REVIEW OF LABELING CHANGES IN MANUFACTURING SUPPLEMENTS

I. PURPOSE

This document establishes procedures that assure the consistent, timely, and accurate review and processing of label changes included in the chemistry, manufacturing and controls (CMC) supplemental applications described in 21 CFR 514.8(b).

II. SCOPE

FDA's regulations and Guidance for Industry (GFI) #83 describe the types of reporting criteria for supplements and reporting for CMC changes to new animal drugs. Specifically, under 21 CFR 514.8(b), a drug sponsor must report a CMC change in either a prior-approval supplement, 30-day changes-being effected supplement, immediate changes-being-effected supplement, or minor changes and stability report (MCSR) based on the change's potential to adversely affect the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug.

This document pertains only to common CMC changes that require corresponding labeling changes to finished drugs or CMC supplements with labeling, even if the sponsor is not actually requesting a labeling change. The majority of CMC changes do not require changes to labeling. The following examples are the most common CMC changes reported in supplemental applications that require labeling changes:

- A change in the size of the container resulting in a change to the labeled amount of drug, or

- A change in the labeled storage conditions.

If the drug sponsor provides updated labeling in an MCSR, the Division of Manufacturing Technologies (DMT) will notify the drug sponsor and request that the sponsor resubmit the updated labeling in an appropriate supplemental application.[1]

III. GENERAL DESCRIPTION OF THE INITIAL LABELING REVIEW PROCESS

DMT personnel will perform an initial screening and administrative review when they receive each CMC supplement.[2]

If the supplement requires a change to the Code of Federal Regulations (CFR), a substantial data review or assessment by the target animal division (TAD), or both, DMT will re-assign the supplement to the appropriate TAD for the primary review responsibility.[3] DMT will obtain concurrence with the appropriate TAD before reassigning any CMC supplement.

Examples of common CMC changes that may require a corresponding change to the CMC information in the CFR, substantial review, or both by the TAD include:

- A change in the size of the container resulting in a change to the labeled amount of drug product,
- Significant changes to the qualitative or quantitative formulation of a drug product that affect the safety or effectiveness of the animal drug, and
- Changes to the primary container closure system that affects the drug delivery volume.

[1] For example, a component and composition change may necessitate a change in the labeling. For multiple related changes, where the recommended reporting categories for the individual changes differ, CVM will ask the sponsor to submit a supplement in accordance with the most restrictive of the reporting categories recommended for the individual changes. Any labeling change must be reported in a supplemental application according to 21 CFR 514.8(c).
[2] See P&P 1243.3020.
[3] "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.

TAD personnel should follow P&P 1243.6020, as appropriate, and request a consulting review from DMT regarding the CMC information.

For reported CMC changes that require labeling changes, DMT will screen the supplemental application to determine whether 1) the applicant has included updated labeling and 2) the availability of Volume 0.[4] If DMT personnel identify a reported CMC change as a change likely requiring a labeling change and the supplement does not include updated labeling, DMT will contact the sponsor and request an amendment to include all components of the labeling. The sponsor will have 7 days to submit the amendment without having the STARS due date reset. If the amendment arrives in DMT after 7 days, then DMT will reset the clock to the receipt date of the amendment.

Before DMT consults with a TAD for labeling review, DMT personnel will determine the availability of Volume 0, not whether Volume 0 has the appropriate labeling for comparison. It is critical to ensure that the STARS coding accurately reflects the presence or absence of Volume 0 for the ANADA or NADA to which the supplement is submitted.

DMT will consult TAD for any reactivated supplement with labeling comments.

IV. REVIEW OF THE SUPPLEMENT WHEN VOLUME 0 EXISTS

A. Request consulting review

DMT personnel will issue all consulting review requests to the TAD for NADAs and ANADAs through STARS no later than 14 days after the CVM Received Date.[5]

The appropriate TAD will receive the A1 package. Include the appropriate directions in the "Action Requested" section on the DCU Routing Slip. For TAD review requests of NADAs, include, for example, "Please review the labeling" in the appropriate section of the DCU Routing Slip.

B. TAD consult

The TAD consulting review process for label changes in CMC supplements is similar to the label review process identified in P&P 1243.6020 (sections V.A. and

[4] Volume 0 is the reference copy of all components of the currently approved labeling for the application.
[5] DMT may delay the request for consult if a labeling amendment is required.

V.B.). TAD personnel should determine as soon as possible whether a Freedom of Information (FOI) Summary, an FR notice, or both would be required. If approval of the supplement requires either or both, then notify DMT to reassign the CMC supplement to the TAD as the primary review group.

The TAD should determine if Volume 0 contains the labeling associated with this supplement. If Volume 0 does not include the labeling associated with the current supplement, then the TAD should follow the appropriate procedures identified in section V.B. below.[6]

The TAD personnel will determine the acceptability of the submitted labeling, as follows:

1. The labeling is acceptable

   Proceed to section IV.C. below.

2. The supplement may be amended to provide revised labeling

   If the labeling cannot be approved, as submitted, determine whether the sponsor can amend the application in a timely manner to correct the observed deficiencies.[7] The TAD should proceed to section IV.D. and DMT will determine whether there is sufficient time to amend the application. DMT will forward any labeling amendment to the appropriate TAD for review. If the amended application can be approved, proceed to section IV.C., otherwise proceed to section IV.D.

3. The labeling is not acceptable

   If it is not possible to approve the labeling (e.g., the sponsor has requested change(s) that are unacceptable or other additional changes to the labeling would be needed), then the TAD's review should state that the supplement is incomplete and provide specific comments to be transmitted to the sponsor. Proceed to section IV.D.

[6] In this instance, TAD should issue the appropriate consult reviews to the Office of Surveillance and Compliance (OS&C) as specified in P&P 1243.6020.
[7] See P&P 1243.3026 for information related to requesting and processing submission amendments.

DMT will issue a supplemental application incomplete letter to the sponsor with the labeling comments and any additional comments from DMT if there are any.

C. If the labeling is acceptable

1. TAD Personnel will:

   a. Prepare a consulting review incorporating information described in P&P 1243.6020 (section V.D.1.),

   b. Update Volume 0 with the new labeling,

   c. Clearly identify within the consulting review any labeling changes that should be made in a future supplement according to P&P 1243.6020 (section V.D.6.). DMT will send the e-mail to DS identifying these types of labeling changes, and

   d. Return the consulting review package to DMT. This package should include the TAD consulting review, a copy of any email to the Division of Surveillance (DS) as described in C.1.c., and the updated Volume 0 (including the old labeling). The TAD consulting review should include the specific language for the approval letter regarding the submission of final printed labeling.

2. DMT Personnel will determine if the submitted CMC information is acceptable.

   a. If the submitted CMC information is acceptable, DMT personnel will:

      i. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement includes labeling changes,

      ii. Send an e-mail to DS regarding the approval status of the supplement and any future labeling changes requested by TAD (see section V.D.6. in P&P 1243.6020),

      iii. Send an e-mail notification to the appropriate personnel in the Generic Animal Drugs Team for a potential update to the Database of Approved Animal Drugs (i.e., Greenbook), and

iv. Prepare the final approval package according to DMT procedures, consistent with ONADE procedures.

b. If the submitted CMC information is not acceptable, DMT personnel will:

i. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement is incomplete,

ii. Meet with the TAD to discuss the disposition of Volume 0, and

iii. Prepare a supplemental application incomplete letter incorporating comments from the TAD, if applicable.

D. If the labeling is not acceptable

1. TAD Personnel will:

a. Prepare a consulting review incorporating information described in P&P 1243.6020 (section V.D.1.), and

b. Return the TAD consulting review and Volume 0 to DMT. The consulting review should include the specific language for the incomplete letter to the sponsor. The TAD should consolidate all of the labeling comments including those from OS&C before forwarding the consulting review to DMT.

2. DMT Personnel will:

a. Determine if the submitted CMC information is acceptable and document their decisions in the Chemist's review,

b. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement with labeling changes is incomplete, and

c. Prepare a supplemental application incomplete letter listing any deficiencies in the CMC information and the deficiencies in labeling based on comments from the TAD.

V. REVIEW OF THE SUPPLEMENT WHEN VOLUME 0 DOES NOT EXIST

A. Request consulting reviews

DMT personnel will issue all consulting review requests to the TAD for NADAs and ANADAs through STARS no later than 14 days after the CVM Received Date.[8] As described below, DMT personnel will also issue consulting review requests to OS&C for NADAs. For ANADAs, the Generic Animal Drugs Team will issue any additional consulting reviews.

1. For dosage form products (NADAs), DMT personnel will:

    a. Request a consulting review from the TAD (A1 Package) and from the DS (A2 Package),

    b. Include the appropriate directions in the "Action Requested" section on the DCU Routing Slip. For example:

        i. For TAD review requests of NADAs, include "Please review the labeling and create Volume 0. DMT has requested an A2 consulting review from the DS", and

        ii. 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. Clearly identify in your review any changes the sponsor must incorporate into the labeling before we can approve the supplement and those labeling changes the sponsor can address in a future supplement. After completion, please return the consulting review to (*name of TAD, HFV-XXX*)."

    c. On the Review Request and Movement Form, route the final OSC consulting review through the appropriate TAD before routing back to DMT.

2. For Type A medicated articles and medicated feeds (NADAs), DMT personnel will:

[8] DMT may delay the request for consult if DMT notifies the applicant that an amendment to the supplement requesting updated labeling is required.

a. Request a consulting review from the TAD (A1 Package), from the Division of Animal Feeds (DAF) (A2 Package) and from DS (A3 Package), and

b. Include the appropriate directions in the "Action Requested" section on the DCU Routing Slip. For example:

   i. For requests for TAD review of NADAs, include "Please review the labeling and create Volume 0. DMT has requested an A2 consulting review from the DAF and an A3 consulting review from the DS."

   ii. For requests for DS review 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. Clearly identify in your review any changes the sponsor must incorporate into the labeling before we can approve the supplement and those labeling changes the sponsor can address in a future supplement. After completion, please forward the consulting review to DAF, *HFV-XXX*."

   iii. For requests for DAF review of NADAs, include "Please review the labeling enclosed with this supplement. Clearly identify in your review any changes the sponsor must incorporate into the labeling before we can approve the supplement and those labeling changes the sponsor can address in a future supplement. After completion, please forward consulting reviews from DAF and DS to (*name of TAD, HFV-XXX*)."

c. On the Review Request and Movement Form, route the final OSC consulting review through the appropriate TAD before routing back to DMT.

B. TAD consult

The TAD consulting review process for label changes in CMC supplements is similar to the label review process identified in P&P 1243.6020 (sections V.A. and V.B.). TAD personnel should determine as soon as possible whether an FOI Summary, an FR notice, or both would be required. If approval of the supplement requires either or both, then notify DMT to reassign the CMC supplement to the TAD as the primary review group.

The TAD personnel will determine the acceptability of the submitted labeling (taking into account any comments from DAF and DS) as follows:

1. The labeling is acceptable

   Proceed to section V.C. below.

2. The supplement may be amended to provide revised labeling

   If the labeling cannot be approved, as submitted, determine whether the sponsor can amend the application in a timely manner to correct the observed deficiencies.[9] The TAD should proceed to section IV.D. and DMT will determine whether there is sufficient time to amend the application. DMT will forward any labeling amendment to the appropriate TAD for review. If the amended application can be approved, proceed to section V.C., otherwise proceed to section V.D.

3. The labeling is not acceptable

   If it is not possible to approve the labeling (e.g., the sponsor has requested change(s) that are unacceptable or other additional changes to the labeling that would be needed), then the TAD's review should state that the supplement is incomplete and provide specific comments to be transmitted to the sponsor. Proceed to section IV.D.

   DMT will issue a supplemental application incomplete letter to the sponsor with the labeling comments and any additional comments from DMT if there are any.

C. If the labeling is acceptable

1. TAD Personnel will:

   a. Prepare a consulting review incorporating information described in P&P 1243.6020 (section VI.E.1.),

   b. Create Volume 0 for the application,

[9] See P&P 1243.3026 for information related to requesting and processing submission amendments.

Use the facsimile labeling (or FPL, if submitted) as being approved in this supplement to create Volume 0.[10]

c. Clearly identify within the consulting review any labeling changes that should be made in a future supplement according to P&P 1243.6020 (section VI.E.6.). DMT will send the e-mail to DS identifying these types of labeling changes, and

d. Return the consulting review package to DMT.

This package should include the TAD consulting review, consulting reviews from DAF and DS, and Volume 0. The TAD consulting review should include the specific language for the approval letter regarding the submission of final printed labeling.

2. DMT Personnel will determine if the submitted CMC information is acceptable.

a. If the submitted CMC information is acceptable, DMT personnel will:

i. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement includes labeling changes,

ii. Send an e-mail to DS regarding the approval status of the supplement and any labeling changes requested by TAD (see section VI.E.6. in P&P 1243.6020),

iii. Send an e-mail notification to the appropriate personnel in the Generic Animal Drugs Team for a potential update to the Database of Approved Animal Drugs (i.e., Greenbook), and

iv. Prepare the final approval package according to DMT procedures.

b. If the submitted CMC information is not acceptable, DMT personnel will:

i. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement is incomplete,

ii. Meet with the TAD to discuss the disposition of Volume 0, and

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

iii. Prepare a supplemental application incomplete letter incorporating comments from the TAD, if applicable.

D. If the labeling is not acceptable

1. TAD Personnel will:

   a. Prepare a consulting review incorporating information described in P&P 1243.6020 (section VI.E.1.),

   b. Return the consulting review package and Volume 0 to DMT including the TAD consulting review and consulting reviews from DAF and DS. The TAD consulting review should include the specific language for the incomplete letter to the sponsor. The TAD should consolidate all of the labeling comments including those from OS&C before forwarding the consulting review to DMT.

2. DMT Personnel will:

   a. Determine if the submitted CMC information is acceptable and document their decisions in the Chemist's review,

   b. Complete the STARS "Review Summary" field. Specifically, this field will state that the CMC supplement with labeling changes is incomplete, and

   c. Prepare a supplemental application incomplete letter listing any deficiencies in the CMC information and the deficiencies in labeling based on comments from the TAD.

VI. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

514.8, Supplemental new animal drug applications

CVM Guidance for Industry

83, Chemistry, manufacturing and controls changes to an approved NADA or ANADA

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)

1243.6020, Review of NADA and ANADA labeling supplements

VII. VERSION HISTORY

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