review and returning the paper copies of all OSC consulting reviews through STARS to the TAD personnel within the assigned consulting review timeframe, and

iv. Sending an electronic copy of all OSC reviews directly to the TAD personnel when the paper copies are returned.

B. Determine the currently approved labeling for the application

TAD personnel will use STARS to determine the most recent approved versions of all labeling components. For many applications (un-supplemented original approvals and many significant supplemental approvals), the most recent approval will likely contain all components of labeling. In other applications, the currently approved components of labeling may exist in multiple supplements because the

complete labeling may not have been submitted and approved when only minor changes were made to individual labeling components. In applications that have a complex approval history, determining the currently approved labeling will require substantial investigative effort.

C. Perform a comparison of all components of the current approved labeling and the proposed labeling from the supplement

The TAD personnel will identify the following:

- The differences between the approved and proposed labeling, and
- Any needed changes to the Code of Federal Regulations (CFR) citation for the approval. Use a printed copy of the eCFR citation for this evaluation.[7]

D. Determine if the supplement can be approved

1. The supplement can be approved

   Proceed to section VI.E.

2. The supplement may be amended

   If we cannot approve the supplement, determine whether the sponsor can amend the application in a timely manner to correct the observed deficiencies.[8] If we can approve the application as amended, proceed to section VI.E., otherwise proceed to section VI.D.3.

3. The supplement cannot be approved

   If it is not possible to approve this supplement because of unacceptable changes in the labeling either:

   - requested by the sponsor in this supplement, or

[7] The most current copy of the approval regulation is located in the electronic Code of Federal Regulations (eCFR; http://ecfr.gpoaccess.gov).
[8] See P&P 1243.3026 for information related to requesting and processing submission amendments.

- there are other additional changes to the labeling that have been made since approval,

then prepare an incomplete letter and the necessary supporting review documentation (e.g., consulting review from scientific reviewers, management, or both) outlining the unacceptable label changes.

E. For supplements that can be approved

The TAD personnel will:

1. Prepare a Memorandum Recommending Approval (MRA) that supports the approval of the supplement.[9] The MRA will:

   a. Document all of the labeling changes requested by the sponsor.

   b. In addition to the changes requested by the sponsor, verify if any of the following specific aspects of the labeling have been changed so that changes to the Center's Database of Approved Animal Drugs can be identified:

      i. Proprietary name,

      ii. Trademark or registration mark (e.g., ™ or ®) associated with the proprietary name,

      iii. Wording of any indication,

      iv. Species of bacteria or parasites named in any indication,

      v. Wording of any caution, precaution, or warning statements,

      vi. Name or address of the sponsor, or

      vii. Patent information, including deleting patent information from labeling,

[9] Use the office template to create the MRA. Instructions for finding and using templates are located on the ONADE Reviewer's Reference Page under Review Aids/Approved Products on the ONADE Templates page.

c. State whether there are any additional changes between the proposed and currently approved labeling, other than those specifically requested by the sponsor (list only substantive changes).

d. State affirmatively that the changes in the labeling requested by the sponsor in this supplement, and any other additional changes the sponsor has made from the approved labeling that were found because of our comparison, are acceptable, and

e. State if there are changes to the labeling the sponsor should make in a future supplement (e.g., addition of any warning or caution statements).

The Team Leader will review the MRA, the outcome of the labeling comparison, and eCFR citation with the TAD personnel to reach concurrence on whether the revised labeling is approvable.

2. Prepare the approval letter

Use the Labeling Supplement Approval Letter template to prepare a letter granting approval of the supplement.[10]

3. Determine the need for a Freedom of Information (FOI) Summary, Federal Register (FR) Notice, or both.

a. FOI Summary

The approval of the supplement needs an FOI Summary only when the supplement has a significant impact on how the drug is used, or requires significant review of data.[11]

b. FR Notice

An FR Notice is needed only when a labeling supplement causes a change in the existing CFR citation for the approved drug. When this occurs, send the Regulations and Policy Staff a request to prepare a draft FR Notice.

[10] Use the office template to create the approval letter. Instructions for finding and using templates are located on the ONADE Reviewer's Reference Page under Review Aids/Approved Products on the ONADE Templates page.
[11] See P&P 1243.5761.

4. Complete the STARS "Review Summary" field.

   This field should contain information that generally documents our findings and actions regarding the supplement.

5. Appropriate routing procedures

   Once the approval package is complete and in final, the following routing procedure should be used to ensure that the approval is executed properly.

   a. For the Divisions of Therapeutic Drugs for Non-food Animals, Production Drugs, and Therapeutic Drugs for Food Animals use the following:

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      HFV-190
      HFV-199

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      HFV-190
      HFV-199

6. Send e-mail to the DS where appropriate

   If ONADE, DS, or DAF identifies additional changes to the labeling that should be incorporated into a future supplement, the TAD personnel will send an e-mail detailing the labeling changes needed in a future supplement to the DS immediately before the TAD forwards the final action package to the DCU. For Type A medicated articles and medicated feeds, the TAD personnel will also include the DAF on the email. The TAD will include a copy of the e-mail on yellow paper in Folder B of the approval package.

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7. Create Volume 0 for the application

   Use the facsimile labeling (or Final Printed Labeling (FPL), if submitted) as being approved in this supplement to create Volume 0.[12]

8. Annotate the ONADE Final Action Form

   In the "Comments/Instructions to DCU" box, identify from which copy of the submission the copy of the labeling components were removed.

VII. DOCUMENTS INCLUDED IN THE APPROVAL PACKAGE

For Folder A and B, the presence of an asterisk (*) immediately preceding the item indicates an item that is required in each approval package. Include those items without an asterisk only when the specific circumstances of the approval dictate their creation or need for documentation.

A. Folder A

1. *Approval letter
2. *MRA
3. FOI summary
4. Draft FR notice

[12] See P&P 1243.3810 for instructions on how to assemble Volume 0.

B. Folder B

1. Consulting review(s) received from the DS, the DAF, or any other scientific reviews

2. A copy of the e-mail to the DS identifying labeling changes that we would like the sponsor to make in a future supplement

C. Volume 0

Place a copy of the facsimile labeling (or, if available, a copy of the FPL) that served as the basis for approval in Volume 0. Volume 0 should accompany the final action package for each approval.

VIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

514.8 – Supplemental new animal drug applications

CVM Program Policy and Procedures Manual

1243.3020 – Managing the review of submissions in the STARS queue

1243.3026 – Amending STARS submissions

1243.3810 – Creating and maintaining a reference copy of the currently approved labeling for an application (Volume 0)

1243.5761 – Freedom of Information (FOI) Summary for original and supplemental new animal drug applications (NADA)

IX. VERSION HISTORY

August 23, 2007 – Original version

March 12, 2008 – Revised to remove hotlinks that did not work.