Chapter 4
ADVISORY ACTIONS

This chapter defines and establishes uniform guidance and procedures for Warning Letters and untitled letters.

This chapter includes the following sections:

4-1 WARNING LETTERS

4-1-1 Warning Letter Procedures

When it is consistent with the public protection responsibilities of the Agency and depending on the nature of the violation, it is the Food and Drug Administration's (FDA's) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. (Prior notice is discussed in Chapter 10.) The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law.

The Agency position is that Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. A Warning Letter is the Agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act).

The Warning Letter was developed to correct violations of the statutes or regulations. Also available to the Agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution to achieve correction. Despite the significance of the violations, there are some circumstances that may preclude the Agency from taking any further enforcement action following the issuance of a Warning Letter. For example, the violation may be serious enough to warrant a Warning Letter and subsequent seizure; however, if the seizable quantity fails to meet the Agency's threshold value for seizures, the Agency may choose not to pursue a seizure. In this instance, the Warning Letter would document prior warning if adequate corrections are not made and enforcement action is warranted at a later time.

Responsible officials in positions of authority in regulated firms have a legal duty to implement whatever measures are necessary to ensure that their products, practices, processes, or other activities comply with the law. Under the law such individuals are presumed to be fully aware of their responsibilities. Consequently, responsible individuals should not assume that they would receive a Warning Letter, or other prior notice, before FDA initiates enforcement action.

FDA is under no legal obligation to warn individuals or firms that they or their products are in violation of the law before taking enforcement action, except in a few specifically defined areas. When acting under the authority of Subchapter C - Electronic Product Radiation Control (formerly the Radiation Control for Health and Safety Act of 1968) of Chapter V of the Act, FDA is required by law to provide a written notification to manufacturers when the Agency discovers products that fail to comply with a performance standard or that contain a radiation safety defect. Because of the legal requirements of Subchapter C, minor variations in the procedures may occur.

A Warning Letter is informal and advisory. It communicates the Agency's position on a matter, but it does not commit FDA to taking enforcement action. For these reasons, FDA does not consider Warning Letters to be final Agency action on which it can be sued.

There are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the Agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation.

2. The violation is intentional or flagrant.

3. The violation presents a reasonable possibility of injury or death.

4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters.

5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing. See Chapter 10, Prior Notice, for other methods of establishing prior notice.

In certain situations, the Agency may also take other actions as an alternative to, or concurrently with, the issuance of a Warning Letter. For example:

1. The product violates 402(a)(3) or 402(a)(4); or

2. There is a violation of CGMPs; or

3. The product contains illegal pesticide residues; or

4. The product shows short contents, subpotency, or superpotency.

Additional instructions for Warning Letters in specific product areas are found in compliance program guidance and in compliance policy guides.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-2 Warning Letters To Government Agencies

Government agencies include federal, state and local agencies. Government establishments should be held to the same standards as nongovernmental establishments. The public health standards are identical, however the method used to ensure compliance with these standards may vary. FDA believes that government establishments will achieve and maintain a higher rate of voluntary compliance with FDA regulations compared with nongovernmental

establishments. Efforts to obtain voluntary compliance should be made and documented before recommending the issuance of a Warning Letter. These efforts may include discussing the violations with the responsible government officials by phone or in a meeting, recommending an untitled letter, or requesting a written corrective action plan and periodic progress reports. The agency's progress should be monitored and a follow-up inspection should be scheduled, within a reasonable time consistent with the noted violations to confirm correction of the violations. Recommend issuing a Warning Letter if the agency does not provide assurance of corrective action or does not complete corrective actions within agreed timeframes. The appropriate Center should review and concur with the issuance of a Warning Letter. The Warning Letter should be addressed to the headquarters office of the government agency.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-3 Issuing Warning Letters - Factors To Consider

The Warning Letter is the Agency's principal means of notifying regulated industry of violations and of achieving prompt voluntary correction. Warning Letters can be issued at the discretion of the district director without center concurrence, except in specific program areas that require prior center concurrence. (See Center Concurrence and Letters Issued by Centers.) Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.)

In determining whether to issue a Warning Letter, District Directors should consider whether:

1. Evidence shows that a firm, product, and/or individual is in violation of the law or regulations and that failure to achieve adequate and prompt correction may result in enforcement action.

2. The Agency policy is clear concerning the violation(s) and the violation(s) are determined to be of regulatory significance.

3. There is a reasonable expectation that prompt correction will occur.

4. The nature of and the circumstances surrounding the violation(s) are appropriate to issuance of a Warning Letter.

5. The violations do not fall within the specific program areas requiring Center concurrence.

4-1-4 Center Concurrence And Letters Issued By Centers

Center concurrence is required prior to issuing Warning Letters in the following areas, or Warning Letters are issued directly by the Center.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

A. ALL CENTERS

1. All labeling violations - except where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins.
2. Computer application and software violations.
3. Bioresearch Monitoring Program violations.
4. Product advertising violations.

Note: Only the Centers issue Warning Letters for violations associated with product advertising, OTC drug monographs, and the Bioresearch Monitoring Program.

B. CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

1. New drug charges - including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements.
2. Adverse drug reaction reporting violations.
3. Novel and unusual tamper-resistant packaging violations.
4. Prescription Drug Marketing Act violations.
5. Investigational drug use violations.
6. CGMP** charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies.
7. CGMP** charges involving all dosage forms, including medical gases.
8. CGMP** charges involving Team Biologics (Core Team) inspections of facilities for therapeutic biologic products regulated by CDER

** CGMP Warning Letters covered by items 6, 7 and 8 above - Forward copies of the proposed Warning Letter, the FDA 483 supporting the alleged violations identified in the proposed Warning Letter, the EIR (without Exhibits), and any written response by the firm (without

attachments) electronically. Attachments to written responses to the FDA 483 and/or Exhibits should be forwarded electronically upon request of the Center. CDER has established a separate mailbox for electronic submission of Warning Letters from district offices. The address is: CDER Drug WL. Send the information to the attention of the Branch Chief, Case Management and Guidance Branch. For any questions, contact the Branch Chief, Case Management and Guidance Branch, HFD-326, voice 301-827-9022, fax 301-827-8908.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

C. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

1. Donor re-entry violations (e.g., HBsAg, anti-HIV-1).

2. Violations relating to drug or device GMPs.

3. Violative inspections of federal government agencies.

4. Violative inspections of Team Biologics (Core Team) inspection of facilities for biologic products regulated by CBER.
5. Viral marker test run deficiencies.** (See below)

6. Violations in areas where specific guidance has not been provided.** (See below)

7. Human tissue for transplantation - the issuance of a Warning Letter to a firm following the issuance of an Order for Recall, Retention, and Destruction is not usually appropriate since enforcement action will have already been taken. If a District identifies circumstances in which a Warning Letter seems to be appropriate, the recommendation should be submitted to CBER for review.

****Viral marker testing violations**: The Districts no longer need Center concurrence regarding viral marker testing violations. However, Center concurrence is required for Warning Letters based on invalidation of viral marker test run deficiencies since Center guidance on this issue is relatively recent.

****Violations in areas where specific guidance has not been provided**: The Center would not be in a strong position to issue a Warning Letter if there is no policy on an issue, or if the agency's policy is not clear. In these situations, we encourage the District to contact the Division of Case Management in CBER's Office of Compliance and Biologics Quality before recommending a Warning Letter to the Center.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for

submitting such letters to OCC, and include timeframes and routing information.

D. CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

1. All 21 U.S.C. 352(j) danger to health violations.

2. Medical device reporting violations which cite failure to report malfunctions as defined in 803.3(n). Center medical and technical expertise is necessary for these evaluations.
3. Restricted device violations.

4. Radiation Control for Health and Safety Act violations - except for sunlamp products and x-ray assemblers.

5. Violation of requirements for post market surveillance studies.

6. Any violation of device tracking regulations other than failure of the firm to implement any form of a tracking system.

7. All suspected violations of the user reporting regulations.

8. Failure to submit a premarket notification (510(k)) or Premarket Approval (PMA) Application.

9. Failure to submit a 510(k) or a PMA supplement for a significant modification(s) and/or the addition of a new intended use(s) to a previously cleared or approved device.
10. All violations arising from pre-approval PMA inspections including supplements to a previously approved PMA application.

11. Mammography Quality Standards Act (MQSA) violations in the following situations, unless superseded by a relevant Compliance Program or other directive:
    (a) Where numerous Level 2 or 3 inspection findings were observed, but no single noncompliance constitutes a Level 1 or repeat Level 2 inspection finding; or
    (b) Any situations not specifically identified as a Level 1 noncompliance or repeat Level 2 noncompliance.

Note: For direct reference situations regarding MQSA violations, reference the instructions contained in Part V of the Compliance Program or other directive.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

E. CENTER FOR VETERINARY MEDICINE (CVM)

1. Product approval violations.

2. Tissue residue violations where no tolerance has been established**, or which involve the use of compounded products.

3. Feed contaminant violations where no tolerance has been established.

4. Adverse drug reaction reporting violations.

5. Low acid canned pet food violations requiring technical review.

6. CGMP violations for medicated feed [21 CFR Part 225], Type A Medicated Articles [21 CFR Part 226], and dosage form drugs [21 CFR Part 211]. Submit complete recommendation package (recommendation, EIR, CRs, all exhibits, and other supporting documents).

**Direct reference authority for tissue residue violations where no tolerance has been established may be given to districts on a case-by-case basis.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

F. CENTER FOR FOOD SAFETY AND APPLIED NUTRITION (CFSAN)

All violations not covered by direct reference authority, in a Compliance Policy Guide, or Compliance Program. These include, but are not limited to, the following examples:

1. Pesticide and chemical contamination violations not covered by direct reference authority.

2. Dietary Supplements, medical foods, and infant formulas.

3. Low acid and acidified canned foods (LACF) violations.

4. Food and color additive violations.

5. Seafood HACCP violations not covered by direct reference authority in the Compliance Program.

6. All situations involving violations of section 402 (a) (4) of the Act, including deviations of CGMP regulations for foods, low acid and acidified canned foods, bottled water and any other CGMP regulation concerning CFSAN issues, e.g., dietary supplements.

7. Mycotoxins

8. Animal drugs in foods (aquaculture chemotherapeutic agents).

9. Food standards

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-5 Letters For Illegal Promotional Activities

Centers should issue Warning Letters, not untitled letters, for promotional activities if the nature of the activity is such that the Center would support further regulatory action. Do not use Warning Letters or untitled letters if the Center would not support regulatory action. The Center should alert the district office of the violation and ask that they bring the promotional activity to the attention of the firm on the next scheduled visit. If the district inspection reveals additional problems, this violation may be included as part of their regulatory action plan. If the problem is urgent the district could request a meeting with the firm to discuss the violations.

4-1-6 Multiple Center Review

When the district is aware that the issues in a Warning Letter will require multiple Center review, the Warning Letter recommendation should be submitted concurrently to each Center involved. However, when the district is unaware that the issues involve more than one Center, then the Centers will review the Warning Letter in sequence. Each Center's 15 working day review time frame will begin at the time the submission is received at that Center. To facilitate a timely review, the lead Center should forward a copy of the recommendation to the other Center(s) and incorporate the other Center's comments into a single document.

4-1-7 Time Frames

Within fifteen (15) working days after completion of the inspection, or, if applicable, sample analysis, the district should submit a Warning Letter recommendation to the appropriate reviewing office for concurrence.

Within fifteen (15) working days after receipt of the Warning Letter recommendation, the Center should review the Warning Letter and notify the district office of its decision. If the Warning Letter is disapproved, the Center will notify the district office of its decision within 15 days of receipt, and will issue a memorandum stating its reasons for disapproval within 30 days, or as soon after that as possible. A copy of the disapproval memorandum should be provided to HFC-210 and HFC-230. If the Warning Letter is approved, the Center will forward its approval memo and the proposed Warning Letter, as appropriate, for further review and concurrence. See Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning

Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

The District compliance officer (or, the Center CSO/Scientist, if the Warning Letter was Center-initiated) assigned to the Warning Letter should diligently pursue and actively monitor the progress of the case through the Agency review process to its conclusion (i.e., voluntary compliance or enforcement action). The Office of Enforcement (Division of Compliance Management and Operations) can assist in situations where significant delays are experienced or assistance is needed to resolve technical, scientific, or policy issues. (Also, see section on Ad Hoc Committees in Chapter 10.)

4-1-8 Warning Letter Follow-Up

The issuing district or Center will evaluate the response to the Warning Letter. If the response is inadequate, or if no response is received, the district or Center will begin follow-up action as necessary to achieve correction.

If the response appears adequate, the district or Center will verify that commitments have been fulfilled and that correction has been achieved, and will notify other appropriate Agency units. Follow-up inspections should be conducted promptly after the agreed upon date of completion of the promised corrections, if necessary to assure that corrections have been implemented

A. ACKNOWLEDGMENT OF RESPONSE TO A WARNING LETTER

The district or Center that issued the Warning Letter should acknowledge responses received to Warning Letters with an appropriate written response with copies to other Agency units involved.

B. FOLLOW-UP ENFORCEMENT

If a firm has been issued a Warning Letter, and it continues to operate out of compliance, districts and Centers should consider further enforcement options. A second Warning Letter should not be issued for similar violations. However, Districts and Centers have the option of conducting a meeting with firm's management prior to pursuing an enforcement action. If prompt voluntary compliance is not achieved, such meetings serve as further prior notice. (See section on Prior Notice in Chapter 10.)

C. INSPECTION CLASSIFICATION

A Warning Letter constitutes official Agency action. Inspections will be classified Official Action Indicated, OAI, whenever a Warning Letter is issued. This procedure provides greater consistency and uniformity in the classification system and regulatory policy. Inspections should not be re-classified from OAI due to failure to meet the 15 working day timeframe for issuing a Warning Letter.

OAI classifications based on tissue residue violations should not have mandated follow-up inspections unless additional violations have been reported to the Agency by the Department of Agriculture's Food Safety and Inspection Service.

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For further information on classification of inspections see Field Management Directive No. 86, or refer to the web site at http://www.fda.gov/ora/inspect_ref/fmd/fmd86.htm

4-1-9 Firm Profile Updates In Facts

The district or Center must promptly update the firm profile in FACTS when a drug, biologic or medical device Warning Letter is issued. Update the profile again when it is determined that corrections have been achieved, if the Warning Letter has been disapproved and the inspections status is changed from OAI to VAI, or when further enforcement action is recommended or taken. For Warning Letters issued under a Bioresearch Monitoring Program, corrective actions may not be verified until the next inspection as requested by the Center. The Centers update the FACTS firm profile for foreign inspections of drug, device, and biologic manufacturers. For more detailed instructions, refer to the Office of Enforcement, Division of Compliance Information and Quality Assurance (DCIQA) Intranet Homepage. Please contact DCIQA, HFC-240 with questions.

4-1-10 Warning Letter Format

Warning Letters can vary in form, style, and content to provide the flexibility needed to accurately and effectively state the nature of the violation(s) found and the response expected. However, the elements listed below are common to Warning Letters:

1. Titled "WARNING LETTER."

2. Delivery - Warning Letters should be sent to ensure overnight delivery and receipt of delivery (e.g., return receipt requested, FedEx) should be documented.

3. Issued to the responsible individual who, based on currently available evidence, is most closely related to the violation, to that person's superior, and to the highest known official (original of letter) in the organization. Each person in the organization issued a copy is identified on the Warning Letter.

4. The dates of the inspection and a description of the violative condition, practice, or product in brief but sufficient detail to provide "prior notice" and provide the respondent opportunity to take corrective action. Include citation of the section of the law or regulation violated.

5. The Warning Letter should appropriately acknowledge corrections promised during the inspection, or annotated on the 483, or provided to the district in a written response.

6. A request for correction and a written response within a specific period of time after the date of receipt of the letter, usually fifteen (15) working days. At the district's discretion, the recipient may be offered an opportunity to discuss the letter with district officials or, when appropriate, with Center officials.

7. A statement in drug and medical device Warning Letters that: "Federal agencies are advised of all Warning Letters about drugs and devices so they may take this information into account when considering the award of contracts." This does not apply to Warning

Letters issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials.

8. Instructions, as appropriate, that the response include: (1) each step that has been or will be taken to completely correct the current violations and to prevent similar violations; (2) the time within which correction will be completed; (3) any reason the corrective action has not been completed within the response time; and (4) any documentation necessary to show that correction has been achieved.

9. A warning statement that failure to achieve prompt correction may result in enforcement action without further notice. Examples of such actions may be cited. Do not include a commitment to take enforcement action.

10. A designated district or Center official to whom the response should be addressed.

11. Issued by the District Director, division director, or higher Agency official. Some program areas will require Center concurrence before issuance.

4-1-11 Warning Letter Distribution

Warning Letter distribution is as follows:

1. Original – Addressee(s)

2. One redacted copy to HFI-35 for public display under FOI regulations. Do not send credit page with drafting, clearance record, or blind copies to HFI-35. Include the name or initials of the person redacting the letter and the date redacted for release on the redacted copy for future reference.

3. One copy each to:

Each person identified in the Warning Letter
HFA-224
HFC-210 (Division of Compliance Management and Operations)
HFC-230 (Division of Compliance Policy)
Center Compliance unit (by special mail, fax, or as otherwise directed by the governing Compliance Program Guidance Manual (CPGM), which may request sending electronic copies to a specified e-mail account). For example:
HFD-300 (CDER)
HFM-610(CBER)
HFZ-300 (CDRH) and, for MDR letters only, HFZ-533
HFV-230 (CVM)
HFS-605 (CFSAN)
HFC-130 ORA - DFI (Foreign (International) letters only)
HFC-170 ORA - DIOP - for Import letters only
Appropriate district office, for all Center-issued Warning Letters.
Appropriate district office, for all establishment locations that receive either an original or a copy of Warning Letter.
HFC-240 (Division of Compliance Information and Quality Assurance) only for drugs, devices and any biological drug or device

Local Distribution, factory file, WL file, resident post, and appropriate federal and state agencies.

4. Offices or individuals identified as blind copies (bcc) on credit page.

4-1-12 Warning Letters To Importers And Foreign Firms

A. IMPORTER WARNING LETTERS

See Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information. Center concurrence is not required, except in certain program areas that require prior Center concurrence.

Warning Letters may be issued to importers of FDA regulated products that engage in business practices that appear designed to evade the lawful regulation of imports. The "Priority Enforcement Strategy for Problem Importers," chapter provides guidance for the use of Warning Letters, and other enforcement actions, against importers.

Generally, it is not appropriate to take enforcement action against a customs broker. The owner, consignee, or importer is normally the responsible party for imported goods. However, if the broker is the owner, consignee, or importer identified on the import documents, or if the broker has authority over the product through prior arrangement with the importer, it may be appropriate to issue a Warning Letter to the broker. Assure that the broker is responsible for the violation.

Import Alert #00-17 contains a list of Warning Letters issued to importers.

Contact DIOP, Policy and Enforcement Branch (HFC-172) 301-443-6553 about issuing or using a Warning Letter involving an importer, consignee, owner, or broker of imported goods.

B. IMPORT BROKERS

By statute, 19 U. S. C. Section 1641, the United States Customs Service (Customs) has the responsibility for ensuring that brokers comply with the law. Customs, not FDA, has the authority to follow through on regulatory action against violators. When a broker fails to fulfill his statutory obligations as a broker, and FDA decides that a warning is appropriate, FDA should send an untitled letter telling the broker of the violation and warning that any future violation will be reported to customs.

There are some cases in which it may be appropriate to send a Warning Letter to a broker such as when the broker is functioning as the importer of record and violates a provision of the Act. The Warning Letter is issued to the broker in his capacity as importer of record. It is often difficult to distinguish between a broker performing his duties as a broker or as an importer of record. The only guidance the Act or its implementing regulations offers on the definition of

owner or consignee is found in 21 CFR 1.83(a). Section 1.83(a) defines an owner or consignee as "the person who has the rights of a consignee under the provisions of Sections 483, 484, and 485 of the Tariff Act of 1930, as amended (19 U.S.C. 1483, 1484, and 1485)." [21 CFR 1.83(a)] Section 483 of the Tariff Act was repealed in 1983. Under Sections 484 and 485, a consignee's rights consist primarily of filing any documentation required to allow foreign goods entry into the United States. [19 U.S.C. 1484, 1485]
The former Section 483 of the Tariff Act says the consignee of imported goods is the consignee declared on the bill of lading or air waybill, unless the consignee conferred its rights to other persons through endorsements on such documents. [19 U.S.C. Section 1483 (repealed 1983)]. The current Section 484(a)(2)(C) says the documentation required to make entry of goods "shall be filed either by the owner or purchaser of the goods or, when appropriately designated by the owner, purchaser, or consignee of the goods, a person holding a valid license under Section 1641 of this title." [19 U.S.C. Section 1484(a)(2)(C)]. While the person "appropriately designated" (that is, a customs broker licensed under 19 U.S.C. Section 1641) is often the importer of record, Sections 484 and 485 of the Tariff Act recognize, as did the former Section 483, that neither the consignee nor the importer of record is necessarily the true owner of the imported goods. So under Sections 484 and 485, only the importer of record (owner or purchaser, or a broker or broker designee) may make customs entry. [Id.; 19 U.S.C. 1485 (a)]

Usually, the broker will not be the party responsible for causing the violation of the import provisions of the Act. While the broker files the entry documentation, he exercises little, if any control over the goods itself. The owner/consignee/importer usually controls the movement of the goods and, therefore, bears the legal responsibility for complying with the Act.

To determine the proper addressee of a Warning Letter, send the letter to the person or entity identified on the entry documents as the importer. Under Sections 484 and 485 of the Tariff Act, the importer of record always has the rights of the consignee. In other words, one must be an owner, consignee, or the authorized agent of either (the customs broker engaged to make entry) to be the importer of record. If there are other individuals with an interest in the goods but FDA is unsure of the extent of the interest, the importer of record should be able to identify those individuals and notify them of the violation. If FDA is aware of other persons or entities with an interest in the goods, the Agency should send courtesy copies of the Warning Letter to them.

C. FOREIGN FIRMS

A Warning Letter may be appropriate if FDA has regulatory authority over the company and is prepared to exercise that control. Firms are placed on detention without physical examination because of repeatedly offering violative products for import. Unless the foreign firm is under the regulatory purview of FDA, issuing Warning Letters should be discussed with the Office of the Chief Counsel. For foreign manufacturers of devices, and drugs, CDRH and CDER issue Warning Letters based on review and concurrence with district recommendations in the foreign inspection reports. For CBER regulated products, administrative actions may also be considered for licensed foreign establishments.

4-1-13 Freedom Of Information (FOI)

Send a redacted copy of all Warning Letters to the Freedom of Information Staff, HFI-35, when

the letters are issued. Do not send the credit page with drafting and/or clearance records, or blind copies to HFI-35. Caution: See procedures below for Release of Warning Letters.

Include the name or initials of the person redacting the letter and the date redacted for release on the redacted copy for future reference.
Warning Letters are available on FDA's Internet Website at http://www.fda.gov/foi/warning.htm and are on public display at the Freedom of Information Staff office.

A. RELEASE OF WARNING LETTERS

District and Centers should use the following procedures before the release of a Warning Letter through a FOI request:

FOI requests for Warning Letters should be sent to the FOI Staff (HFI-35) for response. FOI requests can also be sent by facsimile to (301) 443-1726. Do not accept telephone or electronic requests for Warning Letters.

The address to send written requests for Warning Letters is:

Freedom of Information Staff (HFI-35)
Food and Drug Administration
Room 12A16
5600 Fishers Lane
Rockville, MD 20857
(301) 827-6567

The district or Center may release a redacted Warning Letter directly, if the Warning Letter either needs no non-public information to be redacted or the non-public information has been redacted, the Warning Letter is readily available, and no prepayment is necessary. (See the Information Disclosure Manual, "Freedom of Information Act," "Responsibilities of a Component FOIA Officer," item 2, for further details.) Assure that the addressee has received the original letter prior to releasing a redacted copy of the letter to another party. In that case, the component FOIA Officer may release the Warning Letter and then send a copy of the request, the response, and if appropriate, a copy of the records to the Division of FOI (HFI-35), noting the name and address of the requester, and the charges, if any.

4-1-14 Center For Biologics Evaluation And Research (CBER)

The compliance programs for CBER regulated products are located at: www.fda.gov/cber/cpg/cpg.htm. Evaluate violations to decide if they warrant administrative or regulatory action or both. To help in this determination, refer to Part V of each Compliance Program, which provides information on deviations that may warrant action.

The organizational unit in the CBER Office of Compliance and Biologics Quality (OCBQ) which handles warning letter recommendations is the Division of Case Management, HFM-610. They can be reached at (301) 827-6201.

A. CBER PROGRAM WARNING LETTERS

1. All correspondence to licensed establishments should be addressed to the most responsible person. A copy of the correspondence should also be sent to the authorized official. For unlicensed establishments, correspondence should be addressed to the most responsible individual, e.g., blood bank director or hospital administrator.

2. The lists of significant deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. (See Attachments A and B of CP 7342.001 and CP 7342.002.) Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter. Additionally, districts may consider issuance of a Warning Letter to a firm with a history of similar or substantially similar significant deficiencies about which the manufacturer has been advised.

3. The specific areas that require CBER concurrence for District Directors to issue a Warning Letter are listed above in "Center Concurrence and Letters Issued by Centers." In addition, districts do not have direct reference authority to issue a Warning Letter to other federal agencies. Once the appropriate reviews are completed, Warning Letters are issued directly by the district, with the exception of Team Biologics Warning Letters, which issue from the OE after CBER concurrence.

   Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4. Schedule a follow-up inspection approximately 30 days after the response to the Warning Letter is received to determine the adequacy of the reported corrective actions. When corrective action has not been made or the firm has failed to respond, the district should consider suitable follow-up.

5. Send copies of all Warning Letters to Division of Case Management (HFM-610).

6. Districts should routinely provide copies of Warning Letters to the appropriate state agency or agencies. If the state regulatory office for these products is not known, contact ORA, Division of Federal-State Relations, HFC-150, (301) 827-6906. The letter should be redacted to protect confidential commercial information unless the state officials are commissioned. See Chapter 3 for commissioning procedures.

B. FEDERAL-STATE RELATIONS FOR BLOOD BANK INSPECTIONS

Currently, the Agency has no formal cooperative program with state or local jurisdictions for the inspection or regulation of blood banks. Cooperation with these authorities is encouraged especially if a state or local jurisdiction has a regulatory program for blood banks. Exchange of information should occur with all levels of state government whenever possible.

C. CURRENT GOOD MANUFACTURING PRACTICES (CGMPS) REGULATIONS FOR FINISHED PHARMACEUTICALS: REGULATORY ACTIONS FOR BLOOD ESTABLISHMENTS

21 CFR Part 211, CGMPs, applies to blood establishments. CBER review and concurrence is required for Warning Letters about deviations from Part 211 that are not associated with Part 606, e.g. 21 CFR 211.68. Direct reference authority does not include citing blood establishments for deviations from Part 211 CGMPs in Warning Letters.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

D. ADVERTISING AND PROMOTIONAL LABELING BRANCH PROCEDURAL GUIDE

The Advertising and Promotional Labeling Branch (APLB) in the Division of Case Management, Office of Compliance and Biologics Quality, may initiate regulatory action if the advertising and promotional labeling are not consistent with the approved labeling (package insert), clinical data used to approve the product, or applicable sections of the Act and regulations for labeling and advertising by notifying the manufacturer in writing of the violations.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

E. WARNING LETTERS RECOMMENDATIONS

Send tissue establishment Warning Letter recommendations to CBER for review and concurrence. When an Order for Recall, Retention, and Destruction has been issued for violations involving human tissue for transplantation it is not usually appropriate to issue a Warning Letter because the enforcement action has already been taken.

Send Warning Letter recommendations for CBER to Office of Compliance and Biologics Quality.

For Blood, Plasma and Tissue:
Chief, Blood and Tissue Compliance Branch
Division of Case Management, HFM-614

For Biological Drugs and Devices:
Chief, Biological Drug and Device Compliance Branch
Division of Case Management, HFM-624

Direct CBER Warning Letter questions to the Division of Case Management, HFM-610 301-827-6201.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-15 Center For Drug Evaluation And Research (CDER)

A. PREAPPROVAL INSPECTIONS/PENDING APPLICATIONS - WITHHOLD APPROVAL

Warning Letters are not to be recommended by the District Offices as a follow-up to a preapproval inspection for pending drug or device applications (ANDAs, NDA, PMAs) if no other FDA regulated products are marketed by the firm.

Warning Letters may be recommended by the District Offices for preapproval inspections of drug and device firms if other FDA regulated products are marketed by the firm. These letters should include the following statement: "Due to the deficiencies listed on the attached FDA-483 we are recommending to the Center that approval of the "…" application be withheld."

In 2003, there has been a reassignment of regulatory program responsibility for certain biologic drug products from CBER to CDER. Generally, these products are monoclonal antibodies for diagnosis and therapy, cytokines, immunomodulators, growth factors and thrombolytics. The preapproval inspection operations for these drugs will be conducted by CDER staff.

B. SURVEILLANCE INSPECTIONS FOR ASSESSING COMFORMANCE WITH CGMPs

Warning Letters may be recommended by the District Offices based on findings from surveillance inspections made to assess conformance of a manufacturing site with the CGMP requirement in the Act. See *Standard Charge # 6* in *Section C*, below. In therapeutic biologic drugs, operations to assess their conformance to the CGMP's will be conducted by Team Biologics Investigators. These drugs will be subject to the same regulatory procedures and actions as other drugs regulated by CDER, however, Team Biologics Compliance Officers (rather than the district) will be responsible for initiating and preparing these actions. If there is a question of which regulatory group presides over a therapeutic biologic drug, contact the Branch Chief, Therapeutic Biologic Drug Branch, Division of Manufacturing and Product Quality at 301-827-6886.

C. STANDARD CDER CHARGES

1. Grandfather New Drug Charge: The charge for drugs that claim to have been on the market before 1938 or before 1962:

> 505(a) The articles are new drugs within the meaning of Section 201(p) of the Act and approval of an application filed under Section 505(b) of the Act is not effective for such drugs and a Notice of Claimed Investigational Exemption under Section 505(i) of the Act

and Part 312 of the CFR is not on file for such drugs, and documentation in support of such drugs, and "grandfather" exemption has not been submitted per 21 CFR 314.200(e)(2) which constitutes a waiver of such claims.

2. Back Door New Drug Charge: When the new drug charge (505) cannot be used because of lack of interstate movement of the article to be seized but there is documentation of the interstate movement of a component as a 301(k) sample then the charge is that the product was misbranded while held for sale:

> 502(f)(1) The article of drug, (DRUG NAME), is misbranded in that its labeling fails to bear adequate directions for the use for which the article is represented or suggested (as described above), and it is not exempt from this requirement under regulation 21 CFR 201.115, since the article is a new drug within the meaning of Section 201(p) of the Act and no approval of an application filed pursuant to Section 505(b) of the Act is effective for this drug.

A 502(f)(1) charge is appropriate for OTC drugs for which the directions are “inadequate in fact.” These are drugs which: a) have no directions; b) have directions that deviate from those required by a final monograph; or c) have directions, but those directions lack information which is necessary for the drug to be used safely, such as dosage or frequency of administration. (See 21 CFR 201.5.) However, a 502(f)(1) charge should not be used if “adequate directions for common uses thereof are known to the ordinary individual.” (See 21CFR 201.116.)

A 502(f)(1) charge is appropriate for all prescription drugs that are unapproved new drugs. This includes a drug with an indication that is generally not amenable to lay diagnosis, even if the drug would not ordinarily be thought of as a prescription drug (e.g., shark fin cartilage for the treatment of cancer.)
When the product is not a new drug, the simple misbranding charge should read:

> 502(f)(1) The article of drug, (DRUG NAME) is misbranded in that its labeling fails to bear adequate directions for use for which the article is represented or suggested.

3. Prescription Drug Where There Is No Labeling Bearing Directions for Use
The charge is as follows:

> 502(f)(1) The article(s), (DRUG NAME), is subject to the provisions of Section 503(b)(1) of the Act and it is not exempt from Section 502(f)(1) of the Act in that its labeling fails to bear information required by regulation 21 CFR 201.100, providing adequate directions for use under which a practitioner licensed by law can use the drug safely and for the purposes for which it is intended, including indications; effects, dosages, routes, methods, frequency and duration of administration, relevant hazards; contraindications, side effects, and precautions.

4. Drug Registration and Listing
The charge is misbranding under section 502(o) of the Act but the violation is failure to register and list:

> 502(o) The articles, (DRUG NAMES), are misbranded in that they were manufactured in

an establishment not duly registered under Section 510 of the Act and the articles have not been listed as required by Section 510(j) of the Act.

5. Prescription Drugs

Section 503(b)(1) provides criteria for determining if the article is a prescription drug. Section 503(b)(1) is not a violation charge:

> 503(b)(1) The article, (DRUG NAME), because of its toxicity or other potential for harmful effect, or the method of use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, and is misbranded because it is not dispensed upon prescription by a licensed practitioner.

The charge is:

For a prescription drug:

> 503(b)(4)(A) The article of drug, (DRUG NAME), is subject to Section 503(b)(1) of the Act and is misbranded in that its label fails to bear the symbol, "Rx only."

For an OTC drug that is not to bear the symbol, “Rx only”:

> The article of drug, (DRUG NAME), is not subject to Section 503(b)(1) of the Act and is misbranded in that its label bears the symbol, "Rx only” and it is not entitled to bear such symbol.

The following straight UNAPPROVED NEW DRUG charge may be used when there is interstate movement of the finished, labeled drug product.

> 505(a) The article of drug, (DRUG NAME), is a drug within the meaning of Section 201(g) of the Act which may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act, since it is a new drug within the meaning of Section 201(p) of the Act and no approval of an application filed pursuant to Section 505(b) of the Act is effective for such drug.

For information regarding health fraud issues, contact the Internet and Health Fraud Team at (301) 827-8931.

6. Adulteration Due To Inadequate Conformance with CGMPs

The charge is as follows:

> 501(a)(2)(B) The article(s), (DRUG NAME), is (are) adulterated within the meaning of Section 501(a)(2)(B) of the Act in that the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding fails to conform to, or is not operated or administered in conformity with, CGMP regulations [21 CFR 210, 211].

4-1-16 Center For Devices And Radiological Health (CDRH)

A. VIOLATIONS UNDER THE MAMMOGRAPHY QUALITY STANDARDS ACT (MQSA)

For routine Level 1 or repeat Level 2 noncompliances found during MQSA inspections, districts will not need CDRH concurrence before sending Warning Letters. Also, districts may send a Warning Letter without CDRH concurrence when a facility has performed mammography without a certificate. Under other circumstances, where inspections show numerous Level 2 and 3 noncompliances but no Level 1 or repeat Level 2 noncompliances, districts will need CDRH concurrence before sending a Warning Letter. For any of the situations mentioned above where CDRH concurrence is needed for an MQSA Warning Letter, the district should send the draft Warning Letter to the Division of Mammography Quality and Radiation Programs. (See Part V of the Compliance Program or other directive for additional case guidance.)

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

B. SAMPLE WORDING FOR CHARGES

1. Adulteration

Section 501(f)(1)(B) - in that it is a Class III device under Section 513(f) and does not have an approved application for premarket approval in effect pursuant to Section 515(a) or an approved application for an investigational device exemption under Section 520(g).

Section 501(c) - in that its strength, purity, or quality falls below that which it purports or is represented to possess.

Section 501(h) - in that the methods used in, or the facilities or controls used for, the manufacture, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

2. Misbranding Charges

Section 502(a) INEFFECTIVE or QUACK DEVICE - in that the labeling for the device represents or suggests that the device is adequate and effective for (……), which representations or suggestions are false or misleading or otherwise contrary to fact because the device is not adequate or effective for such purposes.

Section 502(a) REFERENCE TO SECTION 510(k) # - in that the labeling of the device contains the statement, (e.g., "US FDA #K912345"), which is misleading in accordance with 21 CFR 807.97, because such statements create an impression of official approval of the device which is complying with the premarket notification regulations. This device was not approved by the FDA, but was determined to be substantially equivalent within

the meaning of section 513(i)(1)(A) of the Act.

Section 502(a) REFERENCE TO ESTABLISHMENT REGISTRATION OR REGISTRATION # - in that the labeling of the device contains the statement, (e.g. “It is licensed as a Medical Device Establishment by the U.S. Food and Drug Administration” or “Medical Device Establishment Registration Number 1234567”), which is misleading in accordance with 21 CFR 807.39, because such statements create an impression of official approval due to registration or possession of a registration number. Registration of a device establishment or assignment of a registration number does not in any way denote approval of the establishment or its products.

Section 502(b) - in that the device is in package form and its label fails to contain: (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

Section 502(f)(1) INEFFECTIVE or QUACK DEVICE - in that the labeling for the device fails to bear adequate directions for the purposes for which it is intended, because adequate directions cannot be written for (e.g., such purposes, etc.).
Section 502(f)(1) EXPIRATION DATES FOR IVDS - in that the labeling for the device fails to bear adequate directions for use because the labeled expiration dates have not been established by reliable, meaningful, and specific test methods, as required by 21 CFR 809.10.

Section 502(o) - in that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510, was not included in a list required by Section 510(j), and a notice or other information respecting the device was not provided to FDA as required by Section 510(k).

Section 502(o) MODIFICATION OF THE DEVICE in that a notice or other information respecting the device was not provided to FDA as required by 21 CFR 807.81(a)(3)(i), when the device was significantly changed or modified by (describe change).

There is a model plain English Warning Letter for small businesses describing violations associated with the failure to obtain premarket clearance, which is available on the internet at: http://www.cdrh.fda.gov/offices/oc/engwarn.htm.

For examples of model Quality System regulation/MDR Warning Letters, see Compliance Program 7382.845 - Inspection of Medical Device Manufacturers.

CDRH has established a separate mailbox for electronic submission of device Warning Letters from district offices. The address is: CDRH FPB Device WL. Typing “deviceWL” in the address bar will insert the correct address.

C. LETTERS TO X-RAY ASSEMBLERS

Letters issued to assemblers of diagnostic x-ray systems as a result of routine compliance field testing which uncover Class B Violations (see CP 7386.003) will be issued as untitled letters. Letters issued for more serious radiation hazard violations (Class A Violations) which require

immediate corrective action will be issued as Warning Letters. Warning Letters may also issue to x-ray assemblers for "pattern of violations" situations where the Agency is prepared to take enforcement action if the violations continue and/or if failure to correct violations continues. Subchapter C - Electronic Product Radiation Control (formerly the Radiation Control for Health and Safety Act of 1968) of Chapter V of the Act requires the Secretary to notify the assembler/manufacturer concerning noncompliant or defective radiation emitting devices and solicit follow-up corrective action by the assembler/manufacturer whether or not the Agency is prepared to take follow-up enforcement action. If there are specific cases to discuss or a need for further information on this subject, contact CDRH, Office of Compliance, HFZ-300, (301) 594-4692.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-1-17 Center For Food Safety And Applied Nutrition (CFSAN)

CFSAN will provide instructions for priority areas to be covered in Warning Letters in Compliance Programs.

4-1-18 Tracking

IDENTIFICATION OF WARNING LETTERS

To facilitate the tracking of Warning Letters, every Warning Letter issued by a district or Center office should bear a sequential code number. This code number should identify the fiscal year issued, the district or Center issuing the letter, and a sequential number for the Warning Letters issued by that office.

4-2 UNTITLED LETTERS

4-2-1 Policy

An untitled letter cites violations that do not meet the threshold of regulatory significance for a Warning Letter. Therefore, the format and contents of an untitled letter should clearly distinguish it from a Warning Letter. For example:

The letter is not titled.

The letter does not include a statement that FDA will advise other federal agencies of the issuance of the letter so that they may take this information into account when considering the awarding of contracts.

The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.

The letter does not evoke a mandated district follow-up.

The letter requests (rather than requires) a written response from the firm within a reasonable amount of time (e.g., "Please respond within 30 days"), unless more specific instructions are provided in a relevant Compliance Program.

Any appropriate Agency compliance official may issue an untitled letter.

Also, see Exhibit 4-1, the Agency's "Procedures for Clearing FDA Warning Letters and Untitled Letters." All agency components responsible for issuing Warning Letters and Untitled Letters must follow these procedures. Developed to facilitate review of all Warning Letters and Untitled Letters by the Office of Chief Counsel (OCC), the procedures provide instructions for submitting such letters to OCC, and include timeframes and routing information.

4-3 EXHIBIT

4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters

Exhibit 4-1

Procedures for Clearing FDA Warning Letters and Untitled Letters

Revised April 24, 2004

Contents

1. Purpose

To facilitate the Office of Chief Counsel's review of all 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.

3. Background

On November 29, 2001, the 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 (see 8. Change History).

4. Definitions

For the purpose of these procedures:

4.1 A ***Warning Letter***, as explained in the *Regulatory Procedures Manual*, 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 as defined in the *Regulatory Procedures Manual.* 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 sections 6, 7, and 8, 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 The Office of Enforcement will review these procedures every twelve (12) months to evaluate their scope and effectiveness. Any refinements that become identified through the 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 FDA's Agency Information Management System (AIMS). The system provides the capability to enter and track Warning and Untitled Letters upon submission through the approval process. The action office (i.e. the District or Center initiating the recommendation) is responsible for submitting recommendations to AIMS as well as updating data related to their submissions. Instructions for using the AIMS system can be found at the OE Warning Letter Home Page on FDA's Intranet. Submissions are entered into the system via a tracking form and assigned a number (VL number).

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 of all Warning Letters 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 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

If 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. For further guidance, refer to *Instructions and Frequently Asked Questions Regarding Warning Letter Responses* on the Warning Letter Home Page on FDA's Intranet.

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.

Pursuant to OCC's review of Untitled Letters, 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

6.2.1. General Procedures for Direct Reference Warning and Untitled Letters

(a) District Office Responsibilities

(1) Within 15 working days after the completion of an inspection, the sample analysis, or date of evidence collection, submit a draft "final" Warning Letter to OCC for concurrence, and send a copy to ORA's Office of Enforcement's (OE) email account **ORA Warning Letter**.

(2) Within 45 working days after the completion of an inspection, the sample analysis, or date of evidence collection, submit a draft "final" Untitled Letter to OCC for concurrence, and send a copy to OE's email account **ORAWarning Letter.**

(3) To facilitate OCC's review of the Warning or Untitled Letters, send 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 to OCC electronically. Do ***not*** send the EIR attachments or exhibits to OCC.

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

(5) 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.

(6) 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. 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, as appropriate, and drafted by OCC.

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

(8) If OCC concurs with the draft "final" Untitled Letter, issue the letter.

(9) 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.

(10) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter** and the Center whose products are the subject of the letter. Additional copies should be distributed to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(11) 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.

(b) OCC Responsibilities

(1) Review the draft "final" Warning Letter and Untitled Letter within 15 working days.

(2) If concurrence, send concurrence to the District's Director of the Compliance Branch along with a copy of the draft "final" letter with any edits (the District can then issue the letter).

(3) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.

(4) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the District, state ***in writing*** the reason for nonconcurrence, and send a copy to the Director of Compliance of OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

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) Send a copy of the draft "final" letter to OCC for concurrence.

(4) To facilitate OCC's review of the Warning or Untitled Letters, send 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 to OCC electronically. Do ***not*** send the EIR attachments or exhibits to OCC.

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

(6) 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.

(7) 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. 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, as appropriate, and drafted by OCC.

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

(9) If OCC concurs with the draft "final" Untitled Letter, issue the letter.

(10) 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.

(11) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter** and ORA's Office of Regional Operations (ORO), Division of Field Investigations (DFI). Additional copies should be distributed to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(12) 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.

(b) OCC Responsibilities

(1) Review the draft "final" Warning Letter and Untitled Letter 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) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.

(4) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center, state ***in writing*** the reason for nonconcurrence, and send a copy to the Director of Compliance of OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

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 and send a copy to OE's email account **ORA Warning Letter**.

(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 and send a copy to OE's email account **ORA Warning Letter**.

(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, send the Form FDA 483, the endorsement page of the EIR or the FACTS coversheet, the narrative portion of the EIR, the relevant exhibits, and, if applicable, the summary of any sample analysis to the Center electronically. (Refer to the Warning Letter Website on FDA's intranet for instructions regarding electronic submission of information to specific Centers.)

(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 attorney that is conducting the review, as appropriate. 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. 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, as appropriate, and drafted by the office conducting the review (the Center or OCC).

(6) If the Center approves the recommendation and OCC concurs, issue the letter.

(7) 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.

(8) Upon issuance, send a signed copy of the Warning or Untitled Letter to the Center and OE's email account **ORA Warning Letter**. Additional copies should also be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(9) 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.

(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.

(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.

(3) 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 should also copy the District and send a copy of the draft "final" letter to OE's email account **ORA Warning Letter**.

(4) To facilitate OCC's review of the Warning or Untitled Letters, send 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 to OCC electronically. Do ***not*** send the EIR attachments or exhibits to OCC.

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

(6) If the Warning Letter recommendation is ***not*** approved, the Center will notify the District's Director of the Compliance Branch, OCC, and OE of its decision within 15 working days. (OE has an email account for this purpose entitled **ORAWarning Letter Nonconcur**) 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.

(7) If the Untitled Letter recommendation is ***not*** approved, the Center will notify the District's Director of the Compliance Branch, OCC, and OE of its decision within 45 working days. (The same OE email account entitled **ORA Warning Letter Nonconcur** should be used for this purpose.) 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.

(c) OCC Responsibilities

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

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

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

(4) Send a copy of the concurrence to the Center and to OE's email **account ORA Warning Letter**.

(5) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the District, state ***in writing*** the reason for nonconcurrence, and send a copy to the Director of Compliance, OE at OE's email account **ORA Warning Letter Nonconcur**.

(d) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

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) Submit a draft "final" Warning Letter or Untitled Letter to OCC.

(3) To facilitate OCC's review of the Warning or Untitled Letters, send 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 to OCC electronically. Do ***not*** send the EIR attachments or exhibits to OCC.

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

(5) 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.

(6) 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. 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, as appropriate, and drafted by OCC.

(7) If OCC concurs, the Center can issue the letter.

(8) 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.

(9) Upon issuance send a signed copy of the Warning or Untitled Letter to the District's Director of the Compliance Branch where the recipient of the letter is located and to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(10) 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 as necessary, to quickly address OCC's concerns.

(b) OCC Responsibilities

(1) Review the draft "final" Warning Letter within 15 working days.

(2) Review the draft "final" Untitled Letter 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) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.

(5) If ***non***concurrence or the letter is flagged because it raises significant issues, contact the Center, state ***in writing*** the reason for nonconcurrence, and send a copy to the Director of Compliance, OE at OE's email account **ORA Warning Letter Nonconcur**.

(c) OE Responsibilities

Maintain a repository of all Warning and Untitled Letters that have been issued.

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) Send a copy of the draft "final" letter to OCC for concurrence.

(3) To facilitate OCC's review of the Warning or Untitled letter, send the evidence to OCC that supports the issuance of the letter.

(4) If OCC concurs, issue the letter.

(5) Upon issuance, send a signed copy of the Warning or Untitled Letter to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or RPM Chapter 4.

(6) 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.

(b) OCC Responsibilities

(1) Review the draft "final" Warning Letter within 15 working days.

(2) Review the draft "final" Untitled Letter 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) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.

(5) 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.

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, 7, and 8 (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 to OCC within the 3 working day period.

(3) To facilitate OCC's review of the letter, the Health Hazard Evaluation and the pertinent evidence that establishes that a danger to health exists should be submitted to OCC electronically.

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

(5) 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.

(6) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**. Additional copies should be distributed, as necessary, to all Agency components identified in the Compliance Program and/or 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) Send a copy of the concurrence to OE's email account **ORA Warning Letter**.

(4) 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 Untitled Letters that have been issued.

6.3.2 License Revocation (For Cause)

(a) Center Responsibilities

(1) 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.

(2) If the issuance of a letter is appropriate, submit a draft "final" letter to OCC for their concurrence.

(3) To facilitate OCC's review of the letter, the Center should send the recommendation and any additional supporting documents to OCC electronically.

(4) If OCC concurs, issue the letter.

(5) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**.

(6) 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.

(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) Send a copy of the concurrence to OE's email account **ORA Warning 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 Untitled Letters that have been issued.

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 to OCC for their concurrence.

(3) To facilitate OCC's review of the NOIR letter, the recommendation should be sent to OCC electronically.

(4) If OCC concurs, issue the letter.

(5) Upon issuance, send a signed copy of the letter to OE's email account **ORA Warning Letter**.

(6) In the case of ***non***concurrence or the letter is flagged because it raises significant issues, the Center will work with OCC.

(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) Send a copy of the concurrence to OE's email account **ORA Warning 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 Untitled Letters that have been issued.

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

Districts are required to submit every fifth Warning Letter and every fifth Untitled Letter

through the routine procedures in this document. For all other letters that meet the criteria for direct reference authority in this program, districts may issue them directly, using the model letters identified for such use (available on the Warning Letter Website on FDA's intranet). These model letters must be followed for all letters under this program issued on or after the associated effective date

At the district's discretion, 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 every fifth letter.

(b) District Responsibilities

Use the model letter for all untitled letters and warning letters issued on or after the effective date. Each district must set up a system whereby every fifth untitled letter and every fifth warning letter are submitted for OCC review using the procedures in this document. All other letters matching the audit review criteria may issue without OCC review. The system established must be available for review to determine conformance with these procedures.

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

None. This option relates only to letters for which the field has direct reference authority.

(d) OCC Responsibilities

Review untitled letter and warning letter recommendations submitted by the field, representing every fifth letter in each category to be issued by a particular district on or after the effective date, 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. Review conformance with these procedures as part of the periodic evaluation.

6.4.1 Radiological Health Letters

Currently, the only model letter approved under this audit program is the Notification to X-Ray Assemblers of Defect or Noncompliance as the Result of Field Testing. The link to this letter can be found on the Warning Letter Website on FDA's intranet. The effective

date for use of this letter is March 1, 2004.