U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

4-1 - WARNING LETTERS

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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; and,

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 is adulterated under Section 402(a)(3) or 402(a)(4) of the Act;
2. There is a violation of CGMP;
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 establishments should be held to the same standards as nongovernment 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 nongovernment 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 government establishment'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.

Whenever significant violations are observed at a government establishment, or if attempts to achieve compliance have been ineffective, the district (or center) should arrange a meeting with OE, OCC, and the relevant center to determine a strategy to achieve timely and effective compliance. The meeting should include ORO/DFSR if the government establishment is a state or local 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.

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 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. Warning Letters may also be generated through work done at agency headquarters (ORA or centers), processed under appropriate procedures and issued under the authority of a division or office director. (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.)

1. ***General Considerations***:
   In determining whether to issue a Warning Letter, district directors and center or other officials with authority to issue should consider whether:
   a. 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 agency consideration of an enforcement action;
   b. The violation(s) are determined to be of regulatory significance, and the issuance of a Warning Letter is appropriate and consistent with agency policy, as described in Compliance Policy Guides or elsewhere; and,
   c. There is a reasonable expectation that the responsible firm and persons will take prompt corrective action.
2. ***Ongoing or Promised Corrective Actions***
   Corrective action may be undertaken or promised during an establishment inspection or addressed in correspondence to the agency after an inspection. Ongoing or promised corrective actions generally do not preclude the issuance of a Warning Letter. In addition to being the agency's primary means to achieve prompt, voluntary compliance, Warning Letters remain a primary means to establish prior notice (see Chapter 10) and serve to ensure that the seriousness and scope of the observed violations are understood by top management and that the appropriate resources are allocated to fully correct the violations and to prevent recurrence.

   When a firm is in the process of correcting the violations or has made a written promise to take prompt corrective action, a district or center should consider the following factors when determining whether or not to issue a Warning Letter:
   a. The firm's compliance history, e.g., a history of serious violations, or failure to prevent the recurrence of violations;
   b. The nature of the violation, e.g., a violation that the firm was aware of (was evident or discovered) but failed to correct;
   c. The risk associated with the product and the impact of the violations on such risk;
   d. The overall adequacy of the firm's corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;
   e. Whether documentation of the corrective action was provided to enable the agency to undertake an informed evaluation;
   f. Whether the timeframe for the corrective action is appropriate and whether actual progress has been made in accordance with the timeframe; and,
   g. Whether the corrective action taken ensures sustained compliance with the law or regulations. In the case of Warning Letters being considered for products offered for sale through internet web sites, corrective action to remove claims or inactivate the website is easily reversible, and should be carefully considered, along with the other factors above, in determining whether or not to issue a Warning Letter. Warning Letters for, or involving, internet web sites should be issued in as close proximity as possible to the time when the claims were last observed, and reference to the date on which the claims were observed should be included in the letter.

   If a decision is made not to issue a Warning Letter, see "Response Letter" below. Relying on a firm's promised corrective actions does not preclude consideration of regulatory action should we later observe that the same or similar violations have not been corrected.
3. ***Completed Corrective Actions***
   As a general rule, a Warning Letter should not be issued if the agency concludes that a firm's corrective actions are adequate and that the violations that would have supported the letter have been corrected. If you believe that an exception is necessary due to the facts or circumstances of the case (e.g., the firm's compliance history, the nature of the violation, or the risk associated with the product) discuss this background in the Warning Letter referral package and be sure to adapt the language in the proposed letter to fit the circumstances

(e.g., recite the history and the consequences if there is a recurrence).

If a decision is made not to issue a Warning Letter, see "Response Letter" below. Relying on a firm's completed corrective actions does not preclude consideration of regulatory action should we later observe that the same or similar violations have not been corrected.

4. ***Response Letter***
If a decision is made to not issue a Warning Letter because adequate corrective action has been taken, or because corrective action is being taken or has been promised, it is recommended that an alternative form of communication (e.g., a response letter to the firm's letter promising corrective action) be issued to the responsible individuals at the firm to supplement the record of the violation(s) and reflect the agency's decision to rely on the firm's actions and/or promises. The response letter should indicate that the agency is relying on the firm's corrections or commitment regarding corrective actions. Further, the letter may include a statement that should we later observe that these or similar violations have not been corrected; regulatory action (e.g., seizure, injunction and, if appropriate, civil penalties) may be taken without further notice.
5. ***Verification of Corrective Actions***
Verification of the overall completeness and effectiveness of the corrective action should be undertaken during the next inspection, the timing of which may be expedited or routine as determined by the issuing office.

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

Center concurrence is required prior to issuing Warning Letters in the areas listed below, 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.

1. ***All Centers***
    a. All labeling violations - except where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, and Drug Health Fraud Bulletins;
    b. Computer application and software violations;
    c. Bioresearch Monitoring Program violations; and
    d. Product advertising violations.

    Note: Only centers issue Warning Letters for violations associated with product advertising, OTC drug monographs, and the Bioresearch Monitoring Program.
2. ***Center For Drug Evaluation And Research (CDER)***
    a. New drug charges - including unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements;
    b. Adverse drug experience reporting violations;
    c. Novel and unusual tamper-evident packaging violations;
    d. Prescription Drug Marketing Act violations;
    e. Investigational drug use violations;
    f. CGMP charges involving active pharmaceutical ingredients and other drug component manufacturing deficiencies;
    g. CGMP charges involving all dosage forms, including medical gases;
    h. CGMP charges involving inspections of facilities for therapeutic biologic products regulated by CDER; and
    i. Pharmacy compounding issues.

    The Compliance Management System (CMS) is now being used for electronic submission of Warning Letter recommendations from district offices. All recommendations by the district offices must use CMS for submitting the proposed Warning Letter, the FDA 483 supporting alleged violations, the EIR, and any written response by the firm. For any questions, or if you need to submit a document as a hardcopy, the CDER contact is: Branch Chief, Domestic Case Management and Guidance Branch, voice 301-796-3281, fax 301-847-8741.

    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.
3. ***Center For Biologics Evaluation And Research (CBER)***
    a. Donor re-entry violations (e.g., HBsAg, anti-HIV-1);
    b. Violations relating to drug CGMP*;
    c. Violative inspections of federal government agencies;
    d. Violative inspections of Team Biologics (Core Team) facilities for biologic products regulated by CBER;
    e. Viral marker test run deficiencies** (See below);
    f. Violations in areas where specific guidance has not been provided*** (See below);
    g. Violations relating to HIV and HCV lookback; and
    h. Violative inspections of manufacturers of human cell, tissue, and cellular and tissue-based products (HCT/Ps).

    *CGMP regulations in Part 211 and blood establishments: CBER concurrence is required for Warning Letters involving deviations from Part 211 that are not associated with provisions in Part 606, such as 21 CFR 211.68(b) or 211.113.

    **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: 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.
4. ***Center For Devices And Radiological Health (CDRH)***
    a. All 21 U.S.C. 352(j) danger to health violations;
    b. Medical device reporting violations which cite failure to report malfunctions as defined in 21 CFR 803.3(n). Center medical and technical expertise is necessary for these evaluations;

c. Restricted device violations;
d. Radiation Control for Health and Safety Act violations - except for sunlamp products and x-ray assemblers;
e. Violation of requirements for post market surveillance studies;
f. Any violation of device tracking regulations other than failure of the firm to implement any form of a tracking system;
g. All suspected violations of the user reporting regulations;
h. Failure to submit a premarket notification (510(k)) or Premarket Approval (PMA) Application;
i. 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;
j. All violations arising from pre-approval PMA inspections including supplements to a previously approved PMA application; and,
k. Mammography Quality Standards Act (MQSA) violations in the following situations, unless superseded by a relevant Compliance Program or other directive:
    i. 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
    ii. 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.

5. ***Center For Veterinary Medicine (CVM)***
    a. Product approval violations;
    b. Tissue residue violations involving meat and poultry where no tolerance has been established, extra-label use is documented, and/or those which involve the use of compounded drugs or other drug adulteration;
    c. Tissue residue violations involving aquacultured seafood, and other animal-derived products;
    d. Feed contaminant violations where no tolerance has been established;
    e. Adverse drug reaction reporting violations;
    f. Low acid canned pet food violations requiring technical review; and,
    g. 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).

Districts should *only* submit recommendations, coupled with their supporting evidence, using the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

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.

6. ***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:
    a. Pesticide and chemical contamination violations not covered by direct reference authority;
    b. Dietary supplements, medical foods, and infant formulas;
    c. Low acid and acidified canned foods (LACF) violations;
    d. Food and color additive violations;
    e. Seafood HACCP violations not covered by direct reference authority in the Compliance Program;
    f. All situations involving violations of section 402 (a) (4) of the Act, including deviations from CGMP regulations for foods, low acid and acidified canned foods, bottled water and any other CGMP regulation concerning CFSAN issues, e.g., dietary supplements;.
    g. Mycotoxins;
    h. Animal drugs in foods (aquaculture chemotherapeutic agents);
    i. Food standards; and
    j. Cosmetics.

Districts should ***only*** submit recommendations, coupled with their supporting evidence, to CFSAN via the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

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.

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. 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

For issues in a Warning Letter that require review by more than one center, a designation of "lead center" should be made at the earliest possible opportunity. This is necessary to ensure a timely and appropriately coordinated review process. The lead center is responsible for communication with the other involved center(s), the district, and OCC. The lead center is responsible for shepherding the Warning Letter through the review process, including the review and incorporation of comments as appropriate from the other involved entities.

For issues in a Warning Letter that require review by more than one center, the district should, prior to submission of the recommendation, communicate with each center and identify which center will serve as the lead. The recommendation should identify the lead center and the other involved center(s). The recommendation should be sent electronically via CMS to the lead center, and the lead center will create a consult task to the other reviewing center(s). The centers should conduct concurrent (not sequential) reviews.

If the district did not identify the need for multiple reviews prior to submission of the recommendation, the center receiving the recommendation should communicate with the district and the other involved center(s) to appropriately designate the lead center. The district should then promptly send a copy of the recommendation to the other involved center(s).

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, HFC-230, and HFC-240. 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.

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 Warning Letter contains violations that by their nature are not correctable, then no close-out letter will issue.

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. Usually, the standard for verifying that corrections have been implemented will be a follow-up inspection. Follow-up inspections should be conducted promptly after the agreed upon date of completion of the promised corrections.

1. ***Acknowledgment Of Response To A Warning Letter***
   The district or center that issued the Warning Letter should acknowledge, in writing, receipt of Warning Letter responses. The district or center should save a PDF copy of the issued correspondence under the Final Outcome tab in CMS, identified as doc type = "courtesy acknowledgment correspondence"
2. ***Warning Letter Close-out Letter***
   A Warning Letter close-out letter ("close-out letter") will not be issued based on representations that some action will or has been taken. The corrective actions must actually have been made and verified by FDA.

   The district or center that issued the Warning Letter should issue a close-out letter for Warning Letters issued on or after September 1, 2009, if the violations in the Warning Letter have been adequately addressed, and the following conditions have been met:
   a. The firm replied to the Warning Letter with sufficient information to demonstrate that any listed violations have been adequately corrected; or
   b. A follow-up inspection shows that implementation of the corrective actions was adequate, or, based on other verified, appropriate and reliable information, FDA determines that the follow-up inspection is not needed; and
   c. The follow-up inspection (or other appropriate and reliable information) does not reveal other significant violations.

   The issuing office will evaluate the firm's response to the Warning Letter.

   Where the district is the issuing office, the following procedure should be followed prior to issuance of a close-out letter. If the district performs an inspection to verify correction, the district may, but need not, ask the center whether it has a comment or objection prior to issuing a close-out letter. If the district decides not to inspect to verify correction, and the Warning Letter required center concurrence, the district will ask the center, via CMS, whether it has a comment or objection prior to issuing a close-out letter. The center will enter any comments or objections to the issuance of a close-out letter (i.e., FDA's conclusion that the firm's corrective actions are adequate to address the violations contained in the Warning Letter), via the center documents tab in CMS within 30 working days. If the center requests more time, an additional 30 working days should be granted. At the end of the 30 (or 60) working day period, the district will review the center's comments or objections, if any, providing deference to the center in areas of the center's expertise, and, where the center has provided comments or objections, will issue the close-out letter only if consensus is reached with the center.

   Districts or centers should issue close-out letters within a total of 65 working days of having the necessary information upon which to make a decision. Use the model "close-out letter" in Exhibit 4-2[1]. The issuing district or center is responsible for ensuring that a PDF copy of the final, signed close-out letter is added into CMS.

   A close-out letter does not relieve the recipient from their responsibility for taking all necessary steps to assure sustained compliance with the Act, and all other applicable requirements. If a subsequent inspection reveals problems with the adequacy or sustainability of the corrections that were taken in response to the Warning Letter, such violations would be considered serious. If FDA observes violations during subsequent inspections or through other means, we may take enforcement action without further notice.

   The issuing district or center will ensure that FDA posts a notice on http://www.fda.gov/foi/warning.htm[2] when a close-out letter is issued.
3. ***Requests to Post Response on Internet***
   The agency policy on posting Warning Letter responses on the internet is found at: http://www.fda.gov/foi/warning.htm[3]

   In accordance with this policy, when a recipient of a Warning Letter requests that their response to that Warning Letter be posted on FDA's internet site and provides the response electronically in a word processing format, the agency will post that response. The agency has reserved the right not to post certain responses, such as when posting likely would mislead the public about the safety or efficacy of a regulated product

   The office (district or center) that issued the Warning Letter must redact the response to the extent permitted by the Freedom of Information Act, and send a redacted copy of the response to FDA's Division of Freedom of Information, OMP, and the FOI office will then post the response to the above-referenced website. Submissions should be sent to the attention of Brenda Dorsey.
4. ***Follow-Up Enforcement***
   If a firm has been issued a Warning Letter and has been unable or unwilling to correct the violations, districts and centers should consider

further administrative and/or regulatory actions. When considering further action, one factor to evaluate is prior notice (see RPM Chapter 10). This evaluation is particularly relevant for firms operating multiple facilities and producing a variety of products when administrative and/or regulatory action involving more than one location is being considered. Although a second Warning Letter to the same firm should not be issued for the same or similar violations, ensuring prior notice through issuance of a second Warning Letter in some situations may best support the agency's objectives.

In determining whether to issue a second Warning Letter, district directors and center issuing officials should consider whether:

a. The products, processes, and/or significant violations are different, taking into account that systems-based inspectional observations may transcend individual products and processes and may, thereby, provide prior notice without an additional Warning Letter;
b. The responsible individual(s) is (are) different; or,
c. The Warning Letter will support the agency's objectives (e.g., letters sent to different facilities within a corporation to achieve correction of corporate-wide problems).

Whether or not a second Warning Letter is issued, any proposed administrative or regulatory action must be supported by adequate evidence (inspectional or other). The Office of Enforcement (Division of Compliance Management and Operations) and center office of compliance contacts can assist districts in evaluating the evidence, the prior notice, and in developing a regulatory approach when multiple facilities are involved. (Also, see section on Ad hoc Committees in Chapter 10.)

Districts and centers also have the option of conducting a meeting with firm's management prior to pursuing an administrative or regulatory action. Such meetings also serve as further prior notice. (See sections on Prior Notice and Regulatory Meetings in Chapter 10.)

5. ***Inspection Classification***
A Warning Letter constitutes official but not final, 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.

If an OAI classification is based on tissue residue violations, it is not necessary to conduct a follow-up inspection unless additional violations have been reported to the agency by the Department of Agriculture's Food Safety and Inspection Service, or a follow-up inspection is appropriate for other reasons (e.g., to update evidence prior to initiating an enforcement action).

For further information on classification of inspections see Field Management Directive No. 86, found on the web at http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm061430.htm[4].

4-1-9 - Firm Profile Updates in FACTS

When a profilable firm (i.e., domestic or foreign drug, biologics, or medical device facility) undergoes a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection, the inspected profile classes should be updated by the action office (i.e., the district for domestic inspections or the district and the center for foreign inspections) at each stage in the review process. When a Warning Letter is issued as a result of the inspection, the date and type of letter issued should be entered in the Remarks field for the relevant profile classes, and these profile classes should be changed to unacceptable. When a Warning Letter close-out letter is issued, the Final Profile for the relevant profile classes should be changed to acceptable. For profile procedures, see IOM Exhibit 5-14 or the DCIQA intranet page.

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. Title: "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. The Warning Letter should be addressed to the highest known official in the corporation that includes the facility that was inspected, and a copy should be sent to the highest known official at the facility that was inspected. If you are requesting a separate response from other officials, include them as addressees. Include a suitable notation (e.g., cc, or copy sent to) in the letter and identify each person by name, title, and, if appropriate, address. Issue the letter to each addressee and each person who is identified as having received a copy of the letter, separately and in accordance with the delivery instructions above.
4. The dates of the inspection and a description of the violative condition, practice, or product in brief but sufficient detail to provide the respondent the opportunity to take corrective action. Include citation of the section of the law and, where applicable, the regulation violated. Cite violations of the law using the appropriate section(s) of both the FD&C Act and the U.S. Code, e.g., Section 501(a)(2)(B) of the Act , 21 U.S.C. 351(a)(2)(B). Cite violations of other laws (e.g., the Public Health Service Act) in the same manner.
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 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.
8. A statement in drug Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) about the implications for the award of federal contracts (see paragraph 13 below). If CGMP violations are cited, a statement regarding the potential impact on requests for approval of export certificates and drug applications (see paragraph 13 below.)
9. A statement in device Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) that: "Federal agencies are advised of all Warning Letters about devices so that they may take this information into account when considering the award of contracts."

   For device Warning Letters that include CGMP violations: "Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected."
10. Instructions, as appropriate, that the response include:
    a. each step that has been or will be taken to completely correct the current violations and to prevent similar violations;
    b. the time within which correction will be completed;
    c. any reason the corrective action has not been completed within the response time; and,

d. any documentation necessary to show that correction has been achieved.

11. A designated district or center official to whom the response should be addressed.
12. Issued by the district director, division director, or higher agency official. Some program areas will require center concurrence before issuance.
13. For drug Warning Letters, the information in paragraphs 6-8 and 10, above, should be set forth in closing paragraphs as follows (**bold** type indicates optional/alternative language to be used as appropriate):

    The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist **[at your facility/in connection with your product(s)].** You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that **[you/your firm]** comply**[ies]** with all requirements of federal law and FDA regulations.

    You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. **[If cGMP VIOLATIONS ARE CITED: Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a *[supplier or manufacturer]* until the above violations are corrected. A reinspection may be necessary.]**

    If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

    Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. **[If you no longer manufacture or market _____, your response should so indicate, including the reasons that, and the date on which, you ceased production.]**

4-1-11 - Warning Letter Distribution

Warning Letter distribution is as follows:

1. Original - Addressee(s)
2. Copy to each person identified in the Warning Letter
3. Blind copy (bcc) to the following:
    a. FDA-MARCS-Compliance Management System (MARCS-CMS) case file. The final, unredacted signed letter should be added to the MARCS-CMS case file under the Final Outcome tab with the file type identified as PDF VERSION Non-Redacted Issued Violation Letter. Once added, this copy becomes available to the full text DOC search within MARCS-CMS. It also serves as an internal copy for FDA that is available through the system to anyone who may need a copy of the issued letter.
    b. Division of Freedom of Information (DFOI) - For more information, see Section 4-1-13 - Freedom of Information (FOI) and the operating instructions within the FOI User's Guide hyperlink in MARCS-CMS located under the User's Guides/Training hyperlink.
        i. Add a PDF version of the redacted Warning Letter into MARCS-CMS. Adobe Acrobat Pro 8 software with the Adobe 8.1.3 patch, or subsequent versions of Adobe (e.g., Pro 9 or greater) should be used. Patched Adobe Pro 8 utilization will:
            - facilitate FDA compliance with the 1996 Electronic FOI Amendments (EFOIA) for posting frequently requested records, and provide the software tool necessary for identifying the location and the extent of every redaction, as required by EFOI, and the statutory exemption which permits the agency to withhold the redacted materials, as required by the Open Government Act of 2007; and
            - facilitate FDA compliance with section 508 of the Americans with Disabilities Act in creating a 508 compliant PDF.
    c. Local Distribution, factory file, WL file, resident post, and appropriate federal and state agencies.
4. One redacted copy of Warning Letters regarding Dietary Supplements to:

    Associate Director
    Division of Advertising Practices
    Federal Trade Commission
    600 Pennsylvania Avenue, N.W.
    Washington, D.C. 20580

    (Or, send a redacted e-copy to: mengle@ftc.gov)

4-1-12 - Warning and Untitled Letters Addressed to Importers, Customs Brokers, and Foreign Firms

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.

Districts should address all Warning Letters to the party responsible for the violation. Therefore, before issuing either a Warning Letter or an Untitled Letter, the issuing office must determine the identity and role of the "responsible party." Districts may make this determination by examining the entry documents or the electronic entry data submitted to FDA's OASIS via CBP's ABI/ACS, or both, or other supporting records. It is particularly important to determine whether the firm identified as the importer-of-record is the actual importer, that is, importing for its own account, or whether the importer-of-record is a customs broker acting as the agent for the actual importer. Generally, customs brokers are merely agents for actual importers and therefore are not the responsible parties to whom districts should address Warning Letters. For more information, see "Customs Brokers" below.

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

Contact DIOP, Operations and Policy Branch (HFC-172), at 301-443-6553 for assistance in issuing a Warning or Untitled Letter to an importer, consignee, owner, or broker of imported goods

1. ***Importers***
    FDA may issue Warning Letters and Untitled Letters to importers, owners, or consignees of FDA-regulated imports when they engage in practices that violate the Act.

Customs Brokers
Generally, it is not appropriate to issue a Warning Letter or Untitled Letter to a customs broker unless that broker also is the owner, consignee, or importer responsible for the imported goods. In cases where a customs broker also is the owner, consignee, or importer, that is, the party initiating the importation, or if the broker has authority over the product through prior arrangement with the importer, it may be appropriate to issue a Warning Letter or Untitled Letter to that broker.

In all cases, districts should ensure that Warning Letters and Untitled Letters are addressed to the party responsible for the violation.

3. ***Foreign Firms***
A Warning Letter or Untitled Letter may be appropriate if FDA has regulatory authority over the company and is prepared to exercise that authority. Firms may be 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 and Untitled Letters should be discussed with the Office of the Chief Counsel. Authorized FDA officials may issue Warning Letters to foreign producers of FDA-regulated products based on establishment inspections or other information. For CBER regulated products, administrative actions may also be considered for licensed foreign establishments.

4-1-13 - Freedom of Information (FOI)

1. ***Internet Posting of Warning Letters***
DFOI will obtain the Redacted Warning Letters using the MARCS-Compliance Management System (MARCS-CMS). When the Action Taken Date (i.e., date on the letter) is entered into MARCS-CMS, an FOI section in the electronic case file for the Warning Letter opens. Identify the district or center FOI officer redacting the letter. After the FOI officer for the issuing district or Center redacts the Warning. ***Do not include "bcc" information, or the "credit page" related to drafting sequence, etc., on the redacted copies***.

MARCS-CMS sends an alert to DFOI that a new, redacted letter is ready for final DFOI review and Internet posting when a redacted violation letter file is added.

For more information, see the operating instructions within the FOI User's Guide hyperlink in MARCS-CMS.

2. ***FOI Requests for Warning Letters***
All FDA-issued Warning Letters (redacted) should be posted on FDA's Warning Letters internet page and thus the public can obtain a copy directly without the need to submit a formal FOIA request. If FDA has not yet posted the Warning Letter on the Warning Letter internet page, the requester should fax the request for a copy of the Warning Letter to DFOI to answer. By following this procedure, the agency will comply with its "first in, first out" policy. Do not disclose a copy of a Warning Letter to the public unless your office receives the FOIA request through DFOI.

DFOI will obtain the issued letter from within MARCS-CMS or DFOI will notify the Office of Enforcement's Division of Compliance Management and Operations if the final letter is not contained in the MARCS-CMS case file per established regulatory procedures.

Refer the public to FDA's procedures in the agency's "Handbook" for submitting a Freedom of Information Act (FOIA) request at: <<http://www.fda.gov/opacom/backgrounders/foiahand.html[5]>>. The Handbook includes DFOI's mailing address and fax number. Generally, do not accept electronic or telephone requests for records, including Warning Letters.

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

The compliance programs for CBER regulated products are located at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation /ComplianceActivities/Enforcement/CompliancePrograms/default.htm[6]. Evaluate violations to decide if they are of regulatory significance. 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) that handles warning letter recommendations is the Division of Case Management, HFM-610. They can be reached at (301) 827-6201.

1. ***CBER Program Warning Letters***
   a. 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.
   b. The lists of deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter.
   c. 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.
   d. 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.
   e. Send copies of all Warning Letters to Division of Case Management (HFM-610).
   f. 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 or the sharing is authorized by law. See Chapter 3 for commissioning procedures.

2. ***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.

3. ***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.

4. ***Warning Letters Recommendations***
Send Warning Letter recommendations to CBER's Office of Compliance and Biologics Quality
   a. For Blood, Plasma and HCT/Ps:
   Chief, Blood and Tissue Compliance Branch
   Division of Case Management, HFM-614
   b. For Biological Drugs and Devices:
   Chief, Biological Drug and Device Compliance Branch
   Division of Case Management, HFM-624 (Except therapeutic biological drugs, which are submitted to CDER for concurrence.)

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.

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

1. ***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, NDAs, BLAs) 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 or device firms if other FDA regulated products are marketed by the firm and the issue(s) affect marketed products or the inspection has extended to marketed products which are included on the FDA 483. 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."
2. ***Surveillance Inspections For Assessing Conformance With Adulteration Provisions of the Act, Including CGMP***
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 adulteration provisions of the Act, including CGMP. See Standard Charge i, in Section 3, below. The lists of deviations (those that may lead to enforcement action if not promptly and adequately corrected) serve as guides for determining the recommended course of action. Any significant deviation, whether repetitive or an isolated occurrence, may warrant the issuance of a Warning Letter. In therapeutic biologic drugs, operations to assess their conformance to the adulteration provisions, including CGMP, will be conducted by appropriately trained investigators, preferable Level III certified drug investigators. These drugs will be subject to the same regulatory procedures and actions as other drugs regulated by CDER. If there is a question of which center presides over a therapeutic biologic drug, contact the Branch Chief, Manufacturing and Pre-Approval Compliance Branch, Division of Manufacturing and Product Quality, CDER, at 301-796-3275.
3. ***Standard CDER Charges***
   a. Grandfather New Drug Charge: The charge for drugs that claim to have been on the market before 1938 or before 1962:

      505(a), 21 U.S.C. 355(a) - The articles are new drugs within the meaning of Section 201(p) of the Act, 21 U.S.C. 321(p), and approval of an application filed under Section 505(b) of the Act, 21 U.S.C. 355(b), is not effective for such drugs and a Notice of Claimed Investigational Exemption under Section 505(i) of the Act, 21 U.S.C. 355(j), and 21 CFR Part 312 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.

   b. 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), 21 U.S.C. 352(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, 21 U.S.C. 321(p), and no approval of an application filed pursuant to Sections 505(b) and 505(j) of the Act, 21 U.S.C. 355(b) and (j), 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 21 CFR 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.)

   c. When the product is not a new drug, the simple misbranding charge should read:

      502(f)(1), 21 U.S.C. 352(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.

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

      502(f)(1), 21 U.S.C. 352(f)(1) - The article(s), (DRUG NAME), is subject to the provisions of Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and it is not exempt from Section 502(f)(1) of the Act, 21 U.S.C. 352(f)(1), 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.

e. 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), 21 U.S.C. 352(o) - The articles, (DRUG NAMES), are misbranded in that they were manufactured in an establishment not duly registered under Section 510 of the Act, 21 U.S.C. 360, and the articles have not been listed as required by Section 510(j) of the Act, 21 U.S.C. 360(j).

f. 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) 21 U.S.C. 353(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:

i. For a prescription drug:
503(b)(4)(A), 21 U.S.C. 353(b)(4)(A) - The article of drug, (DRUG NAME), is subject to Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and is misbranded in that its label fails to bear the symbol, "Rx only."

ii. For an OTC drug that is not to bear the symbol, "Rx only":
503(b)(4)(B), 21 U.S.C. 353(b)(4)(B) - The article of drug, (Drug name), is not subject to Section 503(b)(1) of the Act, 21 U.S.C. 353(b)(1), and is misbranded in that its label bears the symbol, "Rx only" and it is not entitled to bear such symbol.

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

505(a), 21 U.S.C. 355(a) - The article of drug, (DRUG NAME), is a drug within the meaning of Section 201(g) of the Act, 21 U.S.C. 321(g), which may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act, 21 U.S.C. 355(a), since it is a new drug within the meaning of Section 201(p) of the Act, 21 U.S.C. 321(p), and no approval of an application filed pursuant to Section 505(b) of the Act, 21 U.S.C. 355(b), is effective for such drug.

h. For information regarding health fraud issues, contact the Internet and Health Fraud Team at (301) 796-3342.

i. Adulteration Due To Inadequate Conformance with CGMP

The charge is as follows:

501(a)(2)(B), 21 U.S.C. 351(a)(2)(B) - The article(s), (DRUG NAME), is (are) adulterated within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B), 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].

j. Adverse Drug Experience Reporting Violations and NDA Field Alerts Reporting Violations

The charge is as follows:

505(k)(1), 21 U.S.C. 355(k)(1) - Your firm failed to establish and maintain records and report data relating to clinical experience, along with other data or information for drugs for which an approved application is in effect, as required by Section 505(k)(1) of the Act, 21 U.S.C. 355(k)(1).
Failure to comply with Section 505(k) is a prohibited act under Section 301(e) of the Act, 21 U.S.C. 331(e).

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.

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

1. ***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.)

Most Level 1 and repeat Level 2 inspection observations will not result in Warning Letters (see Part V of the Compliance Program).

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.

2. ***Sample Wording For Charges***
   a. Adulteration Charges
      i. Section 501(f)(1)(B), 21 U.S.C. 351(f)(1)(B), in that it is a Class III device under Section 513(f), 21 U.S.C. 360c(f), and does not have an approved application for premarket approval in effect pursuant to Section 515(a), 21 U.S.C. 360e(a), or an approved application for an investigational device exemption under Section 520(g), 21 U.S.C. 360j(g).
      ii. Section 501(c), 21 U.S.C. 351(c), in that its strength, purity, or quality falls below that which it purports or is represented to possess.
      iii. Section 501(h), 21 U.S.C. 351(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.

iv. Section 501(i), 21 U.S.C. 351(i), in that it is a device for which an exemption has been granted under section 520(g), 21 U.S.C. 360j(g), for investigational use and the person who was granted such exemption or an investigator who has used the device under such exemption has failed to comply with a requirement imposed by or under such section.

b. Misbranding Charges

i. Section 502(a), 21 U.S.C. 352(a), 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.

ii. Section 502(b), 21 U.S.C. 352(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.

iii. Section 502(f)(1), 21 U.S.C. 352(f)(1), 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.)

iv. Section 502(f)(1), 21 U.S.C. 352(f)(1), in that the labeling for the device fails to bear adequate directions for use because the labeling does not contain an expiration date based upon the stated storage instructions, as required by 21 CFR 809.10.

v. Section 502(o), 21 U.S.C. 352(o), in that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510, 21 U.S.C. 360, was not included in a list required by Section 510(j), 21 U.S.C. 360(j),, and a notice or other information respecting the device was not provided to FDA as required by Section 510(k), 21 U.S.C. 360(k).

vi. Section 502(o), 21 U.S.C. 352(o), 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).

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.

3. ***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, Diagnostic X-Ray Devices Branch, HFZ-240, 240-276-3332.

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.

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.

Districts should ***only*** submit recommendations, coupled with their supporting evidence, to CFSAN via the Compliance Management System (CMS), an electronic case submission system. This system is available from the IT Applications page on FDA's intranet site.

4-1-18 - Tracking

1. ***Identification Of Warning Letters***
All Warning Letters must be entered into the Compliance Management System (CMS); whether they are generated by a district or center, and whether they are approved and issued or not. Every Warning Letter that is issued should bear the CMS-assigned number or a sequential code number assigned by the issuing district or center. If a district or center assigned number is used, this number should be recorded in CMS to facilitate tracking.
2. ***Updating Firm Profile Status in FACTS***
When a violation letter is the result of a Current Good Manufacturing Practice (CGMP) or Quality System (QS) inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in the Field Accomplishment and Compliance Tracking System (FACTS) is to be appropriately updated at each stage in the review process. The action office (i.e., the district or center initiating the recommendation) is responsible for entering the status of the violation letter into FACTS. (See Exhibit 4-1, 5.4, and Chapter 4 "Firm Profile Updates in FACTS" for more information.)"

Links on this page:

1. /FDAgov/downloads/ucm180009.pdf
2. /ICECI/EnforcementActions/WarningLetters/default.htm
3. /ICECI/EnforcementActions/WarningLetters/default.htm
4. /ICECI/Inspections/FieldManagementDirectives/ucm061430.htm
5. /RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm
6. /BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/default.htm