Exhibit 4-1

Procedures for Clearing FDA Warning Letters and Untitled Letters

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1. Purpose

To facilitate the Office of Chief Counsel's review of certain types of Warning Letters and Untitled Letters, prior to their issuance, for legal sufficiency and consistency with Agency policy.

2. Policy/Scope

These procedures apply to all of the agency components that are responsible for recommending, evaluating or issuing Warning Letters and Untitled Letters. Therefore, the applicability of these procedures is not limited to ORA and the Centers' Offices of Compliance.

The OCC review provisions in these procedures apply only to Warning and Untitled Letters described below:

CFSAN

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

2. Warning Letters involving medical foods.

3. Warning Letters involving section 502(f)(1) drug misbranding charges.

4. Warning Letters involving section 403(a) false or misleading food labeling.

5. Warning Letters involving section 403 (r)(1)(A) (unauthorized nutrient content claim) or section 403 (r)(1)(B) (unauthorized health claims) charges.

6. Warning Letters for dietary supplements with a new drug charge based in whole or in part on promotional use of scientific studies to market the product for disease uses.

7. Warning Letters with violations of the general CGMP regulations.

8. Warning and Untitled Letters with violations of the dietary supplement CGMP regulations.

9. Warning Letters with adulteration and/or misbranding charges related to cosmetics.

In addition, cyber letters (letters resulting from web sites promoting dietary supplements with drug claims) will be reviewed under the audit review program in 6.4 with OCC reviewing every 10th letter.

CDRH

1. Any warning or untitled letter involving a novel, controversial, or sensitive legal issue.

2. Advertising/promotion warning/untitled letters.

3. Warning/untitled letters with unapproved device charges under section 501(f)(1)(B) if the firm contests that the product is a device or any other warning/untitled letter in which the firm contests that the product is a device.[1]

[1] The term "contests" in this list means that FDA has had prior contact with the firm, e.g., through an inspection, a 483 response, a prior issuance of an untitled letter, email, or telephone, and the firm has asserted that its product is not a "device."

4. Warning/untitled letters with section 502(a) charge-labeling of the device is false or misleading.

5. Warning/untitled letters with 502(j) charge-device is dangerous to health when used in the manner or with the frequency or duration prescribed, recommended or suggested in the labeling thereof.

6. Warning/untitled letters with section 502(o) charge-notice/information of modification of the device not provided to FDA.

7. Warning/untitled letters with section 502(o) charge-notice/information of new intended use of the device not provided to FDA.

8. Warning/untitled letters with section 502(t)(3)-firm has failed or refused to comply with a requirement under section 522.

9. Warning and untitled letters involving bioresearch monitoring not covered by the December 8, 2005 agreement between OCC and CDRH's Office of Compliance.

CVM

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

2. Warning Letters involving bioresearch monitoring.

3. Warning Letters with violations of 21 CFR 589.2000 (ruminant feed ban) and/or 21 CFR 589.2001 (new animal feed ban).

4. Warning and Untitled Letters involving advertising and promotion.

5. Warning Letters with section 502(a) false or misleading labeling drug misbranding charges.

6. Warning Letters related to turtles.

7. Warning and Untitled Letters involving new animal drug compounding.

CBER

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

2. Warning Letters (and notice of initiation of disqualification proceedings and opportunity to explain, or "NIDPOEs") involving clinical investigators and

IRBs. OCC will reevaluate the need to continue such reviews in six months.

3. Warning Letters involving advertising or promotion, except for those involving only straightforward omission of risk (e.g., no risk information whatsoever).

4. Warning and Untitled Letters involving product jurisdiction.

5. Warning and Untitled Letters involving unregistered or unlicensed blood banks.

CDER

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

2. Warning Letters (and notices of initiation of disqualification proceedings and opportunity to explain, or "NIDPOEs") involving clinical investigators and IRBs. OCC will continue to review these Warning Letters for six months; thereafter, OCC and CDER's Office of Compliance will evaluate the need to continue such reviews.

3. Warning Letters involving advertising or promotion, except for those involving only straightforward omission of risk (e.g., no risk information whatsoever).

4. Warning and Untitled Letters involving compounding.

5. Warning and Untitled Letters involving unapproved new drugs, except health fraud, over-the-counter drugs subject to final monographs, and Warning Letters that contain both GMP and unapproved new drug charges.

ORA

1. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.

3. Background

On November 29, 2001, then Deputy Secretary of the Department of Health and Human Services directed "…the Food and Drug Administration (FDA) to submit all Warning Letters and Untitled Letters to FDA's Office of Chief Counsel (OCC) prior to their issuance so that they can be reviewed for legal sufficiency and

consistency with Agency policy." To implement this directive, a cross-agency working group established procedures to integrate OCC review into the agency's existing procedures for the review of enforcement correspondence. These procedures were implemented in March 2002. In August/September of 2009, the OCC review provisions of these procedures were modified, on an interim basis, to apply only to the Warning and Untitled Letters described in section "2. Policy/Scope." The 2009 interim procedures were evaluated as described in section 5.1 and finalized in December 2010.

4. Definitions

For the purpose of these procedures:

4.1 A ***Warning Letter*** is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act.

4.2 An ***Untitled Letter*** is an **initial** correspondence with regulated industry that cites violations that do not meet the threshold of a Warning Letter. Untitled Letters are intended to cover those circumstances where the Agency has a need to communicate with regulated industry about violations that do not meet the threshold of regulatory significance as described above. The three types of letters related to licensed products that are issued by CBER and CDER, pursuant to section 6.3 of these procedures, do not necessarily fall within this definition of an Untitled Letter; however, they are still Untitled Letters that are covered by the scope of these procedures.

5. Responsibilities

5.1 FDA's Office of Policy, Planning, and Budget conducted a qualitative and quantitative evaluation of the OCC review provisions in the 2009 interim procedures. OCC, in coordination with other agency components, reviewed the results of this evaluation and concluded that the interim procedures should be finalized.

Any refinements to these procedures that become identified through periodic evaluation or otherwise, that may facilitate the review, streamline

or focus the process, or enable better management of the workload, while maintaining the overall intent, are implemented through established, internal agency review procedures. In addition, the Council will monitor the timeframes to determine whether they need to be modified based on the agency's experience with these procedures.

5.2 Each Office involved in implementing these procedures is responsible for documenting additional internal procedures as needed.

5.3 Violation letters are tracked using the Compliance Management System (CMS or MARC-CMS). CMS provides the capability to enter and track Warning and Untitled Letters through the approval process. The action office (i.e., the District or Center initiating the recommendation) is responsible for entering all violation letters into CMS; as well as updating data related to their submissions. The issuing office of the violation letter is also responsible for ensuring that a PDF copy of the final, signed violation letter is added into CMS.

Instructions for using CMS are available in the User's Guide link within the application and further information is available within the link to Frequently Asked Questions.

5.4 When a violation letter is the result of a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in the Field Accomplishment and Compliance Tracking System (FACTS) is to be appropriately updated at each stage in the review process. The action office (i.e., the District or Center initiating the recommendation) is responsible for entering the Final Profile Status in FACTS. (See Chapter 4 "Firm Profile Updates in FACTS" for more information.)

6. Procedures

6.1 Timeframes

6.1.1 Warning Letters

The Agency did not establish new timeframes for ORA and the Centers. In these procedures, the agency recommits to the established timeframes at each level of review. To ensure the applicability of evidence to the present situation, the agency will strive to issue Warning Letters within four months from the appropriate reference date. Examples of the appropriate reference date are: the last day of the inspection, the date of sample analysis, or the date of evidence collection.

The timeframe for OCC review, when OCC review is required, is fifteen (15) working days. If OCC does not respond to Direct Reference Warning Letters and those issued pursuant to foreign inspections within this timeframe, the District or Center can presume concurrence and may send the letter out without additional input. All other categories of letters requiring OCC review should await an OCC decision prior to being issued. For all categories of Warning Letters receiving a decision by OCC, OCC will either concur, concur with changes, not concur with written reasons, or flag the letter because it raises significant issues and questions, e.g., jurisdictional issues or insufficient evidentiary support.

The period for OCC review officially begins once OCC has received the full packet of materials that serve as support for the agency's issuance of the Warning Letter. If the basic elements of the case are not provided (the basic elements are identified in the District and center responsibility sections of these procedures), OCC will return the materials to the originator. If, as a part of their review, OCC asks for an exhibit or attachment that accompanied the Establishment Inspection Report (EIR) or Form FDA 483 response, **a copy of the document** should be sent to OCC electronically, via fax or by mail.

6.1.2 Warning Letter Responses

When OCC review of the Warning Letter was required, and it is reasonably clear from the Warning Letter response that the individual or firm is going to contest the findings as set out in the Warning Letter, OCC should be consulted and provided with the relevant documents. This is not necessary when the disputed issues are scientific or technical.

6.1.3 Untitled Letters

There are no agency timeframes for the issuance of Untitled Letters. However, pursuant to these procedures, the working group established timeframes for the review of Untitled Letters. In most cases, the timeframes for Warning Letters are tripled for the review of Untitled Letters. The exceptions to this rule are the letters for licensed products that are issued by CBER or CDER pursuant to section 6.3 of these procedures. To ensure the applicability of evidence to the present situation, the agency will strive to issue Untitled Letters within six months from the last day of the inspection, the date of sample analysis, or the date of evidence collection.

When OCC's review of an Untitled Letter is required, OCC will either concur, concur with changes, not concur with ***written*** reasons, or flag the letter because it raises significant issues and questions, e.g., jurisdictional issues or insufficient evidentiary support. However, the default provisions do not apply to Direct Reference Untitled Letters and Untitled Letters issued pursuant to a foreign inspection. The period for OCC review officially begins once OCC has

received the full packet of materials that serve as support for the agency's issuance of the Untitled Letter. If the basic elements of the case are not provided (the basic elements are identified in the District and Center responsibility sections of these procedures), OCC will return the materials to the originator. If, as a part of their review, OCC asks for an exhibit or attachment that accompanied the EIR or Form FDA 483 response, **a copy of the document** should be sent to OCC electronically, via fax or by mail.

6.2. Procedures for the Review of Agency Warning and Untitled Letters

All Warning Letters and Untitled Letters must be entered into the Compliance Management System (CMS or MARC-CMS), where they are available for review.

6.2.1. General Procedures for Direct Reference Warning and Untitled Letters

(a) District Office Responsibilities

(1) When OCC review of a Warning or Untitled Letter is required:

- Submit a draft "final" Warning Letter via CMS to OCC for concurrence, within 15 working days after the completion of an inspection, the sample analysis, or date of evidence collection.
- Submit a draft "final" Untitled Letter via CMS to OCC for concurrence within 45 working days after the completion of an inspection, the sample analysis, or date of evidence collection**.**
- To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.
- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- If the District receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- If the District receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled Letter, the District should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response (including whether the response has changed the District's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail and also added into the

case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the District's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

- If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.
- If OCC concurs with the draft "final" Untitled Letter, issue the letter.
- If the District receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, you should issue the letter.
- In the case of **non**concurrence or the letter is flagged because it raises significant issues, the District will work with OCC, and the Director of Compliance, OE and the Center as necessary, to quickly address OCC's concerns.

(2) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) OCC Responsibilities

(1) Review any draft "final" Warning Letter and Untitled Letter requiring OCC review within 15 working days.
(2) If concurrence, send concurrence to the District's Director of the Compliance Branch and the district's compliance officer who proposed the action, along with a copy of the draft "final" letter with any edits (the District can then issue the letter).
(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the District, and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.2.2. General Procedures for Warning and Untitled Letters Pursuant to a Foreign Inspection

(a) Center Responsibilities

(1) Within 15 working days after the receipt of the EIR, the Center will determine if a Warning Letter is appropriate.
(2) Within 45 working days after the receipt of the EIR, the Center will determine if an Untitled Letter is appropriate.
(3) When OCC review of a Warning or Untitled Letter is required:

- Send a copy of the draft "final" letter via CMS to OCC for concurrence.

- To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.

- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.

- If the agency receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response should accompany the draft "final" Warning or Untitled Letter.

- If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled Letter, the Center should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail, and should also be added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

- If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.

- If OCC concurs with the draft "final" Untitled Letter, issue the letter.

- If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.

- In the case of ***non***concurrence or the letter is flagged because it raises

significant issues, the Center will work with OCC and the Director of Compliance, OE and ORO's DFI as necessary to quickly address OCC's concerns.

(4) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Send a copy to ORA's Office of Regional Operations (ORO), Division of Field Investigations (DFI), and distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) OCC Responsibilities

(1) Review any draft "final" Warning Letter and Untitled Letter requiring OCC review within 15 working days.
(2) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center, and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.2.3. Warning and Untitled Letters that Require Center Concurrence

(a) District Office Responsibilities

(1) Within 15 working days after the completion of the inspection, the sample analysis, or collection of evidence, submit a recommendation and a draft "final" Warning Letter to the Center through CMS.
(2) Within 45 working days after the completion of the inspection, the sample analysis, or collection of evidence, submit a recommendation and a draft "final" Untitled Letter to the Center through CMS.
(3) To the extent that this information is not included in the recommendation, and to facilitate the Center's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include all evidence necessary to support issuance of the letter or other relevant information. For example, the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, the relevant exhibits, product labels and labeling, and, if applicable, the summary of any sample analysis.
(4) If the District receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter recommendation, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the

District's assessment of the response should accompany the draft "final" Warning or Untitled Letter.

(5) If the District receives the Form FDA 483 response while the draft "final" Warning or Untitled Letter is being reviewed, the District should notify the Center and, for letters requiring OCC review, the attorney that is conducting the review, as appropriate. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the District's assessment of the response (including whether the response has changed the District's view on whether to issue the letter) should also be submitted to the appropriate reviewer(s) electronically, via fax, or by mail and also added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

(6) If the Center approves the recommendation and, OCC review is not required, issue the letter.

(7) When OCC review of a Warning or Untitled Letter is required:

- If OCC concurs, issue the letter.
- If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- In the case of **non**concurrence by OCC or the letter is flagged because it raises significant issues, the District will work with OCC and the Director of Compliance, OE and the Center as necessary to quickly address OCC's concerns.

(8) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) Center Responsibilities

(1) Within 15 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Warning Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 15 working day timeframe and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.

(2) Within 45 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Untitled Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 45 working day

timeframe and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.

(3) When OCC review of a Warning or Untitled Letter is required:

- If the recommendation is approved, the Center will send its concurrence and the draft "final" letter with any edits to OCC for concurrence. The Center's "final" letter with any edits should be added to the Center documents tab in CMS and should clearly identify via the document description any letter that require OCC review and concurrence. For instance, the description field within CMS should indicate "FOR OCC REVIEW."
- To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.
- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.

(4) If the Warning Letter recommendation is ***not*** approved, the Center will notify the District's Director of the Compliance Branch and OCC if the letter required OCC review, of its decision within 15 working days. The Center will also issue a memorandum to the District's Director of the Compliance Branch that states its reasons for nonconcurrence within 30 working days, or as soon as possible. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.

(5) If the Untitled Letter recommendation is ***not*** approved, the Center will notify the District's Director of the Compliance Branch, and OCC if the letter required OCC review, of its decision within 45 working days. The Center will also issue a memorandum to the District's Director of the Compliance Branch that states its reasons for nonconcurrence within 60 working days, or as soon as possible. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.

(c) OCC Responsibilities

(1) Once the Center has approved the recommendation, review any draft "final" Warning Letter requiring OCC review within 15 working days.

(2) Once the Center has approved the recommendation, review any draft "final" Untitled Letter requiring OCC review within 45 working days.

(3) If concurrence, send concurrence to the District's Director of the Compliance Branch and the district's compliance officer who proposed the action, along with a copy of the draft "final" letter with any edits (the District can then issue the letter).

(4) If nonconcurrence or the letter is flagged because it raises significant issues, contact the Center involved and the District, and state in writing the reason for nonconcurrence.

(d) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.2.4. Warning and Untitled Letters that Issue Directly from the Center

(a) Center Responsibilities

(1) Make the decision to issue a Warning Letter or an Untitled Letter
(2) When OCC review of a Warning or Untitled Letter is required:

- Submit a draft "final" Warning Letter or Untitled Letter via CMS to OCC.

- To facilitate OCC's review, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.

- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.

- If the agency receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response should accompany the draft "final" Warning or Untitled Letter.

- If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled Letter, the Center should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail, and also added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

- If OCC concurs, the Center can issue the letter.

- If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- In the case of nonconcurrence by OCC or the letter is flagged by OCC because it raises significant issues, the Center will work with OCC and the Director of Compliance, OE as necessary, to quickly address OCC's concerns.

(3) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Send a copy to the District's Director of the Compliance Branch where the recipient of the letter is located and distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) OCC Responsibilities

(1) Review any draft "final" Warning Letter requiring OCC review within 15 working days.
(2) Review any draft "final" Untitled Letter requiring OCC review within 45 working days.
(3) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
(4) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center, and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.2.5. Letters that Issue Directly from the Centers' Promotion and Advertising Staffs

(a) Center Responsibilities

(1) Make the decision to issue a Warning Letter or an Untitled Letter.
(2) When OCC review of a Warning or Untitled Letter is required:

- Send a copy of the draft "final" letter via CMS to OCC for concurrence.

- To facilitate OCC's review, ensure that the violation letter documents within CMS include the evidence that supports the issuance of the letter.

- If OCC concurs, issue the letter.
- In the case of *non*concurrence by OCC or the letter is flagged by OCC because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.

(3) Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) OCC Responsibilities

(1) Review any draft "final" Warning Letter requiring OCC review within 15 working days.
(2) Review any draft "final" Untitled Letter requiring OCC review within 45 working days.
(3) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
(4) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center and state **in writing** the reasons for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued, and actively monitor CMS to identify missing letters, if any.

6.3 Licensed Products Letters

Violation Letters associated with licensed biological therapeutics may fall under CBER or CDER responsibility. A listing of such products that have been transferred under CDER's jurisdiction can be viewed at: http://www.fda.gov/cber/transfer/transfprods.htm. Additional information can be found at: http://www.fda.gov/cder/biologics/default.htm.

Recommendations and other correspondence related to 6.3.1 – 6.3.3 (below) that are associated with CDER products should be forwarded to CDER, Office of Compliance, Division of Manufacturing and Product Quality (HFD-320). Recommendations and correspondence related to CBER products should be referred to CBER, Office of Compliance and Biologics Quality, Division of Case Management (HFM-610).

6.3.1 License Suspension

(a) Center Responsibilities

(1) Within three (3) working days after receiving information that a danger to health exists, the Center will gather the pertinent evidence, convene a Health Hazard Evaluation meeting with the applicable product office, and draft a Letter of Suspension.
(2) If the determination is made that a danger to health exists, a draft "final" Letter of Suspension will be submitted by the Center via CMS to OCC within the 3 working day period.

- To facilitate OCC's review, ensure that the documents within CMS include the Health Hazard Evaluation and the pertinent evidence that establishes that a danger to health exists.

- If OCC concurs, the Center's Office of Compliance and the Office of the Center Director will process and issue the letter.

- In the case of ***non***concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.

(3) Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

(b) OCC Responsibilities

(1) Review the draft "final" letter within 5 working days.
(2) If concurrence, send concurrence to the appropriate Center along with a copy of the draft "final" letter with any edits.
(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the appropriate Center and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all License Suspension Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.3.2 License Revocation (For Cause)

(a) Center Responsibilities

- Within 30 working days after receipt of a Recommendation for a License

Revocation, the Center will evaluate the recommendation to determine whether the issuance of a letter requesting the revocation of a license is appropriate.

- If the issuance of a letter is appropriate, submit a draft "final" letter via CMS to OCC for their concurrence.
  - To facilitate OCC's review of the letter, ensure that the documents within CMS include the recommendation and any additional supporting documents.
  - If OCC concurs, issue the letter.

  - In the case of ***non***concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.

(3) Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

(b) OCC Responsibilities

(1) Review the draft "final" letter within 30 working days.
(2) If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits.
(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center, and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all License Revocation Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.3.3 Notice of Intent to Revoke

(a) Center Responsibilities

(1) Within 30 working days after the receipt of a Recommendation for a Notice of Intent to Revoke (NOIR), the Center will evaluate the recommendation to determine whether the issuance of a (NOIR) letter is appropriate.

(2) If the issuance of a NOIR is appropriate, submit a draft "final" NOIR letter and any accompanying documentation via CMS to OCC for their concurrence.

  - If OCC concurs, issue the letter.
  - In the case of *non*concurrence or the letter is flagged because it raises

significant issues, the Center will work with OCC.

(3) Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

(b) OCC Responsibilities

(1) Review the draft "final" letter within 30 working days.
(2) If concurrence, send concurrence to the Center, along with a copy of the draft "final" NOIR letter with any edits.
(3) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center and state ***in writing*** the reason for nonconcurrence.

(c) OE Responsibilities

Maintain a repository of all NOIR Letters that have been issued and actively monitor CMS to identify missing letters, if any.

6.4 Enforcement Correspondence Under an Audit Review

Periodically, the agency may determine, through the periodic evaluations or otherwise, that certain Untitled and Warning Letters may be reviewed by OCC on an audit basis rather than a letter-by-letter review. The agency may institute such an audit review under those circumstances in which policy is clear and well established, and model letters have been developed and cleared through OCC for use by the originating organization. Specific areas and criteria for audit review will be developed for the relevant letters.

If, during the evaluation or otherwise, any problems are identified in the use of the models, quality of issued letters, conformance with the audit requirements or other criteria in this procedure, audit review may revert back to full letter-by-letter review.

(a) Introduction

Audit letters are automatically identified by the Compliance Management System (CMS), using the audit schedules in 6.4.1 based on the nationwide count of that category of letter. The system will automatically indicate those letters subject to OCC review while the remaining letters in that audit category may be issued without such review. The model letters must be followed for all letters under this audit review program issued on or after the associated effective date.

If the same model is used for both Warning Letters and Untitled Letters, the audit schedule must be followed for each type of letter. This means that

Untitled Letters and Warning Letters are to be counted separately to identify the audit letter to be submitted for OCC review using the procedures in this document.

At the discretion of the issuing office, letters that represent unique circumstances that warrant OCC review may continue to be submitted for review through the routine procedures in this document, in addition to the required submission of audit letters.

(b) District Responsibilities

Use the relevant model letter for all letters to be issued under the audit program. Once the action is added into Compliance Management System (CMS), the district must identify the OCC audit program under which the letter falls in order to determine whether the letter is subject to audit submission to OCC. For letters that require Center concurrence, the district should likewise identify that the proposed action letter falls within one of the OCC audit programs and follow the routine procedures in this document. For direct reference letters, submit audit letters to OCC for review using the procedures in this document. The other letters may issue without OCC review but must still be added into CMS in order for the agency to keep accurate accounting for the issuance of the letter.

Districts must continue to be diligent to ensure the high quality and timeliness of any letters that are issued and must otherwise follow the appropriate procedures in the RPM, Compliance Programs, or elsewhere.

Conformance with these procedures and use of the model letter is required. Audit review can be rescinded if warranted.

(c) Center Responsibilities

Use the relevant model letter for all letters to be issued under the audit program. Once the action is added into Compliance Management System (CMS), the Center must identify the OCC audit program under which the letter falls in order to determine whether the letter is subject to audit submission to OCC. In most instances, this information should be completed by the recommending district; however, Centers will review as well to ensure an audit program is identified when appropriate. For letters for which the Center is responsible for obtaining OCC concurrence, submit audit letters to OCC for review using the procedures in this document. The other letters may issue without OCC review.

When a Center submits an “audit letter” to OCC for review, the transmittal memo approving the recommendation will contain the notation “Audit Letter – OCC concurrence is required” under the heading “Warning Letter –

Approved." This identifies the letter as one that requires OCC review and concurrence under the audit review program before it can be issued.

Centers must continue to be diligent to ensure the high quality and timeliness of any letters that are issued and must otherwise follow the appropriate procedures in the RPM, Compliance Programs, or elsewhere.

Conformance with these procedures and use of the model letter is required. Audit review can be rescinded if warranted.

(d) OCC Responsibilities

Review Untitled Letter and Warning Letter recommendations submitted by a District or Center, representing the audit letters of that type to be issued by that District or Center on or after the effective date of the model (shown below) in accordance with the routine procedures in this document. Determine conformity with the model letter. Report any perceived problems to the Office of Enforcement.

(e) OE Responsibilities

Maintain a repository of all Untitled Letters and Warning Letters issued and actively monitor CMS to identify any missing letters. Review conformance with these procedures as part of the periodic evaluation.

6.4.1 Model Letters and Audit Schedules

The following model letters and audit schedules have been approved for use under this audit review program. The links to these letters can be found in the Warning Letter page on the Office of Enforcement's intranet site.

Center	Type of Letter	Audit Schedule
CFSAN	CFSAN Dietary Supplement Cyber Letters (resulting from web sites promoting dietary supplements with drug claims) with: • Disease Claims • Disease and Structure-Function Claims The effective date for use of these letters is August 6, 2009.	Every Tenth Letter