GUIDE TO INSPECTIONS OF FOREIGN MEDICAL DEVICE MANUFACTURERS

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This guide was prepared to address concerns about consistency and uniformity of inspection between the domestic and foreign inspection programs. Consistency and uniformity of inspection and enforcement represent high priority goals for the Office of Regulatory Affairs (ORA). This guide sets forth clear instructions regarding the approach to the foreign inspection.

This guide was prepared by the FDA's Office of Regulatory Affairs (ORA) and the Center for Devices and Radiological Health (CDRH).

Each inspection of a foreign device manufacturer should be a thorough GMP inspection in accordance with CP 7382.830, with emphasis on the following key points:

A. PRE-INSPECTIONAL ACTIVITY:

The MDR/PRP data base should be reviewed prior to starting the inspection. A trend analysis can be performed of the data to determine whether there are any potential product and/or process problems. These can then be used to provide focus during the inspection. Printouts of MDR/PRP reports can be provided as part of the pre-inspection package from International and Technical Operations Branch (ITOB). If a printout is not received, contact ITOB (301) 443-9894.

In certain circumstances, prior to performing the inspection, ITOB may arrange for an in-house or telephone briefing for the investigator with the Field Programs Branch, HFZ-306 and/or other CDRH reviewers. The purpose of the briefing is to make the investigator aware of problems with specific companies or products, and to provide inspectional guidance as needed. Other CDRH reviewers (such as MDR, and recall reviewers) may also provide a briefing.

B. 510(k) DEVICE INSPECTIONS:

A majority of inspections will cover devices which are marketed via a 510(k) premarket notification. The inspection should determine whether all devices being shipped to the U.S. have a 510(k) which has been found substantially equivalent. For these devices, it should be determined if the company is complying with any product and/or process specifications listed in the 510(k). Also, if significant product and/or process changes have occurred, it should be determined if a new 510(k) has been submitted.

In some cases, the initial importer submits the 510(k) and the foreign manufacturer may not see the submission. If so, determine who are the initial importers of the device.

In addition, some inspections may be driven by the 510(k) preclearance inspection program. In these instances, the investigator must FAX a short summary of inspectional findings, along with the FDA 483 (if issued) to HFC-135 immediately after the inspection.

C. PMA DEVICE INSPECTIONS:

Some inspections will be for premarket approval (PMA) devices. The inspection may be a

pre-approval type for either an original PMA or a PMA supplement or it may be a post-market inspection. In either instance, the inspection must be conducted in accordance with Compliance Program 7383.001. The investigator will be provided with the appropriate manufacturing sections of the PMA.

Some routine inspections will be conducted for PMA devices which have previously received clearance, and are not subject to the post-approval inspection criteria of the Compliance Program. These inspections should determine if the company is manufacturing, and shipping to the U.S., any variations of the device which do not have PMA clearance. Also, it should be determined if there are any significant changes in either the device's design or in the manufacturing process, and whether PMA clearance has been obtained for these, or whether the manufacturing site has changed.

D. ELECTRONIC PRODUCT RADIATION PRODUCING DEVICES:

During the inspection, determine whether the firm manufacturers any devices subject to Sub Chapter C - Electronic Product Radiation Control, formerly the Radiation Control Health and Safety Act (RCHSA). If so, determine whether the firm has submitted initial reports. Are any of the devices subject to performance standards? If so, are they meeting the performance standards? Determine whether the firm reported all Accidental Radiation Occurrences (AROs) to FDA. Determine whether the firm performed any Corrective Action Plans (CAPS) without notifying FDA.

E. CRITICAL DEVICES:

1. If any critical devices are being manufactured for export to the U.S., these should be given priority coverage. Determine whether the critical device sections of the GMPs have been applied to the critical device. In particular:

a. which components are critical, what mechanism (i.e., FMEA) was used to define critical components, and what types of tests are performed on incoming critical components prior to acceptance.

b. which operations are considered critical, what mechanism (i.e., FMEA) was used to define critical operations, and how are critical operations documented.

F. ALL DEVICE INSPECTIONS:

1. Complaint Handling System - This should be the beginning point of every inspection to determine whether the firm has received complaints of possible (or potentially) defective devices. The review of complaints should not extend to just products or lots shipped to the U.S., but to all lots shipped by the firm. Any complaints received can be used to focus on a potential problem area during the inspection. Collect hard copies of enough complaints to provide a representation of actual complaints and a print-out or copy of the complaint database if there are numerous complaints.

Even if the firm states they have never received complaints, or have no complaint file, determine whether a complaint handling unit has been formally designated. As long as the item is placed on the FDA 483, the next inspection of the firm can use the newly-established complaint file to focus in on problem areas. If the firm has received complaints from non-U.S. customers, but none from their U.S. customers, try to determine whether U.S. distributors are forwarding complaints to the firm.

If the firm repairs and services devices they produce, they must have an adequate system in place for screening repair and service requests to assure whether any of these meet the definition of a complaint. Also, repair and service requests, shipments of spare parts/assemblies, and warranty replacements to distributors should be screened to determine whether there are infant mortality

problems, or failures within the warranty period, and to detect problems with particular components, subassemblies or design. Repairs/replacements are often performed by the distributor or subsidiary to save shipping costs to/from the manufacturer. In such cases, review shipments of spare parts to determine if product failures are occurring.

Complaints, service or repair records for devices shipped to the U.S. should be reviewed for MDR reporting. Also, it should be determined whether the foreign manufacturer or the initial importer has responsibility for MDR related event review and reporting.

2. Failure Investigation and Analyses System - Determine whether there is a formal failure analysis program in place that includes written records of the actual failure investigations. It should be remembered that the complaint section of the GMP (21 CFR 820.198) refers to possible device failures, and performing investigations to determine whether the complaint can be confirmed. Once the complaint is confirmed as an actual failure of the device, the failure investigation section of the GMP (21 CFR 820.162) takes effect. Keep in mind that this section requires that any failures of released devices must be investigated. If the foreign firm has a formally documented system, a review of failure investigation records from the date of the last inspection or two years, whichever is longer, should indicate the types of problems the firm has experienced. These may provide clues on areas or products to focus on during the inspection.

3. In-Process and Finished Device Rejects and Rework - Records should be examined to determine whether there has been excessive lots, or portions of lots, rejected during either in-process or finished device inspection for failing to meet any or all of the product's specifications. Excessive rejects may be an indication of poor process control. Instances of release and distribution of lots which failed to meet any or all specifications should be reported and documented. Records should be examined to determine whether any lots which have failed specifications were reworked/reprocessed, and whether this reprocessing is adequate to assure that specifications will be met without affecting the safety or performance of the device.

All sampling plans for inspection and rework should be examined to determine whether they are based on an acceptable statistical rationale (i.e., MIL STD 105E). The sampling plan used should be examined to determine whether adequate samples are obtained for inspection, and should be described in the EIR.

4. Change Control Procedures Evaluation - The inspection should determine if any changes have been made to the device and/or process. These may have occurred as a result of complaints, failure investigations, in-process/ finished device inspection, or rework/reinspection, and can be determined by examining the change control documents.

If changes have been made to either the device design or the device manufacturing process, determine whether they have been adequately validated (820.100(a)(2) and 820.100(b)(3)) to assure that: the change does indeed correct the problem; and, the change does not adversely affect any other component/subassembly in the device. Avoid getting bogged down in cosmetic changes. However, changes for economic reasons (i.e., to cut costs) may sometimes lead to performance problems with the device.

One way to determine if the change has not been adequately validated is if a series of change orders (found by reviewing the DMR and various Engineering Drawings) are found for the same device which are intended to sequentially correct the same or similar problems. Or, complaints may be received on lots manufactured after the design change. This may indicate that the original change was not effective, and subsequent changes have been, or, are being made to correct the problem.

5. Validation - The inspection should determine whether adequate validation of significant

manufacturing processes has been performed (820.100(a)(1)). Validation should ensure that the product will consistently meet specifications if the process is controlled within established parameters; and, that the validation, either prospective or retrospective, has addressed the limits of these parameters. Validation, depending on the scope of the operation, can cover all aspects from the selection of components, to various manufacturing processes, to end-product testing. Note that retrospective validation requires extensive device history records and a protocol which includes the limits of the operation and historical data. Refer to the Guideline on General Principles of Process Validation.

6. Components - The proper selection and assurance of acceptance of components is crucial. It should be determined whether a manufacturer has component specifications and the methods used to assure that received components meet these specifications. Particular attention should be paid to critical components and those components which would require special handling or storage to maintain their integrity. Be wary of numerous changes of suppliers, and situations where a manufacturer has relaxed component specifications because the supplier could not meet the original specifications.

Vendor audits, at this time, are not required and failure to perform them should not be placed on the FDA 483, unless it is required by the firm's own written procedures.

7. Audits - Finished device manufacturers are required to conduct planned and periodic audits of their quality assurance programs. The quality audit is the foundation of the quality assurance program. You should determine if the manufacturer has a written procedure for conducting quality audits and how often these audits are conducted. It is recommended that the time between audits not exceed a 12 month period. Audits more frequently than 12 months may be needed if the firm has GMP problems.

8. Initial Distributors - The inspection should determine who are the initial distributors (U.S.) for each device. The EIR must include the complete name and address of the initial distributors and the specific device(s) distributed by each must be identified. This information is vital for determining MDR reporting requirements. Foreign firms are not subject to MDR because they are not required to register. However, in cases where there is joint ownership and control, knowledge of a reportable event by the foreign manufacturer is imputed to it's U.S. subsidiary, i.e., the initial distributor. In all cases, the initial distributor is subject to reporting when it becomes aware that it's foreign manufacturer has information that meets the threshold requirements of MDR.

Foreign firms that are owned or jointly controlled by a U.S. firm are subject to MDR. If a U.S. firm provides the foreign firm with device specifications then this is considered to be joint control. If the U.S. firm owns part of the foreign firm and has the right to dictate policy, orders, etc., then this is considered to be joint ownership.

During the inspection, the initial distributor should be identified for all MDR reportable complaints found. Also, determine whether the foreign firm has received any complaints from initial distributors.

9. Product Labeling - Collect specimens of representative labels and labeling including product brochures and catalogues, and other promotional material. Collect three copies of labels and labeling for all violative devices, e.g., recall, lack of 510(k), etc.

10. Recalls - Collect hard copies of any and all records indicating the possible recall of devices. This includes complaints, change orders, and quality messages to customers.

G. STERILE DEVICES:

1. If the firm is manufacturing sterile devices, the criteria in CP 7382.830A, Attachment A must be followed.

2. There should be documentation showing how the sterilization process has been validated. If there appear to be deficiencies, appropriate records must be obtained to document the deficiencies.

3. Whether or not a sterilization process has been validated, determine whether the firm is producing non-sterile devices. Some of the ways of determining this are:

- Have any lots had positive sterility test results and/or positive biological indicator (BI) results.

- Were any lots reprocessed and then released.

- Are reprocessing procedures adequate, and do they assure device performance or package seals will not be adversely affected.

- Are test methods based on an accepted method and are they performed properly to be able to detect positive sterility/BI test results. If an in-house test method is used, has it been validated to show it is capable of detecting non-sterile units. (Remember that the USP test of 40 samples is unable to detect 15% of the non-sterile units with 95% confidence.)

- Have any lots been released even though cycle specifications have not been met.

- Does the cycle have a sterility assurance level (SAL), or an adequate SAL, for the device being sterilized.

- What is the bioburden on the device, and is the sterilization cycle able to destroy the bioburden to an appropriate SAL level.

H. DOCUMENTATION:

1. FDA 483 - Each listed observation should be clear and concise. The facts should be clearly stated so that, if the company chooses, they can respond appropriately to the pertinent observation.

2. EIR - Make certain that each item on the FDA 483 is fully discussed in the report. Where possible, documentation should be collected to support each observation (even if the documentation is in a foreign language).

3. All EIRs must include the FAX number of the foreign manufacturers, if available. Written correspondence, e.g., Warning Letters, will be mailed and FAXed to foreign manufacturers simultaneously. FAXing the correspondence is necessary to assure that the foreign manufacturer receives the correspondence before it is available under FOI.

I. DISCUSSIONS WITH MANAGEMENT:

During the discussion, do not under any circumstances indicate any inspectional conclusions.

All discussions regarding FDA 483 observations should be made in accordance with IOM 516.

If no FDA 483 is issued, inform the firm that your establishment report is subject to further review and they may or may not hear from the agency. Keep in mind that FDA 483 observations may be determined to be non-supportable upon further review, and in instances where no FDA 483 is issued, further review of the EIR may disclose significant deviations which could result in a regulatory action.

If the firm indicates that a response to FDA 483 inspectional observations will be sent to the agency,

inform the firm that all responses must, (A) include documentation supporting and or showing corrections, (e.g., records, data) and, (B) all records and documents must be translated into English.

J. REINSPECTION OF AUTOMATIC DETENTION FIRMS:

1. If the reinspection has clearly determined that the foreign manufacturer has made corrections and no FDA 483 is issued, then FAX a short note to HFC-135, (301) 443-6919 stating the same and that the firm should be removed from automatic detention. In addition, identify exactly what devices should be removed from automatic detention if there are devices which should remain on automatic detention. After receipt of the FAXed information, HFC-135 will inform the appropriate Division of Enforcement within the Office of Compliance, HFZ-300, of the inspectional findings. The DOE will notify Import Operations, HFC-170, that the automatic detention should be removed.

A foreign manufacturer may be considered for removal from automatic detention when a FDA 483 is issued if the FDA 483 observations are new, insufficient, and/or minor deviations and the reinspection has determined that adequate corrections have been made regarding GMP deviations which resulted in the Warning Letter and Automatic Detention.

2. Foreign manufacturers should remain on automatic detention if the reinspection results in the issuance of a FDA 483 which contains significant continuing, and/or new GMP deviations. If this is the case, then a short note should be FAXed to HFC-135, (301) 443-6919, stating the same and specifying whether any device should be added or removed from the ongoing automatic detention.

K. EXPEDITED REVIEW OF VIOLATIVE FINDINGS:

If an inspection has clearly determined that a foreign manufacturer has significant system-wide GMP deviations, the FDA 483 and a summary of findings should be FAXed to HFC-135, (301) 443-6919. If possible, a few exhibits, (if in English) would also be helpful. After receipt of the FAXed information, HFC-135 will inform the Office of Compliance, HFZ-300, in order that a review of the findings can be expedited prior to completion of the final Establishment Inspection Report (EIR). This will enable streamlining of the issuance of a Warning Letter and potential Automatic Detention.