PART V

REGULATORY/ADMINISTRATIVE FOLLOW-UP

A. QUALITY SYSTEM REGULATORY/ADMINISTRATIVE FOLLOW-UP

1. Compliance Decision

a. Situation I

The district has documented evidence indicating that one or more **major deficiency** with the Quality System regulation has resulted in the inspection being classified as Official Action Indicated (OAI). Examples that may be considered include:

- Total failure to define, document, or implement a quality system or one of the seven subsystems. The following list only provides examples and is not all-inclusive:
  - No procedure(s) which address corrective and preventive actions.
  - No procedure(s) on how all the quality data will be analyzed and utilized.
  - Where design controls are required, no design control procedure(s) for a particular device or family of devices, i.e., only high level design control procedures.
  - Where design controls are required, no design change control procedure(s).
  - No documented process validation for a process(s) the results of which cannot be fully verified.
- A deficiency in one or more element(s) of the subsystems. The QSIT Guide focuses on the most important aspects within each subsystem and can be utilized to determine what the Agency believes is critical and therefore would constitute "major" problems if not adequately addressed. Particular attention should be paid to the relationships of requirements. For example, deficiencies in both purchasing controls and acceptance activities can indicate a major deficiency because control of components and suppliers depends on a mix of both of these activities and if there are problems with one or both, assurances are greatly diminished.
- The existence of products which clearly do not comply with the manufacturer's specifications and/or the Quality System regulation and which were not adequately addressed by the Corrective and Preventive Actions Subsystem (CAPA) program.

- Noncorrection or inadequate correction of **major deficiencies** from previous inspection(s). Repeat deficiencies of same or similar deficiencies from previous inspection(s).

If any major deficiencies exist, the district is expected to classify the EIR as OAI and, based on the significance (risk) of the device and the findings, the district should consider which administrative and/or regulatory action to initiate. Such actions include, but are not limited to, issuance of a Warning Letter, injunction, detention, seizure, civil penalty and/or prosecution. See Regulatory Procedures Manual for further guidance.

If any of these deficiencies exist for foreign manufacturers, based on the significance (risk) of the device and the findings, a Warning Letter and/or Warning Letter with Detention without Physical Examination will be considered by CDRH/OC.

IMPORTANT NOTE: If a serious health hazard is identified, and the firm is not cooperative in conducting a voluntary recall, an FDA mandated recall (Section 518(e) of the FD&C Act), administrative detention/seizure or injunction should be considered as the initial action to bring the situation under prompt control.

b. Situation II

The inspection documents QS deficiencies of a quantity and/or type to conclude that there is minimal probability -- in light of the relationship between quality system deficiencies observed and the particular device and manufacturing processes involved -- that the establishment will produce nonconforming and/or defective finished devices. The Form FDA-483, Inspectional Observations, will serve to inform the establishment of any objectionable findings.

IMPORTANT NOTE: A Situation II should not be assigned if the inspection documented major deficiencies and the firm responds only with promised corrections, corrective actions and preventive actions. In order for an inspection to be classified as Situation II, FDA must have documented evidence of effectively implemented corrections and corrective actions taken on any and all major deficiencies observed during the inspection.

2. <u>Contract Sterilizers, Contract Device Manufacturers and Finished Device Manufacturers – Deciding Responsibility When Taking Regulatory Action</u>

a. The following is provided as guidance for deciding which party is to be held responsible when a finished device manufacturer uses a contract sterilizer to perform terminal sterilization on its devices or a contract device manufacturer:

- Contract sterilization and contract manufacturing are considered an extension of the finished device manufacturer's process. The finished device

manufacturer is ultimately responsible for assuring that validations, operations, process controls, quality assurance checks, etc. are appropriate, adequately documented and correctly performed.

- Contract sterilizers and contract manufacturers of finished devices are considered manufacturers for the purpose of applying the Quality System regulation in that they meet the definitions as described in 21 CFR § 820.3(l) finished device and 21 CFR § 820.3(o) manufacturer. Contract sterilizers and contract manufacturers of finished devices are subject to those parts of the Quality System regulation that apply to the operations that are performed.

- The finished device manufacturer bears overall responsibility for the safety and effectiveness of the finished device and must control all contractors under 21 CFR § 820.50 Purchasing controls and 21 CFR § 820.80 Receiving, in-process, and finished device acceptance. However, a contract sterilizer/contract manufacturer of finished devices and the finished device manufacturer are all legally responsible for compliance with the Quality System regulation and for assuring the safety and effectiveness of the finished device.

- Contract manufacturers, to include contract testing or contract laboratories, that are not manufacturing a device meeting the definition of a finished device in 21 CFR § 820.3(l) are not required to meet the Quality System regulation. These contractors, even though they may meet the definition of a "manufacturer," are to be controlled by the finished device manufacturer under 21 CFR § 820.50 Purchasing controls and 21 CFR § 820.80 Receiving, in-process, and finished device acceptance.

- For contract sterilization, the written agreement, between the manufacturer and contract sterilizer, required by 21 CFR 801.150(e), may be referenced to determine how the parties have defined their respective responsibilities. For other contract manufacturers, any written agreements used as part of supplier controls under 21 CFR § 820.50, may be referenced to determine how the parties have defined their activities and respective responsibilities.

b. When deviations are observed, proposed regulatory actions should reflect and identify the shared responsibilities between the contractor and finished device manufacturer. In some situations, it may be appropriate to initiate regulatory action against both the contractor and the device manufacturers:

- Appropriate action should be considered against the contract sterilizer or contract manufacturer of finished devices in areas for which it has the prime responsibility under any written agreement. It may be necessary to inspect more than one customer to develop supporting documentation to demonstrate the particular contractor does not appear to have adequate controls.

- When an inspection of a contractor finds violations in areas that are the responsibility of the finished device manufacturer (such as validation, biological indicators, package seal testing, etc.), these deviations are to be reported to the home district of the finished device manufacturer. Regulatory action consistent with the action of choice for the contractor should be considered for the finished device manufacturer.

- Because the finished device manufacturer is ultimately responsible for the safety and effectiveness of the device and therefore the contractor's activities, serious deficiencies found at a contractor's establishment will indicate consideration of regulatory action against the finished device manufacturer. Copies of Warning Letters issued to a contract sterilizer or contract manufacturer of finished devices should be sent to the finished device manufacturer with appropriate redaction. A copy should also be sent to the home FDA district office of the finished device manufacturer. These documents should be used as a basis for the next scheduled inspection of the finished device manufacturer.

- When a possible health hazard situation exists due to the contractors operation; or an administrative or legal action is contemplated against a contract sterilizer or contract manufacturer of finished devices, the home FDA district office(s) of all finished device manufacturers utilizing that contractor should schedule an immediate follow-up inspection at all affected device manufacturers.

3. Violative Devices Sold to Government Agencies

It is agency policy to treat devices sold to the federal government in the same manner as devices sold to commercial accounts. Consequently, when FDA recommends against acceptance of a device by a government agency because that device, or its manufacturer, is in violation of the FD&C Act, FDA should also recommend appropriate regulatory/administrative action against the same or similar device sold to commercial accounts.

If an establishment has shipped a violative device to a Government agency, appropriate regulatory action consistent with the nature of the violation(s) may be taken even though there have been no shipments to commercial customers. Formal regulatory action in connection with a violative shipment may not be necessary in some cases. (For example, the establishment promptly corrects the violative condition, and the Agency would not require further action if the matter involved a device shipped to a non-government customer). However, where corrections are not or cannot be made promptly, the main concern is preventing the subsequent shipment of the device to another customer. When the device has been shipped solely to a Government agency and is under control of that agency and there is no threat to the public, the ORA/Division of Compliance Information

and Quality Assurance (DCIQA) staff should ascertain the intention of the agency holding the goods (e.g., will they return or destroy the goods; will they request FDA to initiate seizure, etc.). If the procuring agency requests FDA action, ORA DCIQA staff will refer the matter to the home FDA district office for their consideration of an appropriate recommendation.

4. Administrative and Judicial Actions

Actions which may be considered include: FDA requested recall, FDA mandated recall, Warning Letter, seizure, injunction, prosecution, civil penalties and detention.

Corrections and corrective action proposals and documented evidence of those corrections and corrective actions should be submitted by a responsible official of the establishment in writing, detailing the action(s) taken and to be taken to bring the violative process or product into compliance within a specified time frame. Voluntary correction does not preclude the initiation of administrative and/or judicial action.

In determining whether quality systems deviations are sufficient to support legal action, consideration should be given to the significance of the device, the establishment's quality history, and whether the problem(s) is widespread or continuing.

a. Warning Letters

Issuance of all Warning Letters should follow Chapter 4 of the Regulatory Procedures Manual (RPM) http://www.fda.gov/ora/compliance_ref/rpm/. Consult the Office of Enforcement's (OE) Warning Letter page on ORA's intranet website for current instructions for obtaining Office of Chief Counsel (OCC) clearance and for current approved Warning Letter templates.

Districts have DIRECT REFERENCE AUTHORITY for Warning Letters in certain areas which are described in Chapter 4 of the RPM.

NOTE: Regarding direct reference authority for Correction and Removal violations, Warning Letters should only be issued once the districts have checked with their District Recall Coordinator to confirm that the recall is Class I or II.

Districts should obtain CDRH concurrence before issuing Warning Letters related to refurbishing/reconditioning of used devices, reprocessing of single use devices, violations of Part 11 relating to of Electronic Records and Electronic Signatures and other areas as prescribed in Chapter 4 of the RPM.

If the district determines that issuance of the Warning Letter has resulted in appropriate corrections and corrective action by the establishment, the district should, within five (5) working days after confirmation of documented evidence, update the establishment's profile data in FACTS.

b. Violative Follow-Up Inspections

As stated in Part III of this Compliance Program, the post-inspection activities serve to advise manufacturers that the conditions identified by the investigator may be symptomatic of system problems, and that the manufacturer is responsible for investigating, identifying, and correcting system problems. The Warning Letter templates further direct the establishment to discuss in its response how it will address the system problems related to the conditions identified by the investigator.

After issuance of a Warning Letter for Quality System violations, the next inspection should be a Level 3 inspection, as explained in Part III of this program and coverage is dependent upon whether the previous inspection was Level 1 or Level 2 as explained in that Part. When investigators identify the same or additional conditions that meet the criteria for Situation I, the district should consider subsequent enforcement actions, such as seizure, injunction, prosecution, or civil penalties. During Level 3 inspections, the investigator should work closely with the district compliance officer and where appropriate CDRH to assure that appropriate coverage is provided and deviations properly documented.

c. The Recidivist Policy -- Enforcement Strategy For Establishments With Repeated Violative Inspections

(1) Some establishments have a high rate of recidivism. They have developed a pattern of correcting violative conditions in response to a Warning Letter or other administrative/regulatory action, and usually maintain those corrections long enough to pass the follow-up inspection. When FDA next inspects the establishment (sometimes, as a follow-up to a recall), the investigator identifies similar conditions that again meet the criteria for Situation I. This tendency toward recidivism is often due to the failure of the establishment to have an effectively established quality management system being implemented.

(2) When dealing with another violative inspection for such an establishment, the district should consider using the following strategy:

(a) Issue a Warning Letter that follows the Recidivist Warning Letter approved template found on OE's Warning Letter page on the ORA intranet website. This Recidivist Warning Letter requests the manufacturer to submit to the district (for up to 2 years if the district believes that it is necessary) an annual certification by an outside expert consultant stating that it has conducted a complete audit of the establishment's quality management system relative to the requirements of the Quality System regulation. The

manufacturer should submit a copy of the consultant's report[1], and certification by the establishment's CEO that he or she personally has received and reviewed the consultant's report and that the establishment has made or taken all corrections and corrective actions identified in the report. To keep the process on track, schedules, milestones, update reports and other similar activities should be established between the firm and FDA, or by the firm after issuance of the Recidivist Warning Letter.

(b) Compliance Officers have the option of limiting the review of the certification only to the extent necessary to confirm that the consultant and the establishment have met the requirements set forth in the Recidivist Warning Letter. Compliance Officers may also request a technical evaluation of the consultant's report by the appropriate branch within the Office of Compliance (OC) or Office of In Vitro Diagnostics (OIVD) at CDRH. Compliance Officers have no obligations, however, to send to the establishment comments regarding the adequacy of the consultant's report or the establishment's corrections.

(c) Follow-up inspections will normally be conducted 3 – 6 months after the establishment certifies that it has completed all corrections and corrective actions.

(d) If the follow-up inspection indicates that the corrections and corrective actions are satisfactory, the district should notify the establishment that it has no objections. The district office should update the profile data. The district should also remind the establishment that it should continue to submit to the district, in accordance with the schedule specified in the Recidivist Warning Letter, certification by an outside expert consultant that it has conducted an updated audit, has certification by the establishment's CEO that any corrections and corrective actions noted to be necessary by the consultant have been made, and remains in compliance with the requirements of the Quality System regulation. The establishment should continue to submit copies of the audit results.

(3) If conditions identified by the immediate follow-up inspection or subsequent inspections meet the criteria for Situation I, the district should consider action such as injunction or seizure per A.1 above and the RPM.

[1] Establishments may be asked to release consultant's reports as part of their voluntary agreement with FDA. Because of its voluntary nature, the request is not in conflict with 21 CFR 820.180(c).

(4) If the evidence indicates that the consultant's or establishment's certifications are fraudulent, the district is encouraged to advise and seek assistance from the Office of Criminal Investigations. When there is clear evidence that the establishment falsified its status report to the district, the district should initiate appropriate action under 18 USC 1001.

d. Recalls

If the district believes that prompt removal of a violative device from channels of commerce is necessary, it should proceed in accordance with the requirements of 21 CFR § 806 and established recall procedures found in Chapter 7 of the RPM and 21 CFR Part 7 (Enforcement Policy), Subpart C (Recalls). In the event of serious adverse health consequences or a death, CDRH may order a firm to discontinue further distribution and advise customers of the problem, and may subsequently order the recall of a device to the user level in accordance with Section 518(e) of the Act.

e. Seizure

A seizure is an action that is intended to take quick control over the violative product and put it under the possession or custody of the Court. A seizure should be recommended if appropriate, as stated in Chapter 6 of the RPM.

f. Administrative Detention/Seizure

Prior to invoking an administrative detention, for a period of 20 or 30 days, the district director should have reason to believe: (1) the device is misbranded or adulterated; (2) the establishment holding the device is likely to quickly distribute or otherwise dispose of the device; and (3) detention is necessary to prevent use of the device by the public until appropriate regulatory action may be taken by the Agency.

District Directors should consult via telephone with CDRH, OC, Office of the Director and the Office of Chief Counsel (OCC) concerning administrative detention. Concurrence should be given by the Director, OC, CDRH, based on a recommendation by the OC and/or OIVD staff and OCC staff.

The district should **immediately** recommend seizure of the detained devices to assure continued control of the violative device after the 20/30 days of administrative detention expire.

g. Injunction

If an establishment has a continuing pattern of significant deviations in spite of past warnings, injunction will usually be the recommended action of choice. If a

serious health hazard exists, the recommendation should include a request for a temporary restraining order (TRO) to prevent the distribution of devices that have been manufactured under the violative conditions documented by the inspection report per the instructions in Chapter 6 of the RPM.

The recommendation should be accompanied by copies of all necessary documents, e.g., complete inspection reports, Warning Letters issued, sample analyses reports, establishment's response(s) to Warning Letters and/or Form FDA-483.

In the absence of physical samples, the inspectional evidence should clearly show that the establishment has deviated from the requirements of the Quality System regulation and/or other regulations and the establishment meets the requirements of OAI. These deviations should be well documented and should show continuing system deficiencies, not just an isolated event.

h. Citation

A citation should be recommended, if appropriate, as stated in Chapter 5 of the RPM.

i. Prosecution

The criteria stated in Chapter 6 of the RPM are the criteria for consideration of prosecution of individuals in violation of the requirements of the Quality System regulation.

j. PMA Disapproval/Withdrawal

Refer to Compliance Program 7383.001, Part V.

k. Detention without Physical Examination

In general, detention without physical examination should be recommended by the Office of Compliance whenever there is documented evidence of an OAI situation for a foreign manufacturer when the criteria for a domestic seizure, injunction, or other regulatory remedies beyond a Warning Letter are met.

l. Civil Money Penalties

Section 303(f)(1)(B)(i) of the Act states that civil money penalties shall not apply to QS violations “unless such violation constitutes (I) a significant or knowing departure from such requirements, or (II) a risk to public health.” Section 303(f)(1)(B)(iii) further stipulates that civil penalties shall not apply to “section 501(a)(2)(A) which involve one or more devices which are not defective.”

For additional information, see the draft "Guidance for FDA Staff: Civil Money Penalty Policy" at http://www.fda.gov/cdrh/comp/penalty.pdf. Also refer to "Guidance for Industry and FDA Staff: Reduction of Civil Money Penalties for Small Entities" at http://www.fda.gov/OHRMS/DOCKETS/98fr/010049gd.pdf.

5. Facilitating Review of Regulatory Recommendations

a. The district should contact the appropriate CDRH/OC Division Director or the CDRH/OIVD Deputy Director by phone when the district believes they have an OAI situation for which a recommendation for seizure, injunction, civil penalties, or prosecution may be appropriate.

CDRH fully supports the concept of "Up Front" loading so as to be fully aware of a potential situation and to provide guidance on how to proceed. At the discretion of the district, notification to CDRH may occur prior to an inspection, while the inspection is ongoing, or after issuance of the Form FDA-483. Notification would typically be made by a compliance officer, but could be made by the investigator and/or district management. The CDRH/OC and CDRH/OIVD organization charts are shown in Attachment A and B.

b. When the district knows a regulatory action will be recommended as a result of the inspection, it should FAX a copy of the issued Form FDA-483 to the appropriate division in OC or OIVD. The review process can begin within CDRH while the EIR and recommendation are being written by the district. A copy of the Form FDA-483 annotated with exhibit numbers, and EIR page numbers, helps the reviewers.

c. It is the responsibility of district management to ensure that the documentation and evidence presented with each legal action recommendation is sufficient to justify and support each charge. The material submitted should include only the basic documentation needed to support each QS charge/example.

d. All necessary samples and other supporting documentation should be tabbed and their location cross referenced in the recommendation in order to assist in a timely review. It is highly recommended that you provide a table that cross references the violation with the Form FDA-483 item number, the inspection report page number and the exhibit number.

e. All significant questions, problems, or other weaknesses in the evidence regarding the recommended action should be stated, along with pertinent district comments. Deficiencies/observations should be presented in descending order of importance.

f. The recommendation should begin with the most serious deviation from the regulations with reference to the EIR pages, exhibits and sample results that

document the violation. Each charge should be parenthetically referenced in the recommendation memorandum and the page location of the supporting evidence given. Each deviation should be related to its effect on device quality in light of overall controls, and should be separated according to the type of manufacturing activity.

g. Physical samples are not required to support QS deviations, and should not be routinely collected for QS cases. If the district should reference violative documentary or physical samples as evidence to support QS deviations, the results should be tied to the QS deviation to show a cause/effect relationship.

h. Information regarding previous warning and other past or ongoing regulatory actions should be referenced along with a description of corrections and corrective actions. If the recommendation or current EIR references a previous report, the district should copy the cited EIR pages.

i. All legal action recommendations shall be sent to CDRH/HFZ-306 for processing.

B. MDR REGULATORY/ADMINISTRATIVE FOLLOW-UP (SEE ATTACHMENT C)

The district should consider a Warning Letter when the following MDR violation(s) was disclosed during the inspection. This list only provides examples and is not all-inclusive.

- Firm fails to report, within five workdays, after becoming aware that a reportable MDR event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health.
- Firm fails to submit an MDR death report.
- Firm fails to submit an MDR serious injury report.
- Firm fails to develop, maintain and implement written MDR procedures.

When the firm has already received a Warning Letter for MDR violations and still fails to comply with the MDR regulation, then the district should consider recommending a seizure, injunction, civil money penalty or prosecution.

All failures to comply with MDR should be listed on the FDA-483.

IMPORTANT NOTE: Warning Letters based on failure to report malfunctions should have CDRH review/concurrence per the instructions in Chapter 4 of the RPM.

C. TRACKING REGULATORY/ADMINISTRATIVE FOLLOW-UP (SEE ATTACHMENT D)

The district should consider a Warning Letter when the following tracking violation(s) was disclosed during the inspection. This list only provides examples and is not all-inclusive.

- Firm distributes tracked device and does not have a tracking system.
- Firm does not have written standard operating procedures for collection, maintenance and auditing of the data for its tracked device(s).
- Firm's tracking system is not effective in locating tracked devices during recall/notification.
- Firm does not perform audits of their tracking system.

When the firm has already received a Warning Letter for tracking violations and still fails to comply with the tracking regulation, then the district should consider recommending a seizure, injunction, civil money penalty or prosecution.

All failures to comply with the tracking regulation should be listed on the FDA-483.

IMPORTANT NOTE: CDRH concurrence is required for a warning Letter for any violation of device tracking regulation requirements other than failure of the firm to implement any form of tracking system per the instructions in Chapter 4 of the RPM.

D. CORRECTIONS AND REMOVALS REGULATORY/ADMINISTRATIVE FOLLOW-UP (SEE ATTACHMENT E)

The district should consider a Warning Letter when the following Corrections and Removals regulation violation(s) was disclosed during the inspection. This is only an example and is not all-inclusive.

- Firm fails to submit a Corrections and Removals report to the District within 10 working days of initiating a corrective action which would involve a Class I or II recall situation.

When the firm has already received a Warning Letter for Corrections and Removals violations and still fails to comply with the Corrections and Removals regulation, then the district should consider recommending a civil money penalty or prosecution.

All failures to comply with the Corrections and Removals regulation should be listed on the FDA-483, once the investigator has confirmed with their District Recall Coordinator that the situation would likely be classified as a Class I or II recall situation.

E. REGISTRATION AND LISTING REGULATORY/ADMINISTRATIVE FOLLOW-UP

Chapter 4 of the RPM states agency policy is that Warning Letters should only issue for violations of regulatory significance. Generally, registration and listing violations, as a sole finding, should not be the basis of a warning letter.

However, when those violations are found in combination with other findings, such as quality system violations, they should be included on the Warning Letter, after CDRH concurrence.

F. RADIATION EMITTING DEVICE REGULATORY/ADMINISTRATIVE FOLLOW-UP

Refer to Part V in Compliance Programs 7385.014, 7386.001, 7386.002; and 7386.004 through 7386.007 for guidance on regulatory actions related to radiation emitting devices.

G. EXPORTS REGULATORY/ADMINISTRATIVE FOLLOW-UP

When violations meet the criteria for Situation I for those unapproved devices exported under Section 802, note that fact in the Warning Letter. Submit a copy of the Warning Letter to CDRH, Division of Risk Management Operations, Regulatory Policy and Systems Branch (HFZ-307) with a recommendation to rescind all current or unexpired certificates of export.