CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE
ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)	Upon Receipt
	COMPLETION DATE
	Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry Codes: 54 and 56	See Below

56002F- Active Pharmaceutical Ingredient Process Inspections (Drug Quality Assurance)
56008A- Drug Product Surveillance, CDER Initiated
56008H- Drug Product Surveillance, Imported Drugs, CDER and District Initiated Surveys
56R806- Foreign Routine Drug Surveillance Inspections*

FIELD REPORTING REQUIREMENTS

OAI ALERTS

When the district becomes aware of any significant adverse inspectional, analytical, or other information that could or should affect the agency's new product approval decisions with respect to an *active pharmaceutical ingredient manufacturer referenced in an application, *the district should immediately notify HFC-240, Medical Products Quality Assurance Staff, via EMS or FAX. HFC-240 will then convey the information by FAX or equivalent expeditious means to the *Division of Manufacturing and Product Quality (HFD-320) in CDER's Office of Compliance.*

Current Changes

PROCESS PROFILE REPORTING

In December 1995, at the request of CDER, the Medical Products Quality Assurance Staff (HFC-240) added profile classes CSN (Non Sterile API by Chemical Synthesis) and CSS (Sterile API by Chemical Synthesis) to the drug profile classification system. This change was requested because separate profile classes existed for nonsterile and sterile active pharmaceutical ingredients produced by fermentation processes, but the same did not hold true for active pharmaceutical ingredients produced by chemical synthesis processes. In implementing the change, however, MPQAS did not eliminate the profile class "CCS" because deleting the latter would have caused a loss of history in the GWQAP profiling system. Therefore, effective with this program circular, discontinue using Profile class CCS (Chemical Synthesis Crude Drug) and use only the following seven bulk profile classes to report the processes covered during API inspections:

FULL DESCRIPTION	**PROFILE CLASS**
Non Sterile API by Chemical Synthesis	CSN
Sterile API by Chemical Synthesis	CSS
Non Sterile API by Fermentation	CFN
Sterile API by Fermentation	CFS
Plant/Animal Extraction API	CEX
Biotechnology API	CBI
Crude Bulk Not Elsewhere Classified (i.e., producers of bulk intermediates, and contract micronizers of APIs)	CRU*

Current Changes

REPORTING TO FORENSIC CHEMISTRY CENTER (FCC):

*In order to assure that foreign firms supply the requested profile samples and documentation (See Page 12, Items 1 & 2), the Forensic Chemistry Center (FCC) should receive a copy of the coversheet for all inspections of foreign active pharmaceutical ingredient manufacturers. The coversheet endorsement should include a phone and fax number of the contact person at the firm. If a sample is not collected by the investigator during the inspection, the coversheet should also state that the manufacturer was instructed to collect and ship a sample and applicable records directly to FCC as per Appendix B. This will permit proper follow-up by FCC and also serve to identify the investigator who will receive a copy of the annotated collection report prepared by FCC. On a quarterly basis, FCC will send a summary of sample testing results to the Foreign Inspection Team (FIT), HFD-322.

The container/closure and product information obtained from Appendix B will be included in the Active Pharmaceutical Ingredient Databases and made available to District Import Offices to help prevent counterfeit APIs from entering the United States market.*

REPORTING TO CDER□S DIVISION OF MANUFACTURING AND PRODUCT QUALITY:

For domestic inspections of active pharmaceutical ingredient manufacturers, submit a copy of the EIR coversheet, FD-483, and District issued copy of Warning Letters (after CDER review and concurrence) to CDER's Division of Manufacturing and Product Quality, HFD-320, for review and trend analysis.

Current Changes

PART I - BACKGROUND

*Since the late 1980's, the U.S. Food and Drug Administration has intensified its inspectional coverage of active pharmaceutical ingredient (API) manufacturers. This is due, in part, to an increased awareness that API quality plays a potentially significant role in the quality, efficacy, and safety of finished dosage form pharmaceuticals. For example, physical properties of APIs formulated into solid oral dosage forms, suspensions, and topicals may adversely affect drug product dissolution/bioavailability. In addition, extremely small quantities of unidentified or uncharacterized impurities in drugs may cause serious patient side effects.

FDA has long recognized that CGMP concepts, embodied in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR 210 and 211), are valid and can be applied to API processes. These concepts include, among others, building quality into the product, employing appropriately qualified and trained personnel, establishing adequate written procedures and controls, establishing a system of in-process and end product tests, process validation, and ensuring stability of APIs for the intended period of use.*

The *September 1991 FDA Guide to Inspections of Bulk Pharmaceutical Chemicals, reformatted in May 1994 with minor editorial changes, contains general guidance as to the extent and application of GMP/validation concepts to API production and agency expectations regarding tests for impurities and impurity profiles. This guide must be used for inspection of both foreign and domestic facilities to promote inspectional consistency and uniformity.*

*At present, FDA expects API manufacturers to apply CGMPs to all steps of an API process, beginning with the use of starting materials, and to validate critical process steps that impact the quality and purity of the final API. This approach recognizes that the control needed is highly dependent on the manufacturing process and that the level of control increases throughout the synthesis as the process proceeds from early intermediate steps to final isolation and purification steps. This approach also allows □appropriate□ levels of control, depending on the process itself (i.e., fermentation process vs. chemical synthesis) and the risk or criticalness associated with the specific process step being performed.

This "control all manufacturing steps, validate critical process steps" approach is embodied in the draft FDA Guidance for Industry on the Manufacture, Processing or Holding of Active Pharmaceutical Ingredients, which was released for public discussion on September 20, 1996. The latter can be obtained from CDER□s Drug Information Branch, HFD-210, or can be downloaded from CDER□s Home Page at □http://www.fda.gov/cder/api.htm.□*

Current Changes

PART II - IMPLEMENTATION

OBJECTIVE

The primary objective of this compliance program is to provide comprehensive CGMP inspectional coverage of the domestic and foreign active pharmaceutical ingredient (API) industry in all profile classes (processes).

PROGRAM MANAGEMENT INSTRUCTIONS

This program circular applies only to active pharmaceutical ingredients intended for use in drug products. An active pharmaceutical ingredient is defined as any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Although the agency has used the terms □bulk pharmaceutical chemicals□ and □bulk drug substances□ to describe these materials, FDA is aware that the term □active pharmaceutical ingredient□ has international recognition. In light of this and for added clarity, the agency is adopting the term active pharmaceutical ingredient for use in this compliance program.

Owners or operators of all domestic drug establishments, to include APIs, not exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act, as amended, or 21 CFR 207.10 are required to register and to submit a list of every drug in commercial distribution. Foreign drug manufacturers are not required to register, although they are required to list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on drug listing requirements for foreign drug establishments.

Although the current good manufacturing practice (CGMP) regulations, 21 CFR 210 and 211, do not apply to APIs, active pharmaceutical ingredients are subject to the broad requirement of Section 501(a)(2)(B) of the Act in that they must be prepared in conformance with current good manufacturing practice. *No distinction is made between APIs and finished pharmaceuticals in the Act, and failure of either to comply with CGMP constitutes a violation of the Act.* Therefore, in this document, the term CGMP refers to the latter, rather than 21 CFR 210 and 211 provisions.

Current Changes

EXCLUSION

This program circular does not apply to the sterilization and aseptic processing steps of sterile active pharmaceutical ingredients, which are covered by Compliance Program 7356.002A, Sterile Drug Process Inspections. The FDA has long maintained that sterile APIs are finished drug products subject to the CGMP regulation for finished pharmaceuticals (21 CFR 210 and 211) because these are repacked as finished dosage forms under aseptic conditions without further purification or processing.

Current Changes

PART III - INSPECTIONAL

Inspections of active pharmaceutical ingredient manufacturers, whether foreign or domestic, should be conducted by experienced investigators with education and/or training in fermentation, chemical synthesis, recombinant DNA, and other biotechnology manufacturing methods. Use of chemists and/or microbiologists during API inspections is recommended, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, lab procedures and instrumentation), analytical review of methods used to establish impurity profiles, fermentation manufacturing processes, and complex multi-step chemical synthesis processes.

*Investigators conducting API inspections must understand the basic differences between the processes used for the production of APIs and those used for finished dosage forms. APIs are usually produced by chemical synthesis, recombinant DNA technology, fermentation, enzymatic reactions, recovery from natural materials, or combinations of these processes. The production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. Purification is the ultimate objective.

In contrast, finished drug products are formulated from bulk raw materials that are usually subjected to some degree of quality control by the users (dosage form manufacturers). Most important, the manufacturing processes for finished pharmaceuticals typically do not involve purification steps.

For these reasons, the manufacturing and quality controls employed in API production and their application throughout the process (i.e., stringency of controls, written instructions, in-process controls, sampling, testing, monitoring, and documentation employed in early processing steps vs. later isolation and purification steps) differ somewhat from those found in finished dosage form plants. These differences, however, are simply reflections of different manufacturing processes, not inherent differences in the importance of GMPs for the two types of production.*

*Since manufacturers of active pharmaceutical ingredients are often referenced in many drug applications, each inspection should cover as many API processes as is feasible. This strategy will maximize the use of agency resources and avoid repeated visits to the same manufacturing site to cover different API profile classes referenced in subsequent applications. Thus, effective with this CP revision, all inspections of API manufacturers, regardless of how these are initiated, will be "GMP qualifying inspections." Inspections should cover the specific API profile classes referenced in the assignment and all other API profile classes not inspected in the last two years.

Current Changes

For foreign API firms, investigators should only cover profile classes for APIs intended to be marketed or already marketed in the United States.

APIs selected for coverage should include those referenced in drug applications, are therapeutically significant, are intended for use in parenteral drug products, are difficult to manufacture, or those on record as having past compliance problems. However, this does not preclude the selection of less therapeutically significant active pharmaceutical ingredients to evaluate specific API processes (profile classes) not previously given in-depth coverage at the facility.

Investigators conducting API inspections should understand the general inspection strategy set forth in Part II of this program. Recognizing that API firms vary greatly in size, diversity of operations, and quality assurance systems, investigators should carefully plan their inspectional strategy at each firm. Of particular concern are API manufacturing operations located in developing countries. *Impurities and contaminants present in components, process water, and solvents used in the production of APIs may carry over into the active pharmaceutical ingredient and may not be detected by analytical tests conducted by either the API manufacturer or the dosage form manufacturer. During inspections, investigators should review the quality of process water and solvents used in isolation and purification steps, the firm's procedures for preventing API contamination/cross-contamination, procedures for controlling impurities, and the procedures and test methods for establishing a complete impurity profile for each API process.* These are covered in detail in the September 1991 FDA Guide to Inspection of Bulk Pharmaceutical Chemicals and its "Appendix A."

During inspections, investigators should review the batches manufactured during the last year to determine not only those released, but any rejections. The firm□s policy on reprocessing and reworking of APIs should also be examined. Some batches start off as a pharmaceutical grade and then become technical grade. This could indicate a problem with the validated process. In addition, equipment cleaning validation should be reviewed to assure that the firm can remove residues, microbial contamination, and endotoxins to acceptable levels when the end product is intended for parenteral or liquid dosage forms.

For API inspections initiated by a preapproval assignment, review guidance provided in CP 7346.832, Pre-Approval Inspections/Investigations, and assess the authenticity and accuracy of data contained in drug applications and drug master files. Report inspectional time under the appropriate program assignment codes (PACs) referenced in both compliance programs, based on coverage afforded to each program.

Current Changes

*CHANGES IN THE FOREIGN DRUG INSPECTION PROGRAM

Beginning in FY 97, ORA and CDER agreed to implement several changes to the foreign drug inspection program to streamline the compliance review process. The Division of Emergency and Investigational Operations (ORO/DEIO), will continue to work with foreign governments in scheduling foreign inspections, making travel arrangements for inspection teams, and resolving logistical problems. However, new procedures are in effect for handling a foreign firm's response to an FD-483, submitting establishment inspection reports, and commenting on a foreign firm's response to an FD-483.

Investigators should instruct management at foreign firms to submit the original written response to an FD-483 directly to CDER's Office of Compliance with a copy to the lead investigator. The original response with appropriate documentation should be submitted to the following address:

Food and Drug Administration
Foreign Inspection Team, HFD-322
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855-2737

Investigators and analysts will submit written comments regarding a foreign firm's response to an FD-483 directly to CDER's Foreign Inspection Team (FIT). After appropriate district office review and endorsement, all foreign establishment inspection reports (EIRs) will be promptly forwarded to FIT for review and final classification. FIT will continue to issue Warning Letters, Untitled Letters and other correspondence to foreign firms. FIT will also recommend automatic detention of foreign firms/products, make recommendations to review units, and request follow-up inspections, as appropriate.*

INSPECTION

Review the September 1991 FDA Guide to Inspections of Bulk Pharmaceutical Chemicals, (Reformatted May 1994) to become familiar with the various areas and topics that must be considered when conducting API inspections. Appendix □A□ of this CP program is a summary of areas to be covered during API inspections. Photocopy this appendix and take with you

Current Changes

during inspections. Also obtain a copy of the drug application and/or Drug Master File (DMF), as applicable, and review these before initiating the inspection.

Third (field) copies of applications, *supplements and annual reports* are now required (Refer to 21 CFR 314.440) and such copies are submitted by domestic firms directly to the applicant's home FDA district office. Foreign *applicants* are required to submit third copies of applications to the same headquarters units receiving the first and second copies. These are made available by DEIO to investigators before initiation of foreign inspections.

Investigators should review all available information including prior inspectional information, FD-483s and responses, any Warning Letters, the firm's compliance history, sample analysis results, complaints, recalls, etc., to prepare for the inspection. For domestic inspections, the information is available from the Pre-Approval Monitors (PAMs) at each District Office. For foreign inspections, the information is available from DEIO or FIT.

Additional suggested references that Investigators and Chemists should be familiar with include: the draft Guidance for Industry - Manufacture, Processing or Holding of Active Pharmaceutical Ingredients; USP <1086> Impurities in Official Articles; and the recent changes in tests for the presence of foreign substances and impurities, contained in Page 3636 of USP-NF Supplement 6, effective May 15, 1997. In addition, the Investigator should contact the Forensic Chemistry Center (FCC) to determine which APIs should be sampled, so that duplicates are not collected during different inspections.

The Investigator should consult the CDER Case Officer for clarification of the assignment to assure that they are aware of the previous deficiencies at the firm. During the inspection, assure that all the firm□s promised actions are effective at correcting the problems. If the inspection determines that the firm has resolved all the deficiencies, submit the information for input into the CARS computer system.

Conduct a "GMP qualifying inspection" at each API manufacturer covering the products and processes specified in the assignment. In addition, cover in as far as possible, API processes that have not been inspected in the last two years. Also, conduct an in-depth inspection, to include examining pertinent systems and processes, whenever the District receives adverse information regarding a firm's ability to produce APIs of acceptable quality.

During inspections of API manufacturers:

Current Changes

1. *Determine if the firm has made process changes by comparing current operations against the Establishment Inspection Report (EIR) for the previous inspection. Also compare the current operations with those filed in the Drug Master File or the drug application to determine whether the firm is complying with commitments made to the agency. The following changes are typical of those that would warrant *extensive coverage* during the inspection:

   a. New potential for cross-contamination arising through changes in API processes or product lines, to include processing numerous APIs of varying therapeutic significance in common equipment and/or facilities.

   b. Use of new technology requiring new expertise, significantly new equipment or new facilities.

   c. *Recent changes in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, and computer software that are not referenced in the DMF or application.*

2. Verify that the size of the largest batch does not exceed the maximum working capacity of the firm's largest blender that is used for blending of API batches.

3. Review the firm's complaint file. Determine whether the pattern of complaints (or other information available to the District) and the firm's records of internal rejection or *reprocessing/reworking* of API batches warrant expanding the inspection. Look for weaknesses in the firm's processes, systems or controls.

4. Investigate the return of APIs for any reason. Determine whether the firm conducts investigations on returned products to find out if these APIs failed to meet specifications or were contaminated. Also determine the final disposition of returned APIs, i.e., whether reprocessed or destroyed.

5. If the inspection is initiated because the firm *is referenced as an API supplier in a drug application (NDA, ANDA, AADA), evaluate operations against commitments in the application and/or drug master file. Also, verify the authenticity and accuracy of data submitted in the application and/or DMF.*

Current Changes

6. *Obtain a copy of the impurity profile for each active pharmaceutical ingredient process covered during the inspection and compare these to the impurity profiles submitted in the Drug Master File.*

All Establishment Inspection Reports for API manufacturers must include:

1. History of business, and any corporate affiliations.

2. Names, titles, *and complete mailing address of most responsible officials who should receive correspondence from FDA.*

3. A list of APIs manufactured (or categories of products if many) along with the general manufacturing process for each (for example, chemical synthesis non-sterile, fermentation, extraction of natural products, etc.).

4. *For foreign API manufacturers, the names, titles, complete mailing address, telephone and Fax number of the firm's U.S. Agent, Regulatory Agent, and/or Importer/Broker.*

5. *For foreign API manufacturers, a report of all active pharmaceutical ingredients imported into the United States in the last three years, their consignees, and an estimate of the frequency and quantity of shipments to these consignees.*

6. A description of areas/processes inspected (i.e., what areas, systems and processes were inspected, who was interviewed, what manufacturing activities were ongoing during the inspection).

7. A description of any non-drug manufacturing activities conducted by the firm, such as processing pesticides or other toxic chemicals. If non pharmaceuticals are processed in the same facility and/or equipment with APIs, report precautions taken by the firm to prevent or minimize the potential for cross-contamination.

8. A description of all API micronizing or milling operations, whether conducted in-house or by a contract micronizer. Fully describe the precautions taken by the firm to prevent or minimize the potential for cross-contamination. During inspections of contract micronizers,

Current Changes

obtain a complete list of all active pharmaceutical ingredients micronized and report the source (owners) of these materials.

9. *A copy of the firm's process validation protocol. Report the status of all validation efforts. If not completed, obtain and submit the firm's written timetable showing when process validation will be completed.*

10. A report of any adverse findings as required by the Investigations Operations Manual (IOM).

SAMPLING

1. *A profile sample of the active pharmaceutical ingredient should be collected for analysis by the Forensic Chemistry Center, FCC (HFR-MA500) and Northeast Regional Lab (NRL). These samples of the API should not be confused with profile samples of actives collected together with finished product samples under the Pre-Approval Inspections/Investigations Compliance Program, CP 7346.832.

Depending upon the cost, the sample should consist of 25 - 50 grams of active drug substance from three different lots, collected in duplicate. Documentation that should accompany the sample must include:

- A flowchart and brief narrative description of the API manufacturing process;

- A material safety data sheet for the active pharmaceutical ingredient;

- A Certificate of Analysis *(COA)* for each lot; *in addition, a description of the computer system that was utilized to generate the COA and the precautions taken by the firm to safeguard the integrity of the computer data against employee manipulation.*

- A copy of any potential/established impurity profiles and applicable methodologies;

- The analytical methodology (if the inspection involves a new chemical entity).*

Current Changes

2. *During foreign inspections, it is often difficult for the investigator to collect profile samples of APIs. If a sample is not collected, the investigator should identify the lot (s) to be sampled and instruct the manufacturer to collect and ship the sample and applicable records directly to the FCC. The FCC will prepare an annotated collection report and forward the duplicate portion and copy of records to the NRL. An information copy will also be sent to the lead investigator.*

3. *When collecting samples for profile analysis, protect these from trace contamination. In all instances, avoid using metal spatulas. Use a plastic container and closure for sampling and submit an empty container as a control sub. If a plastic spatula is used, also submit an unused spatula as a sub-sample. Identify each container with the sample number, the product name and lot number, manufacturer, date and initials of the sampler. Wear disposable, talc-free, polyethylene gloves during the sampling activity. The preferred sampling method is by direct transfer and replacing the gloves between each subsample. Multiple product lots may be submitted under one collection report.*

4. To establish a labeling/container forensic data base, obtain the following information during inspections of foreign API firms. Identify this information with the firm's name, central file number (CF Number), and street address and send to *FDA/FCC, Bulk Drug Group, HFR-MA500, 1141 Central Pkwy., Cincinnati, Ohio 45202.*

a. Complete telephone and FAX number;

b. Contact person with title;

c. *Decoding of the *lot/batch numbering system;

d. *List* of the actual quantities of each lot of API produced for the last three years. Explain any difference between the batch and lot number. The records should reflect the total quantity *produced* and the amount shipped to the U.S.

e. Description *and/or* specimen of the container closure systems *(if easily obtained)* for APIs intended for U.S. distribution, as domestic packaging is often different:

Current Changes

1) Description *or photograph* and dimension of the container. If the container is plastic, list the color. What is the composition of the container bottom/lid?

2) Description *or photograph* of closure system. Is the lid sealed with a crimped seal? If so, briefly describe the seal and whether it contains any unique identifier. Some companies will have a product and/or company code visible in the crimped lead seal.

3) Provide a brief description *or photograph* of inner packaging (double or single plastic bag) and method of inner bag closure.

4) Provide an actual label specimen for each exported API *if easily obtained*. Has the label design changed since 1991? If so, briefly describe. Does the labeling or packaging contain any unique identifiers (i.e., embedded water marks)?

NOTE: Items (4.) (a - d) should be determined during the inspection. However, unless the firm has prepared summary reports that contain the information for (4.) (e), it is likely the data will not be available before completion of the inspection. This might also be true for (4.) (f) and other items. If so, provide the firm with a copy of Appendix B and obtain a commitment from a responsible individual stating when the information will be sent to FCC. Shipment by overnight carrier is recommended.

5. Collect samples to document any suspected adulteration and misbranding problems encountered during the inspection. Collect physical samples for suspected identity, potency, decomposition, contamination and/or labeling problems.

6. During foreign inspections, collect copies of analytical methods used by API manufacturers that are not from the United States Pharmacopeia. We do not have access to the pharmacopeial standards of other countries.

7. If cross-contamination is suspected, collect samples of the API and samples of the materials that are the suspected contaminants. Include with the Sample Collection Report (C/R) a description of the suspected route of contamination, or mechanism by which it is believed that contamination could have occurred. Any sample collected to document cross-contamination must be protected from contamination during or as the result of collection.

Current Changes

PART IV - ANALYTICAL

ANALYZING LABORATORIES

1. Routine chemical analyses - For sample collections under PACs 56002F, 52R806, 56008A, and 56008H follow the Servicing Laboratories guidance in the applicable compliance programs *and the ORA workplan*.

2. Routine Microbiological examinations - For sample collections under PACs 56002F and 56008A, follow the Servicing Laboratories guideline in the applicable compliance programs *and the ORA workplan. *The current testing laboratories are ATL, MIN, NYK, DEN and SAN.*

3. Chemical cross-contamination analyses by mass spectrometry (MS) - NRL, DAL, SRL, DET, DEN, and LOS. Non-mass spectrometry laboratories should call one of their own regional MS labs and/or the Division of Field Science (HFC-140) to determine the most appropriate MS lab for the determinations to be performed.

4. Antibiotic analyses:

   a. Penicillin by cylinder plate method: All laboratories listed in paragraph number 2 above (microbiological examinations).

   b. Other microbiological-based antibiotic analyses: DEN

   c. Chemical analyses: NRL, BLT *(PHI after 12/99)*, DEN.

5. Bioassays (such as insulin and heparin tests):

   - Division of Research and Testing (HFD-470)

6. Profile Analysis of API's:

   - Quality Test Analysis of Bulk Pharmaceuticals (PAC 56008A) and Bulk Import Samples Collected at Domestic Manufacturers for Quality (PAC 56008H)

Current Changes

Northeast Regional Lab (NRL): [NMR, MS, UV, IR]
850 3rd Ave.
Brooklyn, NY 11232-1593
*Contact: Alfred C. King

Tel: (718) 340-7000 (Extension 5067)
FAX: (718) 340-7003

- Counterfeit Drug Analysis (PAC 56008A) and Bulk Import Samples Collected at Domestic Manufacturers for Fingerprinting (PAC 56008H)

Forensic Chemistry Center (FCC)
1141 Central Pkwy.
Cincinnati, Ohio 45202
*Contact: Either Robert Sharpnack (Ext.114) or Karen Wolnik (Ext.181)

Tel: (513) 684-3505
FAX: (513) 684-6082

ANALYSIS

1. Examine samples for compliance with applicable specifications. Perform check analyses using the official compendial method, or when no official method exists, by other validated analytical procedures. See Compliance Policy Guide (CPG) 7152.01.

2. Confirm the presence of cross-contamination by a second method such as MS, UV, or IR. If a chromatographic procedure was used for the initial analysis, a second chromatographic method (HPLC, GC, TLC, etc.) may be employed provided the separation mechanism is different from that of the initial method.

3. Microbiological examinations should be based on appropriate sections of the United States Pharmacopeia (USP 23), B.A.M., 7th Edition, and A.O.A.C., Chapter 17.

4. USP testing methods may not be appropriate for detecting impurities generated from the synthesis routes of foreign source APIs. Therefore, foreign source APIs should have impurity limit tests based on their synthesis. If this information is lacking, contact the Division of Field Science (DFS) at 301-443-3007 for assistance.

Current Changes

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

All Warning Letters with CGMP charges involving domestic active pharmaceutical ingredient manufacturers require CDER review and concurrence. See Chapter 4, Page 81, of the August 1995 FDA Regulatory Procedures Manual and Chapter I, Page 15, of the October 1994 ORA Warning Letter Reference Guide.

Send Warning Letter recommendations to CDER's Office of Compliance, Division of Manufacturing and Product Quality (HFD-320). Warning Letters to foreign API manufacturers will issue from CDER□s Division of Manufacturing and Product Quality, HFD-320.

When recommending regulatory action, keep in mind that the CGMP regulations (21 CFR 210 and 211) do not apply to the production of active pharmaceutical ingredients (APIs) intended for further manufacturing. Nonetheless, the definition of "drug" in the Federal Food, Drug, and Cosmetic Act encompasses APIs and Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practices. The Act makes no distinction between APIs and finished pharmaceuticals and failure of either to comply with CGMPs constitutes a violation of the Act.

Because of the lack of a GMP regulation specific to APIs, any regulatory action based upon CGMP noncompliance for APIs must closely relate the deviations with actual or potential product defects, product contamination, or product cross-contamination, more so than for finished pharmaceuticals. In addition, consider the critical product attributes of the API, its therapeutic significance, and intended use in finished drug products when recommending regulatory action.

The following list represents examples of deficient practices that CDER believes may warrant issuance of Warning Letters, withholding application approvals, or other appropriate regulatory actions:

1. Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, other chemicals, drug residues, or a reasonable potential for contamination (with demonstrated avenues of contamination) such as airborne contamination or product contact with unclean equipment.

Current Changes

2. Failure to show that API batches conform to established specifications, such as NDA, USP, customer specifications, and label claims. See Compliance Policy Guide (CPG) 7132.05.

3. Failure to comply with commitments in drug applications, including Drug Master Files (DMFs). These documents should be current and accurately reflect the current synthesis process, impurity profile, and other specifications or procedures associated with the manufacture of the API.

4. Distribution of an API that does not conform to established specifications.

5. *Failure to determine actual yields and percentages of expected yields at the conclusion of appropriate phases of manufacturing, processing, packaging, or holding of APIs.*

6. Deliberate blending of API batches to dilute or hide filth or other noxious contaminants, or blending of a batch that does not conform *with critical product attributes* with one meeting specifications in an attempt to obtain one blended batch meeting minimum specifications.

7. *Failure to demonstrate that process water used in the manufacture of active pharmaceutical ingredients is suitable for its intended use and does not adversely alter the quality of the API.*

8. *Failure to validate reverse osmosis, ultrafiltration, deionized water, and distilled water systems that produce process water used in the final isolation and purification steps of non-sterile and sterile APIs.*

9. Lack of a formal written program to validate API manufacturing processes or failure to follow a validation program. The FDA expects API manufacturers to be actively engaged in a validation program for all APIs and *to complete process validation in an expeditious manner in accordance with timetables stipulated in protocols and commitments made to the Agency.* Therefore, regulatory action should not be initiated where the firm has an adequate API validation program in place, including reasonable milestones, and is following the plan.

Current Changes

Regulatory action should be initiated, however, when:

(1) the firm has not established or is not following an adequate plan to validate all APIs;

OR

(2) there is evidence that an API process is not *valid* as demonstrated by repeated batch failures (product non-conformance) due to manufacturing process variability not attributable to equipment malfunction or operator error.

Refer to Compliance Policy Guides 7132c.08 and 7125.38.

10. *Conducting a retrospective process validation for an existing API process when the process has changed significantly, when the firm lacks impurity profile data, or when there is evidence of repeated batch failures caused by process variability.*

Retrospective validation may be acceptable if:

- critical product attributes and critical steps in API processes have been identified and documented

- adequate in-process specifications and controls for critical processes have been established and documented

- there have been no significant changes to the manufacturing *components*, equipment or processes that could adversely affect the critical quality attributes of the API or the critical process parameters that affect these product quality attributes

- there are few process/product failures attributable to process variability

- complete impurity profiles have been established for existing API processes

- in-process and end-product test data show lot-to-lot consistency

Current Changes

11. Failure to demonstrate homogeneity of final blending/mixing operations in API processes where particle size distribution, surface area, or other physical attributes of the active pharmaceutical ingredient are critical to the dissolution and bioavailability of finished drug products. *Do not apply guidance intended for the blend uniformity of finished pharmaceuticals.*

12. *Failure to establish an impurity profile for each API process. FDA expects manufactures to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may derive from the API process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that may appear because of a deliberate or nondeliberate change in the API manufacturing process.*

13. *If reprocessing of APIs is performed and the manufacturer lacks data to show that reprocessing of API batches results in a product that complies with all established standards, specifications, and characteristics.*

14. *Failure to test for residues of organic/inorganic solvents used during manufacturing that may carryover to the API using analytical procedures with appropriate levels of sensitivity.*

15. *Failure to have a formal process change control system in place to evaluate changes in components, facilities, support systems, equipment, processing steps, and packaging materials that may affect the production and quality of APIs.*

16. Failure to keep adequate batch records, including:

- Date (s) manufactured
- Quantity manufactured
- Lot number
- Test results and dates
- Labeling records and specimen of labels used

Current Changes

- The signature of person (s) responsible for accomplishing significant steps, including:

  - determining yields
  - examining labeled containers for correctness of labels
  - testing for conformance to specifications
  - blending, if required
  - assuring conformance with established manufacturing procedure
  - reviewing production and testing records and authorizing release for distribution

17. Failure to record distribution by lot number in a way that would permit prompt recall.

18. *Incomplete stability studies to establish API stability for the intended period of use, and/or failure to conduct forced degradation studies on APIs to isolate, identify and quantify potential degradants that may arise during storage. Expiration dates are not required, except for antibiotics, radiopharmaceuticals, and other APIs with expected expiry dates of two years or less.*

19. Use of laboratory test methods that are inadequate or have not been validated.

20. *If there is a USP reference standard, failure to test each lot of an in-house (secondary reference standard) against the U.S.P primary reference standard before use.*

21. Conducting packaging and labeling operations in a way that introduces a significant risk of mislabeling.

22. *Failure to submit to FDA a list of every drug, including APIs, in commercial distribution. In the case of foreign drug firms, failure to list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on drug listing requirements for foreign drug establishments.*

Current Changes

PART VI - REFERENCE, ATTACHMENTS AND PROGRAM CONTACTS

REFERENCES OR GUIDES

1. September 1991 FDA Guide to Inspection of Bulk Pharmaceutical Chemicals, *Reformatted May 1994 with minor editorial changes*

2. FDA Guide to Inspections of Sterile Drug Substance Manufacturers, July 1994

3. FDA Biotechnology Inspection Guide, November 1991

4. FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, February 1987

5. FDA Regulatory Procedures Manual, Chapter 8-10

6. FDA Office of Regulatory Affairs Warning Letter Reference Guide, October 1994

7. Chapter 15, GWQAP Manual, revised August 1991

8. Drug Process Inspection Compliance Program, CP 7356.002

9. "Process Validation Requirements for Drug Products Subject to Pre-Market Approval," Compliance Policy Guides 7132c.08 and 7125.38, dated August 30, 1993

10. "Performance of Tests for Compendial Requirements on Compendial Products, Compliance Policy Guide (CPG) 7132.05, issued October 1, 1980

11. The United States Pharmacopeia/National Formulary (USP 23/NF 18), including supplements.

12. *Draft Guidance for Industry - Manufacture, Processing or Holding of Active Pharmaceutical Ingredients, released for discussion purposes on September 20, 1996.*

Current Changes

PROGRAM CONTACTS:

Office of Regional Operations (ORO)

1. *Division of Emergency and Investigational Operations, Drug Group (HFC-130), ORO/DEIO
Telephone: (301) 827-5653
FAX: (301) 443-6919*

2. Division of Field Science (HFC-140), ORO/DFS
Telephone: (301) 443-3007

Office of Enforcement (OE)

1. Medical Products Quality Assurance Staff (HFC-240), OE/MPQAS
Telephone: (301) 443-3590

Center for Drug Evaluation and Research (CDER)

1. For questions relating to product quality, the application of CGMPs, and validation of active pharmaceutical ingredient processes contact:

Edwin Rivera Martínez, Rick Friedman, or Patricia Alcock
Foreign Inspection Team, HFD-322
Division of Manufacturing and Product Quality, Office of Compliance

Telephone: (301) 594-0095
FAX: (301) 594-2202 or (301) 827-0145

Office of Regulatory Affairs (ORA)

1. *For questions on profile sampling of APIs contact:

Food and Drug Administration
Forensic Chemistry Center (HFR-MA500)
Telephone: (513) 684-3505, FAX: (513) 684-6082
Contact either Robert Sharpnack (Ext.114) or Karen Wolnik (Ext.181)*

Current Changes

PART VII- CENTER RESPONSIBILITIES

See Drug Process Inspection Compliance Program, 7356.002.

Current Changes

APPENDIX A

The September 1991 Guide to Inspections of Bulk Pharmaceutical Chemicals lists various topics/areas that must be covered when conducting API inspections, to include the following:

A. Inspection

1. Buildings and Facilities

- control of contamination/cross contamination
- water systems and suitability of process water for its intended use or specific synthesis step (i.e., whether used in early steps or later purification steps of a multi-step API process)
- aseptic/sterile processing, if applicable (Refer to CP 7356.002A)

2. Equipment

- Multi purpose equipment
- cleaning and use logs
- located outdoors
- protected environment
- cleaning of product contact surfaces, including validation of equipment cleaning procedures

3. Personnel training, qualifications, experience

4. Raw Materials/Components and Intermediates

- storage/handling practices and controls over quarantined, released, and rejected materials
- adequacy of specifications, and sampling/testing to determine conformance to specifications

Current Changes

APPENDIX A (CONTINUED)

5. Production and Process Controls

- controls involving reuse of mother liquors
- validation of final API blending and mixing operations for API processes where particle size distribution, surface area, or other attributes of the active pharmaceutical ingredient are critical to the dissolution and bioavailability of finished drug products
- validation of API process and control procedures, with special emphasis on critical process steps and synthesis and purification steps in the later stages of the API process that result in the formation of the active pharmaceutical ingredient or the removal of impurities
- procedures for reprocessing of APIs and types of reprocessing conducted (i.e., repeating a crystallization step), including whether these have been approved in the firm's application or DMF
- process change control system
- characterization and control of impurities
- API micronizing/milling procedures, including precautions to prevent cross-contamination

6. In-process Testing

- suitable batch sampling procedures employed and documented
- specified tests performed, recorded and within limits
- adequacy of instrument calibration procedures

7. Packaging and Labeling Operations

- labeling controls
- lot numbering system
- conformance with labeling regulations

8. Expiration Dating/Re-Evaluation Dating Practices

Current Changes

APPENDIX A (CONTINUED)

9. Laboratory Controls
   - ability to conduct tests, adequacy of records
   - adequacy of sampling/testing for raw materials, intermediates, and finished products, including tests for impurities in APIs
   - drug reference standards (source, test results, equivalency with official standards)
   - validation of analytical methods, as appropriate
   - firm's performance of follow-up on unexpected analytical results to determine cause and make any necessary corrections (such as additional chromatographic graphic peaks, retention-time shifts, spectrophotometric maxima peaks, or melting point range changes)
   - firm's quality assurance procedures for instruments and other laboratory equipment

10. Stability Testing Programs/Reserve Samples

11. Records and Reports

    - written procedures
    - batch records, documentation of process
    - computerized process and production records

Current Changes

APPENDIX B

INFORMATION FOR FORENSIC CHEMISTRY CENTER TO BE REQUESTED

FROM FOREIGN ACTIVE PHARMACEUTICAL INGREDIENT MANUFACTURERS

Please send the information to:

Food and Drug Administration
Forensic Chemistry Center (HFR-MA500)
Bulk Drug Group
1141 Central Parkway
Cincinnati, Ohio 45202

Tel: (513) 684-3505 (Extension 184)
Fax: (513) 684-6082

Shipment by overnight carrier is recommended.

1. Firm name, Central File Number (CFN), and street address.

2. Complete telephone and FAX number.

3 Contact person with title.

4. List of APIs, routine batch size and volume per year shipped to the United States.

5. Key to lot/batch numbering system.

6. Description of the container closure systems for bulk products intended for U.S. distribution, as domestic packaging is often different:

a) Description and dimension of the container. If the container is plastic, list the color. What is the composition of the container bottom and lid?

Current Changes

APPENDIX B (CONTINUED)

b) Description *or photograph* and specimen *(if practical)* of the closure system. Is the lid sealed with a crimped seal? If so, briefly describe the seal and whether it contains any unique identifier. Some companies will have a product and/or company code visible in the crimped lead seal.

c) Provide a brief description *or photograph* of inner packaging (double or single plastic bag) and method of inner bag closure.

d) Provide an actual label specimen *(if practical)* for each exported API. Has the label design changed since 1991? If so, briefly describe. Does the labeling or packaging contain any unique identifiers (i.e., embedded water marks).

e) Provide a certificate of analysis (COA) for each product. Has the COA changed since 1991? If so, describe or provide an example. *In addition, provide a description of the computer system that was utilized to generate the COA and the precautions taken by the firm to safeguard the integrity of the computer data against employee manipulation.*

Current Changes