Chapter 46 - NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE
POST APPROVAL AUDIT INSPECTIONS	*Upon Receipt*
	COMPLETION DATE
	Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46843 - NDA/ADA Post Approval 52843 - ANDA/AADA Post Approval 46R807 - NDA/ADA Foreign Post Approval (NEW) 52R807 - ANDA/AADA Foreign Post Approval (NEW)

FIELD REPORTING REQUIREMENTS

1. Inspectional

A copy of the coversheet, the "Audit Findings" section of the EIR, FDA-483 (if issued) and each copy of a sample collection report is to be submitted to the Division of Drug Manufacturing and Product Quality, Investigations and Compliance Evaluation Branch, HFD-324, for each inspection conducted under this program.

NOTE: Districts should assure that each operation performed by direction of this program is entered against the correct Product Code and Program/Assignment Code (P/AC).

Forward all violative Establishment Inspection Reports (EIRs) that include a recommendation to withdraw approved NDA/ANDAs as well as regulatory action, with full documentation of non-compliance with CGMP regulations to HFD-300 Attn: Investigation and Compliance Evaluation Branch HFD-324. Such EIRs are to be submitted within 30 days after

completion of the inspection. Violative GMP inspections that do not impact applications need not be submitted to HFD-324.

Districts are required to update promptly the firm profile in accordance with Chapter 15, GWQAP Manual. As soon as the district becomes aware of any significant inspectional, analytical, or other information that could or should affect the agency's product approval decisions with respect to a drug firm, the district should immediately notify HFC-240, Medical Products Quality Assurance Staff, via EMS or fax, and they will, in turn, convey the information by fax or equivalent expeditious means to HFD-324.

2. General

Each district should appoint a Post-Approval Program Coordinator who is responsible for monitoring this program. The current list of such coordinators is included under Part VI, ORA Field Contacts. The coordinators listed for the Post-Approval compliance program are the same as those who monitor the Pre-Approval compliance program. Any changes in program coordinators should be reported promptly to the Division of Field Investigations, Investigations Branch (HFC-132).

PART I - BACKGROUND

Based on allegations of misconduct in the generic drug industry, FDA conducted a thorough investigation of generic drug manufacturers and uncovered the following major findings:

- Firms submitted fraudulent samples for bioequivalence testing.
- Firms submitted false records or data in their ANDAs to FDA so as to gain approval for marketing.
- Firms deviated from CGMPs for pre-approval batches.
- Firms deviated from CGMPs for commercial batches.
- Firms deviated from the approved formula/manufacturing processes.
- Firms falsified batch records for commercial production so as to conceal from FDA that they were not following the conditions of approval.
- Firms falsified inventory control records, purchasing records, etc. to cover other fraudulent records.

These investigative findings prompted FDA to take a more active role in guarding against these types of violations by more closely monitoring the integrity of the approval process during the pre- and post-approval phases of the NDA/ANDA process.

The purpose of this program is to direct the conduct of post-approval audits of NDA and ANDA establishments and to provide continuing coverage of approved products regardless of whether or not these products were covered under the pre-approval program. It is designed to audit for changes in the production and control practices that occur after approval and to confirm that the approved applications have been appropriately supplemented to reflect those changes.

PART II - IMPLEMENTATION

OBJECTIVES

The main objectives of this continuing compliance program are twofold: (1) to assure that any changes in manufacturing and process control are in compliance with CGMP regulations; and (2) to assure that all changes are documented in supplemental applications or annual reports as required by 21 CFR 314.70. Appropriate regulatory action will be taken against those establishments not meeting these requirements. Additionally, through the use of related compliance programs, a secondary objective of this program is to confirm that NDA/ANDA requirements concerning Adverse Reaction Reports, NDA Field Alerts, Annual Reports are being met. Both foreign and domestic establishments are covered by this program. Such coverage is intended to be consistent to the extent possible.

PROGRAM MANAGEMENT INSTRUCTIONS

This program is designed to provide a structured approach for inspectional audits of drug manufacturers who hold approved applications.[1] The program provides for inspections on both routine surveillance and directed/for cause basis.

Inspection Planning and Priorities

When inspections are made at an NDA/ANDA facility on a biennial basis, some audit inspections should also be conducted. Foreign inspections of application related firms should also address NDA/ANDA committments. They are performed by investigators and analysts who routinely conduct domestic inspections and use the same inspectional guidance. Because of the travel time, costs, and the need to work with foreign governments, foreign inspections are scheduled through the International and Technical Operations Branch (ITOB, HFC-134). Reports are perpared by the district investigators and analysts and endorsements are prepared by the supervisor of the team leader. ITOB acts as the district compliance branch and prepares alerts, recommendations to centers, and schedules follow-up actions.

[1] "Application" as used in this program means NDA, ANDA, Antibiotic Drug Application or Abbreviated Antibiotic Drug Application and their supplements.

Inspection Team

The District should consider using an inspection team consisting of investigators, analysts, engineers, computer experts, or other specialists, as appropriate. The team should be highly skilled in drug manufacturing, analytical technology, and the new drug application review process.

Routine Surveillance

Surveillance inspections will generally be initiated by the pre-approval program manager in each district office. When the districts schedule inspections for program coverage, products that have received approvals within the previous 1-3 years should be given coverage. Coverage should include at least some products where approval was not based on a specific pre-approval inspection. Particular emphasis should be directed at assuring that product reviews, NDA and ANDA annual reports, and other requirements are being met.

Since the districts receive copies of the application and supplemental application approval letters as well as third copies of the chemistry section of such applications, the district coordinators should set up a mechanism, such as a database or tickler file, to ensure that firms are selected during the 1-3 year period subsequent to approval. When such audits are scheduled, a copy of the audit assignment should be sent to the laboratory that is to receive the post-audit sample (which should be the same laboratory that analyzed the original pre-approval forensic sample). In addition, along with the sample, the laboratory should be sent any relevant supplemental changes to the formulation that should be taken into account when comparing the post-approval sample with the original forensic sample.

Directed and For Cause

Directed and For Cause inspections may be initiated at both home districts' and headquarters' direction. These are priority inspections that are likely to be application/product specific. They can be referred from review divisions, forensic testing laboratories (based upon analysis of previously collected forensic samples) or result from CDER market surveillance or district surveillance, etc. Headquarter assignments will be coordinated and issued by HFD-324. A copy of the district-initiated "directed" or "for cause" assignment should be forwarded to HFD-324 at the time of issuance.

PART III - INSPECTIONAL

This program audits the changes a firm has instituted in the manufacturing and process control of NDA/ANDA products which may impact on the approved applications. The program relies, in part, on change control requirements established under the CGMP regulations. This regulation requires the review and approval, by the quality control unit, of proposed changes prior to their implementation (21 CFR 211.22(c)). Also, 21 CFR Part 314.70. requires review and approval by FDA for certain changes to approved applications.

Records and processes should be reviewed for all changes that have occurred from the time the application was approved up to the time of the first inspection under this program. All unapproved changes should be fully documented. Findings of significant deficiencies should result in expanding the depth of the inspection. Findings which bring into question the reliability of the provided records should be corroborated by examination of alternate records and interviews of personnel.

The inspection should confirm that commitments made by a firm at the time the application was approved have been completed or are underway in accordance with those commitments.

Districts should concurrently inspect the firm's operations and compliance with respect to the NDA field alert reporting requirements established under 21 CFR 314.81(b) (See CP 7356.021 for background) and under CP 7353.001 (Enforcement of the Drug Experience Reporting Regulation) when conducting these post-approval audit inspections.

AUDIT PROCESS

The audit process consists of selecting one or more audit points for inspectional coverage for the application(s) being audited. Examples of audit points are: records identifying the Quality Control Unit's approval of revisions in procedures and specifications, annual product reviews (211.180(e)), reprocessing records, records of in-process or finished product rejections, records of the justification for deviations from established laboratory procedures, records of the results of the examination of reserve samples, records of deviations from written procedures (211.100(b)), records of investigations of unexplained discrepancies and batch failure (211.192), records of modifications of established test methods, records of investigations of returned drug products, and stability test results ,changes described in the annual report and "Special Supplements - Changes Being Effected".

The process entails identifying the current or most recent record for the audit point being covered, and all previous versions back to the original document approved at the time of the original NDA/ANDA approval. When the audit of these documents suggests that changes occurred, the audit extends to the records associated with the establishment's change control procedures (quality control unit's approval), the records relating to NDA/ANDA Supplement submissions, and the agency's response to the establishment for each supplement. In audits that show no change has occurred, the investigator should confirm that the current formula, manufacturing processes, analytical method, specification, etc. are the same as that which was approved originally. In addition, the investigator should also review secondary records to verify that no change has occurred.

For example, a selected audit point could be the product's formula. The current version of the Master Formula Record is obtained and its approval date noted together with the product's qualitative and quantitative formulas. The previous versions are obtained and the entire product formulation history is reviewed and audited for changes to the product formula. For each change in formula, the associated records related to the approval of the change by the quality control unit, the records of application supplement submission and the agency's response are evaluated for departures from the requirements. If no change is noted, a spot check of some actual batch records and/or other associated records, e.g., raw material inventory/disbursement records, equipment use and cleaning logs etc., can be made to confirm that no change has occurred. The above approach could also be employed in the reverse manner for those applications for which a Pre-Approval Inspectional Package was provided to the district. The pre-approval Master Formula Record could be followed through its revisions to the current version of the document and the related records, as identified above, reviewed and audited for compliance with the requirements.

Similarly, the various equipment identified for production in the Pre-Approval Package could be reviewed against that used for current production, and if changes are determined, the records and supplements related to the changes should be audited for compliance with the requirements.

A centralized approach could also be used by auditing the records of the quality control units' change control operations. For those changes identified for products of inspectional interest, the records and supplements related to the changes would be audited for compliance with the

requirements. Caution must be exercised, however, as this approach might not detect changes that were implemented outside formal change control procedures.

VERIFICATION OF NDA/ANDA SUPPLEMENTS AND AGENCY'S RESPONSES

CDER will copy the districts with all outgoing NDA/ANDA correspondence so that the district will be aware of FDA- initiated NDA/ANDA correspondence to verify the status (approved/unapproved) and dates of action on application supplement. In the event the district requests further record(s) or has other NDA/ANDA status questions, please contact the Division of Drug Manufacturing and Product Quality, HFD-324, for verification.

Domestic Sample Collections

Physical Samples

The program requires routine collection of samples. These samples should be flagged "Post Approval Forensic Sample, NDA/ANDA/AADA #". Use PAC 46843 (NDA/ADA) or PAC 52843 (ANDA/AADA). The sample is to be submitted to the Philadelphia District Laboratory (MA and SE) or the Northeast Regional Laboratory (NRL) (all other regions). Exceptions include the Division of Drug Analysis (DDA) as the designated forensic laboratory for samples from bilateral inspection agreement countries (MOUs with Canada, Sweden, and Switzerland), and the antibiotic forensic samples. These post-approval samples should be submitted to the same laboratory that conducted the pre-approval forensic analysis, or to NRL, if no pre-approval sample was collected. Only finished dosage forms need to be picked up routinely for sample collections. The other documentation and excipients, shells, dyes, active ingredients, etc. should be picked up later if there are discrepancies associated with the dosage form sample, or on an "as need" basis when a pre-approval forensic sample was not collected. A copy of the master formula record or any approved sample should accompany the sample submitted to the laboratory. The specific details of the changes(s), approved or any unapproved changes found, should be reported in the remarks section of the collection report. A copy of the C/R is to be routed to HFD-324.

Guide for follow-up or special request sample collection:

Finished Dosage Forms

Tablets and capsules	300 units
Injections, single	100 units
Injections, multiple	20 units
Oral liquids	72 ounces

Forensic Sample Size NDA/ANDA

Inactive	40 grams
Capsule Shells	100 units
Colors and dyes	400 mg
Active Drug Substance	*

[* The amount of active drug substance will vary between products. You should collect the amount of active drug substance necessary to produce 500 dosages of the product. The responsible laboratory should be consulted if a physical sample collection would be costly or if there are questions about sample sizes.]

Proper PAC codes, in conjunction with sample flag instructions, should be reported in PAC 46843 for NDA/ADA's and PAC 52843 for ANDA/AADA's.

Establishment Inspection Reporting

Each EIR, written on an inspection, conducted under this program should include a section entitled "Audit Findings". This section should identify each application covered during the inspection, the specific audit points reviewed, the changes detected, and include comments as to whether the changes were in compliance with CGMPs, supplements, and annual reports to the application(s) were properly submitted.

PART IV - ANALYTICAL

The Northeast Regional (all regions except MA and SE) and Philadelphia District (MA and SE) Laboratories will be responsible for most post-approval sample analyses under this program using methods, such as FTIR, to produce "fingerprints" for comparison with the approved products. An exception to this policy includes samples from countries with which the agency has bilateral agreements; these samples will be analyzed by the Division of Drug Analysis (DDA, HFH-300). The results of this analysis will also be utilized for comparison with the pre-approval samples collected under the Pre-Approval Inspections/Investigations Compliance Program (CP 7346.832). Post-approval samples should be sent to the same laboratory which conducted or would have conducted the pre-approval forensic work and the resultant data will be added to a national database. The results of the examination of forensic samples will be reported back to the collecting district and to HFD-324 by the responsible laboratory. Also, copies should be sent to the Northeast Regional Laboratory where a central database is maintained. The post-approval sample information would be added to the data already gathered under the Pre-Approval program.

The above laboratories will provided consultative services to headquarters and field offices for on-going investigations.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The use of application audits is intended to provide an efficient and reliable means of assessing an applicant's conformance with application commitments, the submission requirements for supplements, and the CGMPs.

Findings of significant deviations during the initial audit should result in expanding the level and depth of the inspection to determine and document the nature and scope of all significant deviations. Inspectional findings that bring into question the reliability of the firms's documents, statements, etc., should be brought to the attention of district management as uncovered, and an appropriate inspection strategy developed.

The district should recommend appropriate regulatory and/or administrative action when there are significant deviations from CGMP regulations or from application commitments. Actions which may be considered are Application Integrity Policy, application withdrawal, FDA-requested recall, warning letter, seizure, injunction, and prosecution. Center concurrence is required for warning letters based on unapproved changes or a pattern or practice of unreliable data (AIP).

Significant problems that may be encountered include:

- Scale up(s) not documented or validated prior to commercial distribution of the batches
- lack of data supporting processes and controls, and changes thereto
- lack of controls and records
- inadequate, or lack of, validation
- inadequate change control procedures
- unauthorized process changes
- inadequate stability data, unfulfilled stability testing commitments, unreported stability test failures
- unfulfilled application commitments
- unreported/unapproved changes in manufacturing or testing/QA procedures

- improperly reported *or fraudulent* changes
- non-permitted change to new suppliers, testing, or contract laboratories
- using unapproved suppliers, testing, or contract laboratories

Discrepancies that might suggest fraud or deception, including unreported or inappropriately reported changes in approved applications, need to be evaluated by the district as they are uncovered and the inspection is ongoing. Headquarters is to be advised of such findings.

District recommendations are to be submitted to CDER, Office of Compliance, HFD-300.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

References

A. Code of Federal Regulations, Title 21, Part 210 and 211, Drugs:
Current Good Manufacturing Practices
Part 310, New Drugs
Part 314, New Drug Applications
Part 429, Drugs Composed Wholly or Partly of Insulin
Part 431, Certification of Antibiotics

B. CP 7346.832 - Pre-Approval Inspections/Investigations

C. CP 7356.002 - Drug Process Inspections

D. CP 7356.021 - Drug Quality Reporting System (DQRS), NDA - Field Alert Reporting

E. CP 7353.001 - Enforcement of the Drug Experience Reporting Regulations

F. United States Pharmacopeia, Current Revision, and supplements.

G. Guideline on Preparation of Investigational New Drug Products, March 1991.

H. Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturers, September 1991.

I. Guideline on General Principles of Process Validation, May 1987.

J. Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993.

K. Guide to Inspection of Validation of Cleaning Processes, July 1993.

L. Guide to Inspection of Lyophilization of Parenterals, July 1993.

M. Guide to Inspection of High Purity Water Systems, July 1993.

N. Guide to Inspection of Foreign Pharmaceutical Manufacturing Plants, September 1993.

O. GWQAP Manual, Profile System, Chapter 15.

P. Regulatory Procedures Manual, Chapters 7 and 8.

Q. Inspectional Operations Manual, Subchapter 540.

R. Compliance Policy Guide 7150.09 "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities", 07/01/91.

S. FDA "POINTS TO CONSIDER FOR INTERNAL REVIEWS AND CORRECTIVE ACTION OPERATING PLANS", JUNE 1991.

CONTACTS

A. ORA
Headquarters

Division of Field Investigations
Investigations Branch (HFC-132)
(Domestic): Jack Goodson
Telephone: 301-443-3340

Division of Field Investigations
International Programs and Technical Support Branch (HFC-134)
(Foreign): Peter D. Smith
Telephone: 301-443-1885

Division of Field Science/ORO (HFC-140)
George Salem
Telephone: 301-443-3007

Field Forensic Laboratories

Northeast Regional Laboratory (HFR-NE560)
Marten E. Woodhouse
Telephone: 718-965-5595

Philadelphia District Laboratory (HFR-MA160)
Michael Gurbarg
Telephone: 215-597-4383

B. Center for Drug Evaluation and Research

Laboratory:

Division of Drug Analysis (HFH-300)
Drug Monitoring Branch
1114 Market Street
St. Louis, MO 63101
Telephone: 314-539-2135

New Drug Applications:

Contact Office for NDAs (General):
Document Management & Reporting Branch (HFD-53)
Anna M. Myers
Telephone: 301-443-4320

Pilot Drug Evaluation Staff (HFD-007)
Telephone: 301-443-4250

Office of Drug Evaluation I (HFD-100)
Telephone: 301-443-4330

Office of Drug Evaluation II (HFD-500)
Telephone: 301-443-4080

Abbreviated New Drug Applications:

Office of Generic Drugs (HFD-630)
Robert Pollock
Telephone: 301-443-4080

Office of Compliance
Division of Manufacturing and Product Quality
(HFD-320)
Investigations and Compliance Evaluation Branch
Mark Lynch
Telephone: 301-594-0098

C. Center for Biologics Evaluation and Research

Division of Inspections and Surveillance
Biological Product Inspection Branch (HFM-655)
Telephone: 301-594-1191

(specific contacts will be shown in individual assignments)

D. ORA Field (Program Coordinators):

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Diana Amador
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PART VII - CENTER RESPONSIBILITIES

A. The Division of Manufacturing and Product Quality will:

1. Monitor the compliance status of the drug industry.

2. Communicate results of program operations findings to ORA, and affected headquarters units; application deviations and CGMP deficiencies will be cited with specificity.

B. The Offices of Drug Evaluation and Pilot Drug Evaluation Staff will:

1. Maintain an accurate listing of NDAs/supplements/annual reports. They will also provide copies of requested parts of NDA/supplements when requested by the district.

2. Consult with district investigators and analysts or issues of mutual concern.

C. The Office of Generic Drugs will:

1. Maintain an accurate listing of ANDAs/supplements/annual reports. They will also provide copies of parts of ANDA/Supplements when requested by the district.

2. Consult with district investigators and analysts or issues of mutual concern.

D. The Division of Drug Analysis will:

1. Analyze and compare post-approval sample results to the pre-approval sample profile for those samples analyzed.