U.S. FOOD & DRUG ADMINISTRATION

Regulatory Procedures Manual

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:

Section	Topic	Page
4-1	WARNING LETTERS	3
4-1-1.	Warning Letter Procedures	3
4-1-2.	Warning Letters to Government Agencies	5
4-1-3.	Issuing Warning Letters - Factors to Consider	5
1.	General Considerations	6
2.	Ongoing or Promised Corrective Actions	6
3.	Completed Corrective Actions	7
4.	Response Letter	7
5.	Verification of Corrective Actions	8
4-1-4.	Center Concurrence and Letters Issued by Centers	8
1.	All Centers	8
2.	Center for Drug Evaluation and Research (CDER)	8
3.	Center for Biologics Evaluation and Research (CBER)	9
4.	Center for Devices and Radiological Health (CDRH)	10
5.	Center for Veterinary Medicine (CVM)	11
6.	Center for Food Safety and Applied Nutrition (CFSAN)	12
7.	Center for Tobacco Products	12
4-1-5.	Letters for Illegal Promotional Activities	13
4-1-6.	Multiple Center Review	13
4-1-7.	Time Frames	14

Eye Therapies Exhibit 2267, 1 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

4-1-8. Warning Letter Follow-Up 15
1. Acknowledgment of Response to a Warning Letter 15
2. Warning Letter Close-Out Letter 16
3. Requests to Post Response on Internet 17
4. Follow-Up Enforcement 18
5. Inspection Classification 18
4-1-9. Firm Profile Updates in eNSpect 19
4-1-10. Warning Letter Format 19
4-1-11. Warning Letter Distribution 22
4-1-12. Warning and Untitled Letters Addressed to Importers, Customs Brokers, and Foreign Firms 22
4-1-13. Freedom of Information (FOI) 24
4-1-14. Center for Biologics Evaluation and Research (CBER) 25
4-1-15. Center for Drug Evaluation and Research (CDER) 27
4-1-16. Center for Devices and Radiological Health (CDRH) 32
4-1-17. Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM) 35
4-1-18. Center for Tobacco Products (CTP) Retailer Compliance Check Inspection Program 35
4-1-19. Tracking 36
4-2 UNTITLED LETTERS 37
4-2-1. Format and Content 37
4-2-2. Center Concurrence and Letters Issued By Centers 37
4-2-3. Tracking 38
4-3 USE OF STATE EVIDENCE FOR FDA WARNING LETTERS AND UNTITLED LETTERS 38
4-4 EXHIBITS 39
Exhibit 4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters 40
Exhibit 4-2 Warning Letter Close-Out Letter 63

Eye Therapies Exhibit 2267, 2 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 - Other Procedures.) The use of Warning Letters and prior notice 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 if 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

Eye Therapies Exhibit 2267, 3 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 - Other Procedures, 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 current good manufacturing practices (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

Eye Therapies Exhibit 2267, 4 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

(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 office (or center) should arrange a meeting with OIO, OCC, and the relevant center to determine a strategy to achieve timely and effective compliance. The meeting should include the Office of Partnerships (OP) 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 program office 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.)

Eye Therapies Exhibit 2267, 5 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

1. General Considerations

In determining whether to issue a Warning Letter, program office 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 - Other Procedures) 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 program office 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;

Eye Therapies Exhibit 2267, 6 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 from 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

Eye Therapies Exhibit 2267, 7 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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;

Eye Therapies Exhibit 2267, 8 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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;

i. CGMP charges involving combination products where CDER is the lead center;

j. Pharmacy compounding issues; or

k. Violations related to required postmarketing studies and clinical trials.

The MARCS-Compliance Management System (MARCS-CMS or CMS) is now being used for electronic submission of Warning Letter recommendations from program offices. All recommendations by the program 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 Office of Compliance contact is: CDER-OC-OMQ-Communications.

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* (see below);

c. CGMP violations involving combination products where CBER is the lead center;

d. Violative inspections of federal government agencies;

e. Violative inspections related to licensed biologic drug and device products regulated by CBER;

f. Viral marker test run deficiencies** (see below);

g. Violations in areas where specific guidance has not been provided*** (see below);

h. Violations relating to HIV and HCV lookback; or

i. 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

Eye Therapies Exhibit 2267, 9 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

211 that are not associated with provisions in Part 606, such as 21 CFR 211.68(b) or 211.113.

**Viral marker testing violations: ORA does not 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 programs to contact the Division of Case Management (DCM) in CBER's Office of Compliance and Biologics Quality (OCBQ) 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) "dangerous 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 application (PMA);

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:

Eye Therapies Exhibit 2267, 10 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

l. 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

m. Any situations not specifically identified as a Level 1 noncompliance or repeat Level 2 noncompliance; or

n. CGMP (e.g., 21 CFR Part 211 or Part 820) charges involving combination products where CDRH is the lead center.

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. All drug residue violations involving meat, poultry, aquacultured seafood, and other animal-derived products;

c. Feed contaminant violations where no tolerance has been established;

d. Adverse drug reaction reporting violations;

e. Low acid canned pet food violations requiring technical review; and,

f. 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).

Recommendations, coupled with their supporting evidence, should only be submitted using CMS using 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.

Eye Therapies Exhibit 2267, 11 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

6. Center for Food Safety and Applied Nutrition (CFSAN)

All violations not covered by direct reference authority, including those issues addressed in a compliance policy guide or in a compliance program. These letters requiring Center concurrence or Center issuance include, but are not limited to, the following examples:

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

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

c. Dietary supplements, medical foods, and infant formulas, including dietary supplements CGMPs;

d. Food and color additive violations;

e. Actions involving environmental microbial contamination;

f. All situations involving violations of section 402(a)(4) of the Act, including deviations from regulations for bottled water and any other CGMP regulation concerning CFSAN issues; except districts have direct reference for seafood HACCP violations and 21 CFR Part 110 violations that do not include environmental sampling or allergen issues;

g. Mycotoxins;

h. Animal drugs in foods (aquaculture chemotherapeutic agents);

i. Food standards;

j. Cosmetics; and

k. Egg rule (21 CFR 118) violations.

Recommendations, coupled with their supporting evidence, should only be submitted using CMS to CFSAN via 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.

7. Center for Tobacco Products

a. CTP directly issues Warning Letters for tobacco retailer compliance check violations. Tobacco Retailer Warning Letters are not subject to the time frames established in section 4-1-7 or to the Warning Letter close-out procedures described in section 4-1-8 due to their nature and volume. CTP has developed internal procedures to address time

Eye Therapies Exhibit 2267, 12 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

frames and close-out corresponding WL and close out CTP procedures.

b. CTP directly issues Warning Letters to regulated industry for all other violations of the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Act, and implementing regulations.

4-1-5. Letters for Illegal Promotional Activities

Warning Letters, not Untitled Letters, should be issued for promotional activities if the nature of the activity is such that the center would support further regulatory or administrative action. The warning letters are generally initiated by the Centers and may be issued by the Centers or by the Program Offices.

NOTE: For web-based promotion, appropriate further action may involve, e.g., FDA notification of any Internet Service Providers (ISPs) or other related service providers with whom the offending website has a contractual relationship, or FDA notification of the public through consumer or import alerts, rather than the physical (re) inspection of regulated establishments.

The center should alert the program 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 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” [1] 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 program office, and OCC. The lead center is responsible for shepherding the

[1] Note that a combination product is assigned to a medical product “lead center” (i.e., CBER, CDER, or CDRH) that has primary jurisdiction for the regulation of that specific combination product. The lead center will consult with other centers, as needed, to evaluate inspectional observations for combination products. See SMG 4101 Inter-Center Consult Request Process. Questions on which center is lead for a combination product should be directed to combination@fda.hhs.gov. In most cases, the lead center will coordinate issuance of warning letters for combination products assigned to it. However, there may be cases where a different center issues is responsible for coordination of development and issuance of a warning letter concerning a combination product. For example, if a warning letter is for a facility that manufactures both drug products and device-led combination products and the drug product-related issues are more significant, CDER may be the center that coordinates the warning letter process, though the lead center for the implicated device-led combination products would be CDRH.

Eye Therapies Exhibit 2267, 13 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 program 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 program did not identify the need for multiple reviews prior to submission of the recommendation, the center receiving the recommendation should communicate with the program and the other involved center(s) to appropriately designate the lead center. The program 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, sample analysis, or collection of evidence, the program 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 program of its decision. If the Warning Letter is disapproved, the center will notify the program office of its decision within 15 days of receipt, and will issue a memorandum stating its reasons for disapproval within 30 days. The Center will provide notification by e-mail or similar means to the appropriate ORA program office, and to the Office of Policy, Compliance and Enforcement (OPCE) Division of Compliance and Enforcement (DCE) that the memorandum is available in CMS. 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. If a Program or Office enters a formal agreement with another Center, such as a Concept of Operations (CONOPS), the agreement's timelines supercede the procedures in Exhibit 4-1. Recommendations to the Center and Warning Letter time frames for Human Drug Inspections (Surveillance and For-Cause Inspections) which fall under the review of CDER, can be found in FDA's INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS.

Eye Therapies Exhibit 2267, 14 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

The program 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). OPCE DCE 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 - Other Procedures.)

4-1-8. Warning Letter Follow-Up

The issuing program office or center will evaluate the response to the Warning Letter. If the response is inadequate, or if no response is received, the program office 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 recipient of the Warning Letter is verified to be out of business, then no close-out letter will issue. If the recipient of the Warning Letter ceases operation with respect to the issues presented in the Warning Letter but otherwise continues business, FDA may decide not to issue a close-out letter based solely on the recipient's representation that they have ceased the operations related to the issues presented in the Warning Letter.

In the case of Warning Letters issued for products marketed through internet websites, corrective actions such as claim removal or website inactivation are reversible. FDA also may not be able to conduct follow-up inspections of firms or individuals who sell products online without a physical location. FDA will consider whether the information provided or is otherwise available to the agency demonstrates sustained compliance, and may decide not to issue a close-out letter based solely on website corrections.

If the response appears adequate, the program office 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 program office or center that issued the Warning Letter should acknowledge, in writing or via electronic mail, receipt of Warning Letter responses. The program office 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."

Warning Letter responses regarding CTP Retailer Compliance Check Inspections are acknowledged with "Reply to Warning Letter Response"

Eye Therapies Exhibit 2267, 15 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

letters when necessary, in accordance with internal procedures. CTP should save a PDF copy of the issued Reply letter under the “POST Action Mgt” tab in CMS, identified as doc type = “Letter of FDA’s review of firm’s response.”

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 program office 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

   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

b. 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 program office is the issuing office, the following procedure should be followed prior to issuance of a close-out letter:

If the program office performs an inspection to verify correction, the program office may, but need not, ask the center whether it has a comment or objection prior to issuing a close-out letter. If the program office decides not to inspect to verify correction, and the Warning Letter required center concurrence, the program office 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 program office will review the center’s comments or objections, if any, providing deference to the center in areas of the center’s

Eye Therapies Exhibit 2267, 16 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

expertise, and, where the center has provided comments or objections, will issue the close-out letter only if consensus is reached with the center.

The Program office may also ask other program offices whether they have any comments or objections prior to issuing a close-out letter if the other program office has a potential or open case for the same individual or firm.

Program offices 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. The issuing program office 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 recipients from their responsibility to take 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 program office or center will ensure that FDA posts a notice on FDA Warning and Close-Out Letters webpage when a close-out letter is issued.

3. Requests to Post Response on Internet

Warning Letters are posted publicly on fda.gov. FDA does not remove Warning Letters from its Internet site unless the Agency rescinds or amends the letter. A recipient, however, may submit a request to post and make available to the public their response to the Warning Letter.

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 or legible pdf 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. Note: CTP is not required to post Tobacco Retailer Warning Letter responses on the internet.

ORA DIDP or center 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 (DFOI), Office of the Executive Secretariat, and DFOI will then post the response to the above-referenced website. See 4-1-13 for more information.

Eye Therapies Exhibit 2267, 17 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

4. Follow-Up Enforcement

If a firm has been issued a Warning Letter and has been unable or unwilling to correct the violations, program offices 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 - Other Procedures). 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, program 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). OPCE DCE and center office of compliance contacts can assist program offices 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 - Other Procedures.)

Program offices 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 - Other Procedures.)

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.

Eye Therapies Exhibit 2267, 18 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

For further information on classification of inspections see Field Management Directive No. 86, Establishment Inspection Report Conclusions and Decisions.

4-1-9. Firm Profile Updates in eNSpect

When a profilable firm (i.e., domestic or foreign drug, biologics, medical device, or combination product facility) undergoes a CGMP or Quality System (QS) inspection, the inspected profile classes should be updated by the action office at each stage in the review process. When an inspection is final classified OAI, the date and type of letter 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.

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: Sent to ensure overnight delivery or sent electronically, and receipt of delivery (e.g., signature required (carrier), email response) is documented.
3. Addressed to the highest known official in the corporation that includes the facility that was inspected, and a copy sent to the highest known official at the facility that was inspected. If you are requesting a separate response from other officials, they would be included as addressees. A suitable notation (e.g., cc, or copy sent to) in the letter would be included, and each person would be identified by name, title, and, if appropriate, address. The letter to each addressee and each person who is identified as having received a copy of the letter would be issued separately as warranted (e.g., when sent via carrier) and in accordance with the delivery instructions above. Ensure the recipients of a cc or copy sent electronically are entitled to receive the unredacted Warning Letter.

   Tobacco Retailer Warning Letters are addressed to the legal entity or to the sole owner at the retail establishment that was inspected. The legal entity or sole owner is copied if the entity's business address is different than the inspected retail establishment.

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

Eye Therapies Exhibit 2267, 19 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

opportunity to take corrective action. The citation of the section of the law and, where applicable, the regulation violated would be included, and the 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) would be cited. Violations of other laws (e.g., the Public Health Service Act) would be cited in the same manner.

5. Citations to the appropriate application number, post marketing requirements (PMR) reference number (if appropriate) and the date that the applicant was notified of the PMR for Warning Letters not based on inspections and citing violations of statutory requirements for studies such as PMRs and clinical trials.
6. Appropriate acknowledgement of corrections promised during the inspection, annotated on the 483, or provided to the FDA in a written response. It would reply as to the apparent adequacy of the firm's corrective actions set forth in the response.
7. 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 program office's discretion, the recipient may be offered an opportunity to discuss the letter with program office officials or, when appropriate, with center officials.
8. A warning statement indicating that failure to adequately address the issues that are the subject of the letter may result in regulatory or legal action. Examples of such actions may be cited.
9. In most cases, language to the effect that, if the recipient believes that it or its product is not in violation of the FD&C Act or other laws (e.g. the Public Health Service Act) or FDA regulations, it should provide FDA with its reasoning and any supporting evidence or information for FDA's consideration within a specified period of time.
10. Where appropriate, language to the effect that the recipient should investigate and determine the causes of any violations and take prompt actions to correct any violations and bring products into compliance.
11. Where appropriate, language to the effect that other federal agencies may take the recipient's compliance history into account when considering the award of federal contracts.
12. CTP Retailer Warning Letters (except those issued to online tobacco product retailers) would include language to the effect that, if the recipient believes that the Warning Letter was issued in error, they should preserve any relevant evidence or information in the event FDA initiates regulatory action at a later date.
13. Drug Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) that cite CGMP violations would include a statement to the effect that violations may be the cause for

Eye Therapies Exhibit 2267, 20 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

FDA to withhold issuance of Export Certificates. Where appropriate, these letters would also include language indicating that any violations may be cause for FDA to withhold approval of new applications or supplements listing the recipient as a manufacturer.

14. Device Warning Letters (except those issued to IRBs, clinical investigators, sponsors, and monitors involved in clinical trials) would include language to the effect that, should FDA determine that devices, or other articles as appropriate, or facilities do not meet the requirements of the FD&C Act, requests for Certificates to Foreign Governments (CFG) may not be granted. Device Warning Letters concerning PMAs would include language to the effect that if FDA determines that there has been a specific violation and those violations are not addressed, the PMA may be subject to withdrawal.

    Device Warning Letters that include CGMP violations would include language to the effect that if FDA determines that there are Quality System regulation violations that are reasonably related to premarket approval applications for Class III devices, such devices would not be approved until the violations have been corrected. Where appropriate, these letters may also include language to the effect that failure to address violations of a statutory or regulatory citation may result in the withdrawal of a PMA.

15. A statement in letters that pertain to imported products to the effect that products that appear to be adulterated or misbranded or that appear to be violation of section 505 or another specified violation listed in 801 may be detained or refused admission.
16. Warning Letters may request the recipient cease any violative conduct.
17. 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.
18. A designated program or center official to whom the response should be addressed.
19. “Issued by” the program office director, division director, or higher agency official.

    Some program areas will require center concurrence before issuance.

Eye Therapies Exhibit 2267, 21 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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. 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.
4. If the Warning Letter is to a foreign food facility, contact the U.S. agent for the foreign facility by email, phone, facsimile, or regular mail within 5 business days and inform the agent that a redacted letter is available on the Warning Letter page.
5. Also provide copies to Local Distribution, factory file, WL file, the appropriate program office, and appropriate federal and state agencies.
6. Provide one redacted copy of Warning Letters regarding Dietary Supplements to:

    Associate Director
    Division of Advertising Practices (link)
    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.

Warning Letters should be addressed 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." OIO may

Eye Therapies Exhibit 2267, 22 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

make this determination by examining the entry documents or the electronic entry data submitted to FDA's OASIS via the Automated Commercial System (ACS) of Customs of Customs and Border Protection (CBP). The ACS is used by CBP to track, control, and process all goods imported into the United States. A key component of ACS is the Automated Broker Interface ABI/ACS, which allows qualified participants to electronically file required import data with CPB. OIO may also examine 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 Warning Letters should be addressed. For more information, see "Customs Brokers" below. Contact OIO, Division of Import Operations (DIO) and Division of Import Program Development (DIPD) for assistance in issuing a Warning or Untitled Letter to an importer, consignee, owner, or broker of imported goods. Use the OIO contact information on the OIO intranet page.

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.

2. 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, authorized FDA officials 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 (DWPE) 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 OCC. 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,

Eye Therapies Exhibit 2267, 23 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

administrative actions may also be considered for licensed foreign establishments.

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

1. When submitting redaction requests to ORA DIDP for posting firm Warning Letter responses, ORA-issued Untitled Letters and Pharmacy Compounding (483's, 483 responses, State Hand-Off Letters, and State Referral Letters) create a linked CMS Work Activity, "DIDP Redaction Request." Select "ORA DIDP FOIA" and do not assign to a specific individual. For Warning Letters see below.
2. Internet Posting of Warning Letters

   DFOI will obtain the Redacted Warning Letters for posting using - CMS. When the Action Taken Date (i.e., date on the letter) is entered into CMS, an FOI section in the electronic case file for the Warning Letter opens.

   a. Before selecting redaction office and FOIA officer, upload the warning letter confirmation of delivery receipt to the firm under the "Final Outcome" tab in Documents with the "Confirmation of Delivery" document type.
   b. Select the redaction office and the FOIA officer that will be redacting the letter.
   c. For **ORA-issued warning letters only**:
      1) When submitting redaction requests to ORA DIDP follow the Warning Letter FOI process in CMS. Select "ORA DIDP FOIA" as the redaction office and leave the redaction officer "blank" as the FOIA officer will be assigned by Division of Information Disclosure Policy management. The FOIA officer will confirm there is a "Confirmation of Delivery Receipt" included before proceeding with redactions.
      2) For expedited redaction related to high profile posting, concurrent with a press release, send an e-mail to ORA's DIDP management at oraospopfoiainfodiscpolicydivmgmt@fda.hhs.gov with the subject line "Expeditited Redaction" include the name of firm, FEI # and CMS case number in the body of the e-mail. to process.
   d. The FOI Officer redacts the letter and uploads a redacted Adobe PDF version of the letter into CMS under the "Final Outcome" tab and sets the status to "FOI Office Review" to notify DFOI it is ready for their review prior to posting.

   NOTE: Do not include "bcc" information, or the "credit page" related to drafting sequence, etc., on the redacted copies.

Eye Therapies Exhibit 2267, 24 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

3. 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 the existence of a Warning Letter or release a copy of a Warning Letter to the public unless your office receives the response to the FOIA request through DFOI.

   DFOI will obtain the issued letter from within MARCS-CMS, or DFOI will notify OPCE DCE 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 webpage for submitting a Freedom of Information Act (FOIA) request at: How to Make a FOIA Request. The webpage includes DFOI's mailing address and fax number. Generally, do not accept electronic or telephone requests for records, including Warning Letters.

   CTP Retailer Compliance Check Inspection Warning Letters are posted to the Tobaco Retailer Warning Letters webpage.

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/GuidanceComplianceRegulatoryInform the page for Compliance Programs (CBER). 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 (DCM). The office can be reached at the contact information on the CBER OCBQ intranet page, or at 240-402-9155.

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,

Eye Therapies Exhibit 2267, 25 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 program office directors to issue a Warning Letter are listed above in "Center Concurrence and Letters Issued by Centers." In addition, program offices 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 program office.

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 program office should consider suitable follow-up.

e. Send copies of all Warning Letters to OCBQ DCM.

f. Program offices 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, OP using the contact information available on ORA OP's intranet page. 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 DCM, OCBQ may initiate regulatory action if the advertising and promotional labeling are not consistent with the approved labeling (package insert), clinical data used

Eye Therapies Exhibit 2267, 26 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 Letter Recommendations

Send Warning Letter recommendations to CBER's Office of Compliance and Biologics Quality

1. For Blood, Plasma and HCT/Ps:

   Chief, Blood and Tissue Compliance Branch
   Division of Case Management

2. For Biological Drugs and Devices:

   Chief, Biological Drug and Device Compliance Branch
   Division of Case Management, (except for therapeutic biological drugs, which are submitted to CDER for concurrence.)

Direct CBER Warning Letter questions to the Division of Case Management, 240-402-9155.

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 program 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 program offices for preapproval inspections of drug and 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."

Eye Therapies Exhibit 2267, 27 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

2. Surveillance Inspections For Assessing Conformance With Adulteration Provisions of the Act, Including CGMP

   Warning Letters may be recommended by the program 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. Therapeutic biologic 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 Office of Compliance, CDER, via email using the following email link CDER-OC-OMQ-Communications.

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

Eye Therapies Exhibit 2267, 28 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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.

Eye Therapies Exhibit 2267, 29 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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, prepared, propagated, compounded, or processed 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 and OTC 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

Eye Therapies Exhibit 2267, 30 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 OPCE DCE, Health Fraud Branch using the information on the DCE Staff Contacts page.

i. For information regarding pharmacy compounding issues, contact the Pharmacy Compounding Team at (301) 796-3409.

j. Combination product CGMP charges (violations of 21 CFR part 820 and 21 CFR part 210 and 211):

   i. The products you manufacture at this facility are combination products under section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 353(g) as your products include [drug, device, biological product] constituent parts.

   ii. This warning letter summarizes significant violations of current good manufacturing practice (CGMP) requirements for combination products. See 21 CFR part 4, 21 CFR parts 210 and 211 (drug CGMP), and 21 CFR part 820 (Quality System or QS Regulation).

   iii. Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to drug CGMP requirements, 21 CFR parts 210 and 211, your combination products are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B). In addition, your combination products are adulterated within the meaning of section 501(h) of the FD&C Act, 21 U.S.C. 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with applicable CGMP provisions of the Quality System regulation (21 CFR part 820).

k. 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].

Eye Therapies Exhibit 2267, 31 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

l. 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).

If CDER would like to include a charge related to a violation of 505(o)(3) in a Warning Letter, they should consult with OCC.

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, programs will not need CDRH concurrence before sending Warning Letters. Also, programs 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, programs 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 program 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

Eye Therapies Exhibit 2267, 32 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 CGMP requirements for medical devices which are set forth in the Quality System regulation, as specified in Title 21, Code of Federal

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

Eye Therapies Exhibit 2267, 33 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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 Medical Device Compliance Program 7382.845 - Inspection of Medical Device Manufacturers.

CDRH has established a separate mailbox for electronic submission of device Warning Letters from program offices. The address is CDRHOCWarningLetterResponses.

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, Field Compliance Testing of Diagnostic Medical X-Ray Equipment) 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 In Vitro Diagnostics and Radiological Health, Division of Radiological Health, Diagnostic X-Ray Devices Systems Branch at the contact information provided on the office’s Intranet page.

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. Combination product CGMP charges (violations of 21 CFR part 820 and 21 CFR part 210 and 211):

i. The products you manufacture at this facility are combination products under section 503(g) of the Federal Food, Drug, and

Cosmetic Act (FD&C Act), 21 U.S.C. 353(g) as your products include [drug, device, biological product] constituent parts.

ii. This warning letter summarizes significant violations of current good manufacturing practice (CGMP) requirements for combination products. See 21 CFR part 4, 21 CFR parts 210 and 211 (drug CGMP), and 21 CFR part 820 (Quality System or QS Regulation).

iii. Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to drug CGMP requirements, 21 CFR parts 210 and 211, your combination products are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B). In addition, your combination products are adulterated within the meaning of section 501(h) of the FD&C Act, 21 U.S.C. 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with applicable CGMP provisions of the Quality System regulation (21 CFR part 820).

4-1-17. Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM)

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

Recommendations, coupled with their supporting evidence, should only be submitted using CMS, to CFSAN or CVM via CMS. This system is available from the IT Applications page on FDA's intranet site.

4-1-18. Center for Tobacco Products (CTP) Retailer Compliance Check Inspection Program

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31; 123 Stat. 1776) was enacted on June 22, 2009, amending the Federal Food, Drug, and Cosmetic Act (the Act) and providing FDA with the authority to regulate tobacco products. As required by section 102 of the Tobacco Control Act, FDA published a final rule regarding sales and distribution of cigarettes and smokeless tobacco. This final rule was identical in its provisions to the regulation issued by FDA in 1996 (61 FR 44396, August 28, 1996), with certain specified exceptions. The rule at 21 CFR Part 1140, has two main sections:

1. Access provisions, which consist of restrictions on the sale of cigarettes, smokeless tobacco products, and cigarette tobacco; and

Eye Therapies Exhibit 2267, 35 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

2. Restrictions on advertising, marketing, and promotion of cigarettes and smokeless tobacco products.

The Tobacco Control Act also amended the Act to require that the agency contract with States, where feasible, to carry out inspections of retailers within that State to enforce applicable provisions of the Act and its implementing regulations. Therefore, compliance check inspections of retailers are carried out in accordance with each contract and pursuant with agency authority.

FDA's State Tobacco Compliance Check Inspections of retailers are completed by FDA –commissioned state inspectors. Inspections that result in violations are reviewed by the State Programs Group within the Office of Compliance and Enforcement (OCE) of the Center for Tobacco Products. If it is determined that there has been a violation, OCE initiates appropriate action in the form of a Warning Letter or enforcement action. The program offices are not involved in retailer compliance check inspections or the issuance of related Warning Letters.

Standard tobacco retailer violation charges include:

1. Misbranded tobacco products within the meaning of section 903(a)(7)(B) of the FD&C Act, 21 U.S.C. § 387c(a)(7)(B), in that they are sold or distributed in violation of 21 C.F.R. Part 1140.
2. Adulterated cigarettes with certain characterizing flavors within the meaning of section 907(a)(1)(A) of the FD&C Act, 21 U.S.C. § 387g(a)(1)(A).
3. Violative modified risk tobacco products within the meaning of section 911(b)(2) of the FD&C Act, 21 U.S.C. § 387k(b)(2).

Tobacco Retailer Warning Letters are not subject to the time frames laid out in section 4-1-7 or the issuing of Warning Letter Close-Out Letters in 4-1-8 due to their nature and volume. Additionally, Tobacco Retailer Warning Letters are not routinely acknowledged as stated in 4-1-8. CTP internal procedures to address time frames, acknowledgment of responses, and close-out procedures.

4-1-19. Tracking

1. Identification Of Warning Letters

   All Warning Letters must be entered into the Compliance Management System (CMS); whether they are generated by a program office 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 program office or center. If a program office or center assigned number is used, this number should be recorded in CMS to facilitate tracking.

Eye Therapies Exhibit 2267, 36 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

2. Updating Firm Profile Status in eNSpect

   When a violation letter is the result of a CGMP or QS inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in eNSpect is to be appropriately updated at each stage in the review process. The action office (i.e., the program office or center initiating the recommendation) is responsible for entering the status of the violation letter into eNSpect. (See "Firm Profile Updates in eNSpect" in this chapter and Exhibit 4-1 for more information.)"

4-2 UNTITLED LETTERS

4-2-1. Format and Content

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

1. The letter is not titled.
2. 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.
3. The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.
4. The letter does not evoke a mandated follow-up.
5. 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.

4-2-2. Center Concurrence and Letters Issued By Centers

Center concurrence is required prior to issuing Untitled Letters unless direct reference has been granted.

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.

Eye Therapies Exhibit 2267, 37 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

4-2-3. Tracking

1. Identification Of Untitled Letters

   All Untitled Letters must be entered into CMS; whether they are generated by a program office or center, and whether they are approved and issued or not. Every Untitled Letter that is issued should bear the CMS-assigned number or a sequential code number assigned by the issuing program office or center. If a program office or center assigned number is used, this number should be recorded in CMS to facilitate tracking.

2. Updating Firm Profile Status in eNSpect

   When a profilable firm (i.e., domestic or foreign drug, biologics, or medical device facility) undergoes a CGMP or QS inspection, the inspected profile classes should be updated by the action office at each stage in the review process. When an Untitled 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. For profile procedures, see IOM Exhibit 5-14 or the Government-Wide Quality Assurance Program (GWQAP) intranet page.

4-3 USE OF STATE EVIDENCE FOR FDA WARNING LETTERS AND UNTITLED LETTERS

Evidence obtained by state personnel may be sufficient to support the issuance of Warning Letters and Untitled Letters if the standards and criteria used by state personnel provide reliable support for regulatory actions the agency may take consistent with the agency's guidance on regulatory actions and laboratory procedures.

1. If state evidence involves inspectional observations made solely by state personnel, factors that indicate that the standards and criteria used are reliable for these purposes include, but are not limited to, the following:
   a. The state inspector made the inspectional observations during an inspection conducted pursuant to an agency contract inspection program or a joint inspection program in which FDA participates; or
   b. The state inspector made the inspectional observations after receiving training in relevant law and any specific requirements applicable to the inspection and the establishment or commodity being inspected; or
   c. The state inspector received an "acceptable" rating if audited by a qualified FDA or state auditor under FMD 76, "State Contracts – Evaluation of Inspectional Performance" (or other applicable audit program); or

Eye Therapies Exhibit 2267, 38 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

   d. The state inspector detected and documented the observations in the manner set forth in FDA's inspectional procedures, such as the Investigations Operations Manual, guides to inspections, or comparable inspectional approaches.

2. If state evidence involves laboratory data, factors that indicate that the laboratory data and the methods and procedures used to collect and analyze the sample are valid and reliable include the following:
   a. The procedures involved in the sample collection have been analyzed and found to be reliable in that the sample was collected, handled, and analyzed using procedures that assure sample integrity and chain of custody and a sample size and test method the Director, Office of Regulatory Science (ORS), determines to be appropriate; or
   b. The Director, ORS, designates that the laboratory data from state facilities meet the criteria and standards appropriate for compliance decision-making; or
   c. The Director, ORS, has reviewed and endorsed the state laboratory findings through an evaluation of the laboratory operations, methods, sampling, and evidence documentation.
3. Except for state inspections of retailers to determine compliance with the provisions of the Family Smoking and Tobacco Control Act and its implementing regulations, the program office must review and endorse the state evidence as meeting the criteria for the issuance of a Warning Letter or Untitled Letter in accordance with FDA procedures and agency compliance policy. Warning Letters and Untitled Letters relating exclusively to state inspections of retailers to determine compliance with the provisions of the Family Smoking and Tobacco Control Act and its implementing regulations will be drafted by the Center for Tobacco Products based on sufficient evidence collected and documented by state personnel.
4. The FDA product center with primary jurisdiction over the establishment or commodities inspected and the Office of Chief Counsel concurs with the use of the evidence obtained by state personnel.
5. This section is not applicable where a proposal for a Warning Letter or Untitled Letter is based on FDA-developed evidence to demonstrate the current condition of the commodity or establishment, and evidence obtained by state personnel is used to solely demonstrate prior compliance history.

4-4 EXHIBITS

Exhibit 4-1 Procedures for Clearing FDA Warning Letters and Untitled Letters
Exhibit 4-2 Warning Letter Close-Out Letter

Eye Therapies Exhibit 2267, 39 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

Contents

1. Purpose
2. Scope
3. Background
4. Definitions
5. Responsibilities
6. Procedures
    a. Timeframes
    b. Procedures for the Review of Agency Warning and Untitled Letters
    c. Licensed Products Letters
    d. Enforcement Correspondence under an Audit Review

1. Purpose

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

2. Scope

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

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

a. CFSAN
    i. Any Warning or Untitled Letter involving a novel, controversial, or sensitive legal issue.
    ii. Warning Letters involving medical foods.
    iii. Warning Letters involving section 502(f)(1) drug misbranding charges.
    iv. Warning Letters involving section 403(a) false or misleading food labeling.

Eye Therapies Exhibit 2267, 40 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

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

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

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

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

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

b. CDRH

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

ii. Advertising/promotion warning/untitled letters.

iii. Warning/untitled letters with unapproved device charges under section 501(f)(1)(B) if the firm contests that the product is a device or any other warning/untitled letter in which the firm contests that the product is a device.2

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

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

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

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

---

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

Eye Therapies Exhibit 2267, 41 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

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

c. CVM

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

ii. Warning Letters involving bioresearch monitoring.

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

iv. Warning and Untitled Letters involving advertising and promotion.

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

vi. Warning Letters related to turtles.

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

d. CBER

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

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

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

iv. Warning and Untitled Letters involving product jurisdiction.

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

e. CDER

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

ii. Warning Letters involving clinical investigators and IRBs.

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

Eye Therapies Exhibit 2267, 42 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

iv. Warning and Untitled Letters involving compounding.

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

f. ORA

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

3. Background

On November 29, 2001, then Deputy Secretary of the Department of Health and Human Services directed "…the Food and Drug Administration (FDA) to submit all Warning Letters and Untitled Letters to FDA's OCC prior to their issuance so that they can be reviewed for legal sufficiency and consistency with Agency policy." To implement this directive, a cross-agency working group established procedures to integrate OCC review into the agency's existing procedures for the review of enforcement correspondence. These procedures were implemented in March 2002. In August/September of 2009, the OCC review provisions of these procedures were modified, on an interim basis, to apply only to the Warning and Untitled Letters described in section "2. Scope." The 2009 interim procedures were evaluated as described in section 5.1 and finalized in December 2010.

4. Definitions

For the purpose of these procedures:

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

b. An Untitled Letter is an initial correspondence with regulated industry that cites violations that do not meet the threshold of a Warning Letter. Untitled Letters are intended to cover those circumstances where the Agency has a need to communicate with regulated industry about violations that do not meet the threshold of regulatory significance as described above. The three types of letters related to

Eye Therapies Exhibit 2267, 43 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

licensed products that are issued by CBER and CDER, pursuant to subsection 6.3 of Exhibit 4-1 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

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

Any refinements to these procedures that become identified through periodic evaluation or otherwise, that may facilitate the review, streamline or focus the process, or enable better management of the workload, while maintaining the overall intent, are implemented through established, internal agency review procedures. In addition, FDA will monitor the timeframes to determine whether they need to be modified based on the agency's experience with these procedures.

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

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

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

d. When a violation letter is the result of a CGMP or QS inspection of a domestic or foreign drug, biologics, or medical device facility, the firm's profile status information in eNSpect is to be appropriately updated at each stage in the review process. The action office (i.e., the Program office or Center initiating the recommendation) is responsible for entering the Final Profile Status in eNSpect. (See Chapter 4 "Firm Profile Updates in eNSpect" for more information.)

Eye Therapies Exhibit 2267, 44 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

6. Procedures

a. Timeframes

i. 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.

If a Program or Office enters a formal agreement with another Center, such as a Concept of Operations (CONOPS), the agreement's timelines supercede this procedure. Recommendations to the Center and Warning Letter time frames for Human Drug Inspections (Surveillance and For-Cause Inspections) which fall under the review of CDER, can be found in FDA's INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS. If the agency anticipates pursuing further enforcement action after issuance of the Warning Letter but prior to a follow-up inspection or other verification activities, an expedited timeframe for Warning Letter issuance may be warranted to ensure applicability of the evidence to the present situation (i.e., within four months from the appropriate reference date).

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

The period for OCC review officially begins once OCC has received the full packet of materials that serve as support for the agency's issuance of the Warning Letter. If the basic elements of the case are not provided (the basic elements are identified in the Program office 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.

ii. Warning Letter Responses

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

iii. 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 subsection 6.3 of this exhibit. To ensure the applicability of evidence to the present situation, the agency will strive to issue Untitled Letters within six months from the last day of the inspection, the date of sample analysis, or the date of evidence collection.

When OCC's review of an Untitled Letter is required, OCC will either concur, concur with changes, not concur with written reasons, or flag the letter because it raises significant issues and questions, e.g., jurisdictional issues or insufficient evidentiary support. However, the default provisions do not apply to Direct Reference Untitled Letters and Untitled Letters issued pursuant to a foreign inspection. The period for OCC review officially begins once OCC has received the full packet of materials that serve as support for the agency's issuance of the Untitled Letter. If the basic elements of the case are not provided (the basic elements are identified in the Program office 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.

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

All Warning Letters and Untitled Letters must be entered into CMS, where they are available for review.

Eye Therapies Exhibit 2267, 46 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

i. General Procedures for Direct Reference Warning and Untitled Letters

a. Program office Responsibilities

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

- Submit a draft "final" Warning Letter via CMS to OCC for concurrence, within 15 working days after the completion of an inspection, the sample analysis, or date of evidence collection.
- Submit a draft "final" Untitled Letter via CMS to OCC for concurrence within 45 working days after the completion of an inspection, the sample analysis, or date of evidence collection.
- To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the eNSpect coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.
- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- If the Program office 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 Program office's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- If the Program office receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled Letter, the Program office 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 Program office's assessment of the response (including whether the response has changed the Program office's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail and also added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and

Eye Therapies Exhibit 2267, 47 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

restart upon OCC's receipt of the Form FDA 483 response and the Program office's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

- If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.
- If OCC concurs with the draft "final" Untitled Letter, issue the letter.
- If the Program office receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, you should issue the letter.

  In the case of nonconcurrence or the letter is flagged because it raises significant issues, the Program Office will work with OCC as necessary to quickly address OCC's concerns.

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

b. OCC Responsibilities

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

c. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

Eye Therapies Exhibit 2267, 48 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

a. Center Responsibilities

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

- Send a copy of the draft "final" letter via CMS to OCC for concurrence.
- To facilitate OCC's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the eNSpect coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.
- If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
- If the agency receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
- If the agency receives the Form FDA 483 response while OCC is reviewing the draft "final" Warning or Untitled Letter, the Center should notify the attorney that is conducting the review. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response (including whether the response has changed the agency's view on whether to issue the letter) should also be submitted to the assigned attorney electronically, via fax, or by mail, and should also be added into the case file for the proposed action within CMS. The review clock will

Eye Therapies Exhibit 2267, 49 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a result of the FDA-483 response will be discussed with the initiating office.

- If OCC concurs, or if OCC does not review the draft "final" Warning Letter within 15 working days, issue the letter.
- If OCC concurs with the draft "final" Untitled Letter, issue the letter.
- If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
- In the case of nonconcurrence or the letter is flagged because it raises significant issues, the Center will work with OCC and the programs and divisions in ORA as necessary to quickly address OCC's concerns.

4. Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS.

b. OCC Responsibilities

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

c. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

iii. Warning and Untitled Letters that Require Center Concurrence

a. Program office Responsibilities

Eye Therapies Exhibit 2267, 50 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

1. Within 15 working days after the completion of the inspection, the sample analysis, or collection of evidence, submits a recommendation and a draft "final" Warning Letter to the Center through CMS.
2. Within 45 working days after the completion of the inspection, the sample analysis, or collection of evidence, submit a recommendation and a draft "final" Untitled Letter to the Center through CMS.
3. To the extent that this information is not included in the recommendation, and to facilitate the Center's review of the Warning or Untitled Letters, ensure that the violation letter documents within CMS include all evidence necessary to support issuance of the letter or other relevant information. For example, the Form FDA 483, the endorsement page of the EIR or the eNSpect coversheet, the narrative portion of the EIR, the relevant exhibits, product labels and labeling, and, if applicable, the summary of any sample analysis.
4. If the Program office 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 Program office's assessment of the response should accompany the draft "final" Warning or Untitled Letter.
5. If the Program office receives the Form FDA 483 response while the draft "final" Warning or Untitled Letter is being reviewed, the Program office should notify the Center and, for letters requiring OCC review, the attorney that is conducting the review, as appropriate. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. A copy of the Form FDA 483 response (without the exhibits or the attachments) and the Program office's assessment of the response (including whether the response has changed the Program office's view on whether to issue the letter) should also be submitted to the appropriate reviewer(s) electronically, via fax, or by mail and also added into the case file for the proposed action within CMS. The review clock will stop when OCC is notified and restart upon OCC's receipt of the Form FDA 483 response and the agency's assessment. Any changes to the proposed letter as a

Eye Therapies Exhibit 2267, 51 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

result of the FDA-483 response will be discussed with the initiating office.

6. If the Center approves the recommendation and OCC review is not required, issue the letter.
7. When OCC review of a Warning or Untitled Letter is required:
   - If OCC concurs, issue the letter.
   - If the agency receives the Form FDA 483 response after OCC has concurred with the issuance of the draft "final" Warning or Untitled Letter, the letter should be issued.
   - In the case of nonconcurrence or the letter is flagged because it raises significant issues, the Center will work with OCC and the programs and divisions in ORA as necessary to quickly address OCC's concerns.
8. Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

b. Center Responsibilities

1. Within 15 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Warning Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 15 working day timeframe and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.
2. Within 45 working days after the receipt of the recommendation, the accompanying documents, and the draft "final" Untitled Letter, the Center should review and approve or nonconcur with the issuance of the letter. The Center will issue the approval memo within the 45 working day timeframe and add a copy of the Center decision document for the violation letter into the Center documents tab in CMS.
3. When OCC review of a Warning or Untitled Letter is required:

Eye Therapies Exhibit 2267, 52 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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

4. If the Warning Letter recommendation is not approved, the Center will notify the Director of the Compliance Branch and OCC if the letter required OCC review, of its decision within 15 working days. The Center will also issue a memorandum to the Director of the Compliance Branch that states its reasons for nonconcurrence within 30 working days, or as soon as possible. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.
5. If the Untitled Letter recommendation is not approved, the Center will notify the Director of the Compliance Branch, and OCC if the letter required OCC review, of its decision within 45 working days. The Center will also issue a memorandum to the Director of the Compliance Branch that states its reasons for nonconcurrence within 60 working days, or as soon as possible. The Center will add a copy of its Center decision memorandum for the violation letter into the Center documents tab in CMS.

c. OCC Responsibilities

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

Eye Therapies Exhibit 2267, 53 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

2. Once the Center has approved the recommendation, review any draft "final" Untitled Letter requiring OCC review within 45 working days.
3. If concurrence, send concurrence to the Director of the Compliance Branch and the program office's compliance officer who proposed the action, along with a copy of the draft "final" letter with any edits (the Program office can then issue the letter).
4. If nonconcurrence or the letter is flagged because it raises significant issues, contact the Center involved and the Program office, and state in writing the reason for nonconcurrence.

d. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

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

a. Center Responsibilities

1. Make the decision to issue a Warning Letter or an Untitled Letter
2. When OCC review of a Warning or Untitled Letter is required:
   - Submit a draft "final" Warning Letter or Untitled Letter via CMS to OCC.
   - To facilitate OCC's review, ensure that the violation letter documents within CMS include the Form FDA 483, the endorsement page of the EIR or the eNSpect coversheet, the narrative portion of the EIR, and, if applicable, the summary of any sample analysis.
   - If there is no Form FDA 483 or EIR, send the evidence to OCC that supports the issuance of the letter.
   - If the agency receives the Form FDA 483 response prior to submitting the draft "final" Warning or Untitled Letter to OCC, a copy of the Form FDA 483 response (without the exhibits or the attachments) and the agency's assessment of the response

Eye Therapies Exhibit 2267, 54 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

should accompany the draft "final" Warning or Untitled Letter.

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

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

b. OCC Responsibilities

1. Review any draft "final" Warning Letter requiring OCC review within 15 working days.
2. Review any draft "final" Untitled Letter requiring OCC review within 45 working days.

Eye Therapies Exhibit 2267, 55 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

3. If concurrence, send concurrence to the Center along with a copy of the draft "final" letter with any edits (the Center can then issue the letter).
4. If nonconcurrence or the letter is flagged because it raises significant issues, contact the Center, and state in writing the reason for nonconcurrence.

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

a. Center Responsibilities

1. Make the decision to issue a Warning Letter or an Untitled Letter.
2. When OCC review of a Warning or Untitled Letter is required:
   - Send a copy of the draft "final" letter via CMS to OCC for concurrence.
   - To facilitate OCC's review, ensure that the violation letter documents within CMS include the evidence that supports the issuance of the letter.
   - If OCC concurs, issue the letter.
   - In the case of nonconcurrence by OCC or the letter is flagged by OCC because it raises significant issues, the Center will work with OCC to quickly address OCC's concerns.
3. Upon issuance, add a PDF signed copy of the Warning or Untitled Letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

b. OCC Responsibilities

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

Eye Therapies Exhibit 2267, 56 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

c. Licensed Products Letters

Violation Letters associated with licensed biological therapeutic drugs may fall under CBER or CDER responsibility. Contact the Centers if the jurisdiction is not clear.

Recommendations and other correspondence related to 6.3.1 – 6.3.3 (below) that are associated with CDER products should be forwarded to CDER, Office of Compliance, and Office of Manufacturing Quality. Recommendations and correspondence related to CBER products should be referred to CBER, OCBQ, DCM.

i. License Suspension

a. Center Responsibilities

1. Within three (3) working days after receiving information that a danger to health exists, the Center will gather the pertinent evidence, convene a Health Hazard Evaluation meeting with the applicable product office, and draft a Letter of Suspension.
2. If the determination is made that a danger to health exists, a draft “final” Letter of Suspension will be submitted by the Center via CMS to OCC within the 3 working day period.
   - To facilitate OCC’s review, ensure that the documents within CMS include the Health Hazard Evaluation and the pertinent evidence that establishes that a danger to health exists.
   - If OCC concurs, the Center’s Office of Compliance and the Office of the Center Director will process and issue the letter.
   - In the case of nonconcurrence or the letter is flagged because it raises significant issues, the Center will work with OCC to quickly address OCC’s concerns.
3. Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS. Distribute additional copies in accordance with any applicable Compliance Program and RPM Chapter 4.

b. OCC Responsibilities

1. Review the draft “final” letter within 5 working days.

Eye Therapies Exhibit 2267, 57 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

2. If concurrence, send concurrence to the appropriate Center along with a copy of the draft “final” letter with any edits.
3. If nonconcurrence or the letter is flagged because it raises significant issues, contact the Center, and state in writing the reason for nonconcurrence.

c. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

ii. 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 via CMS to OCC for their concurrence.
3. To facilitate OCC’s review of the letter, ensure that the documents within CMS include the recommendation and any additional supporting documents.
4. If OCC concurs, issue the letter.
5. In the case of nonconcurrence 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, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

b. OCC Responsibilities

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

Eye Therapies Exhibit 2267, 58 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

c. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

iii. Notice of Intent to Revoke

a. Center Responsibilities

1. Within 30 working days after the receipt of a Recommendation for a Notice of Intent to Revoke (NOIR), the Center will evaluate the recommendation to determine whether the issuance of a (NOIR) letter is appropriate.
2. If the issuance of a NOIR is appropriate, submit a draft "final" NOIR letter and any accompanying documentation via CMS to OCC for their concurrence.
   - If OCC concurs, issue the letter.
   - In the case of nonconcurrence or the letter is flagged because it raises significant issues, the Center will work with OCC.
3. Upon issuance, add a PDF signed copy of the letter into the Final Outcome tab for the action within CMS.

b. OCC Responsibilities

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

c. OPCE DCE Responsibilities

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

d. 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

Eye Therapies Exhibit 2267, 59 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

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.

i. Introduction

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

If the same model is used for both Warning Letters and Untitled Letters, the audit schedule must be followed for each type of letter. This means that Untitled Letters and Warning Letters are to be counted separately to identify the audit letter to be submitted for OCC review using the procedures in this document.

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

ii. Program office Responsibilities

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

Eye Therapies Exhibit 2267, 60 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

Program offices 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.

iii. Center Responsibilities

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

When a Center submits an “audit letter” to OCC for review, the transmittal memo approving the recommendation will contain the notation “Audit Letter – OCC concurrence is required” under the heading “Warning Letter –Approved.” This identifies the letter as one that requires OCC review and concurrence under the audit review program before it can be issued.

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

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

iv. OCC Responsibilities

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

v. OPCE DCE Responsibilities

Eye Therapies Exhibit 2267, 61 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

DCE will facilitate the discussion to quickly address significant issues, policy misalignment, novel, political, appearance or other controversial issues when notified by the Program office, Center or OCC.

vi. Model Letters and Audit Schedules

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

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

Eye Therapies Exhibit 2267, 62 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563

Exhibit 4-2 Warning Letter Close-Out Letter

Mr. John Doe,
President J.D. Laboratories, Inc.
Somewhere, USA

Dear Mr. Doe:

The Food and Drug Administration has completed evaluation of (your /your firm's) corrective actions in response to our Warning Letter [insert WL # and Date]. Based on our evaluation, it appears that you have addressed the violation(s) contained in this Warning Letter. Future FDA inspections and regulatory activities will further assess the adequacy and sustainability of these corrections.

This letter does not relieve you or your firm from the responsibility of taking all necessary steps to assure sustained compliance with the Federal Food, Drug, and Cosmetic Act and its implementing regulations or with other relevant legal authority. The Agency expects you and your firm to maintain compliance and will continue to monitor your state of compliance. This letter will not preclude any future regulatory action should violations be observed during a subsequent inspection or through other means.

Sincerely,

Official [issuing program/office]

bcc: Establishment File

Home District of Corporate HQ (or of receiving firm if issued by a Center) FOI Office for Posting (typically no redaction needed; electronic through CMS

CMS case file (electronic copy)

Eye Therapies Exhibit 2267, 63 of 63
Dr. Reddy's v. Eye Therapies - IPR2024-00563