SUBJECT: PRE-APPROVAL INSPECTIONS / INVESTIGATIONS	IMPLEMENTATION DATE: Upon receipt
* REVISION: March 2004 revisions to the PAI Program update mail codes and contact information in Field Reporting Requirements and Part VI, CONTACTS, and Program Assignment Codes. (Other material from 2003 issuance has not been updated.) *	COMPLETION DATE: Continuing

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	(SEE BELOW)

PROGRAM/ASSIGNMENT CODES

46832	NDA Pre-Approval Inspections/Methods Validation
46832B	NDA Forensic Sample Collection/Analysis
46832C	NDA Biotest Sample Collection/Analysis
*46832M	Therapeutic Biologics Products (main program is 56002M)*
52832	ANDA Pre-Approval Inspections/Methods Validation
52832B	ANDA Forensic Sample Collection/Analysis
52832C	ANDA Biotest Sample Collection/Analysis

FIELD REPORTING REQUIREMENTS:

1. Inspectional

   A. The District Director or person acting in this position must submit a written response to the Division of Manufacturing and Product Quality within 10 calendar days. Their response should list their concurrence with the approval of each NDA/ANDA or state the reasons why approval should not be granted. This will be in response to a written CDER request. The response should also include a listing of all pre-approval samples collected, including forensic (and biotest facility) and method validation or verification samples, or if not collected, reasons for such non-collection.

   B. Forward all violative Establishment Inspection Reports (EIRs) to HFD-300, Attention: Investigations and Compliance Evaluation Branch, with a recommendation to withhold NDA/ANDA approval and full documentation of non-compliance with CGMP regulations. Such EIRs are to be submitted within 30 days after completion of the inspection.

   C. Submit a summary of findings and district recommendations, via EMS/FAX, to *HFD-322* within 10 days after completion of the inspection. Districts must not wait for completion of inspection reports before notifying the Center of the District's recommendation about the approval of an application. Therefore, use the FDA-483 and the judgement of highly trained employees as the basis for the District's recommendation. If the recommendation is to concur with approval, no further documentation need be sent.

      Districts should closely monitor corrections made by firms for those conditions deemed unacceptable. Reinspections of firms should be completed within 30 days of a firm's certification, indicating the problems have been corrected.

   D. Special time frames apply in IND inspections. Assignments identified as "Treatment IND" or "Treatment Protocol" inspections must be completed within 10 calendar days of receipt.

   E. Districts are required to update promptly the firm profile in accordance with Chapter 15, GWQAP Manual when inspections are conducted.

2. Laboratory

   A. Forward all laboratory reports on NDA and ANDA method validations to the CDER unit that requested the validation. Forward any laboratory examination results, including forensic, to the home district of the

application's sponsor for regulatory consideration.

B. Worksheets covering samples analyzed under this program are to be forwarded to the home district. Forensic samples and copies of worksheets for such samples found to be in compliance will be stored in an orderly and retrievable fashion by the designated analyzing laboratory. This will enable complete and accurate comparison of results on samples collected during the pre-approval inspection to the biotest samples, innovator samples, and post-approval samples collected at a later date.

C. Report suspicious laboratory results, indicating possible fraudulent preapproval samples, to the home district and to *HFD-322* as soon as possible.

3. General

Each district must appoint a Pre-Approval Program Coordinator who is responsible for monitoring this program. A list of current coordinators will be maintained by the Division of Field Investigations, Investigations Branch (*HFC-130*). Therefore, each region will submit names of coordinators to FIS.

PART I - BACKGROUND

The Food, Drug, and Cosmetic Act provides that FDA may approve a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity.

The applicant is required to submit information in the NDA/ANDA to the Center for Drug Evaluation and Research (CDER), which contains among other things a method of analysis and details as to how the firm proposes to manufacture, and control the manufacture, of the product which is the subject of the application. This information is reviewed by CDER scientists (chemists, microbiologists, etc.) to determine whether the specifications in the application meet the agency's standards. The District(s) examine the adequacy of the firms' facilities from a CGMP standpoint and audit the information submitted in the application.

Thus, in summary, CDER's role in the preapproval process is to review data submitted to the agency as part of pre-market new drug applications and generic drug applications, and establish specifications for the manufacture and control of the resulting drug product based on the submitted data. The Districts' role is to assure CGMP compliance, verify the authenticity and accuracy of the data contained in these applications, and report any other data which may impact on the firm's ability to manufacture the product in compliance with GMP's.

This program is designed to provide close inspectional and analytical attention to the authenticity and accuracy of data in applications and to provide information regarding facilities. Such coverage is necessary to assure that applications are not approved if the applicant has not demonstrated an ability to operate with integrity and in compliance with all applicable requirements. This program defines the roles of District investigators and analysts and CDER scientists in the preapproval process and expects a high level of direct communication between each group.

PART II - IMPLEMENTATION

OBJECTIVE

The objective of this continuing compliance program is to assure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and new drug substances are audited: 1.) through on-site inspections for compliance with CGMPs 2.) for conformance with application commitments 3.) to assure data is authentic and accurate, and 4.) through laboratory testing of products, including evaluations of the adequacy of analytical methodology.

Both foreign and domestic establishments are covered by this program. Such coverage is intended to be consistent to the extent possible.

This program provides guidance for establishment inspections and related investigations, and for laboratory evaluations of methods of analysis proposed by applicants in NDA and ANDA submissions. FDA management has determined that these District activities are essential parts of the application approval process providing an "authenticity check" for the data submitted for review by CDER scientists. The program describes the different but complementary roles of District and CDER personnel. It also includes program contacts in the CDER application review offices, and in each District, to provide an efficient means for the responsible District investigators/analysts and CDER chemists to quickly and easily communicate with each other. The program also provides guidance for both headquarters and field initiated pre-approval inspections.

PROGRAM MANAGEMENT INSTRUCTIONS

Before any application[1] is approved by the Center for Drug Evaluation and Research, a determination will be made whether all establishments that will participate in the manufacture, packaging or testing of the finished dosage form or new drug substance are in compliance with CGMP and application commitments. This determination may be made by conducting pre-approval inspections. Method validations, method verifications, and forensic analyses will be performed to confirm the authenticity of the pre-approval product and to ensure that it can be accurately assayed with the proposed regulatory methods. Post-approval inspections will monitor and enforce these requirements.

CDER will request inspections in accordance with pre-established criteria. Optional preapproval inspections may be performed by the District(s) where circumstances warrant. **Every effort will be made to assure that the inspections are completed and reported in the time frames given in the ORA new**

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

drug approval management plan.

District objectives and responsibilities in conducting pre-approval inspections,compared with the responsibilities assigned to CDER scientists, are set forth below. **Note: It is critical that the District(s) conduct the pre-approval inspections promptly and report the results specifically to CDER within the time frames required by this program so that an agency decision can be made on the approvability of the application. The items identified with an asterisk will no longer be required to be submitted to the application. These items will be evaluated in the plant by the field investigator as part of CGMP inspection of the facility. The exception is with regard to the validation of sterile processes. In such instances, it will continue to be required that the validation data and associated information be submitted to the application for review by a CDER microbiologist (refer to the section on Product (CGMP) Controls below).**

- Biobatch Manufacturing: Inspection to determine the establishment's compliance with CGMP requirements, including a data audit of the specific batches upon which the application is based (e.g. pivotal clinical, bioavailability, bioequivalence, and stability) is a Field responsibility. CDER scientists are responsible for the review and evaluation of the records and data submitted in the application, including the components, composition, batch instructions, in-process and finished product test points and specifications established for the resulting drug product.

- Manufacture of Drug Substance(s): Inspection to determine CGMP compliance of the establishment is a Field responsibility. CDER chemists are responsible for the scientific review and evaluation of the records and data associated with the manufacture of the active drug substance submitted in the application or a properly referenced Type II Drug Master File. The review will include starting materials, key intermediates, reagents and solvents. CDER reviewers are also responsible for the review of process validation required for the manufacturing of biotechnological and certain natural substances.

- Excipients Manufacture: The manufacture of novel excipients may be provided in an application or supporting DMF. Typically these excipients are non-compendial, and are used in specialized dosage forms and drug delivery systems. CDER chemists are responsible for the scientific reviews and evaluation of the records and data associated with the manufacture of these novel excipients. The review will include starting materials, key intermediates, reagents and solvents. CGMP inspections by the Field usually will be performed upon request from CDER.

- Raw Materials (CGMP Controls): Inspection of the establishment for the drug substance and review of data on raw materials to determine compliance with CGMP

requirements is a Field responsibility.

- Raw Materials (Tests, Methods and Specifications): Audit of the data submitted for CDER review in the application is a Field responsibility. CDER chemists are responsible for the scientific review of the associated data, evaluations of the adequacy of the submitted data, and the ultimate approval of the tests, methods and specifications established for the raw materials in the application.

- Composition and Formulation of Finished Dosage Form: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER reviewers are responsible for the scientific review of the composition and formulation to determine, qualitatively and quantitatively, the acceptability of the information submitted in the application.

- Container/Closure System(s): CDER is responsible for the scientific review of the container/closure systems to be used to package the drug product as indicated in the application. The field may audit this data.

- Labeling and Packaging Controls: Inspection to determine the establishment's compliance with CGMP requirements and audit of the data submitted for CDER review in the application is a Field responsibility.

- Labeling and Packaging Materials: CDER reviewers are responsible for the scientific review of the labeling and packaging components associated with the drug product.

- Laboratory Support of Methods Validation: Upon CDER request, field laboratory analysts will conduct laboratory validation of the analytical methods proposed by the applicant. CDER laboratories may participate in certain instances (AADA validations, etc.). CDER chemists are responsible for the review and acceptance/rejection of the analytical methods based on the laboratory results and the established specifications. Contacts between field laboratory analysts and the applicant will include the CDER chemist.

- Product (CGMP) Controls: Inspection of the establishment to determine compliance with CGMP requirements, and review and audit of the data furnished to CDER in the application is a field responsibility. CDER scientists will request information on sterile processes, e.g. laboratory controls for environmental monitoring, sterile fill operations, and evaluation and reduction of microbial contamination, to be submitted to the application for CDER review.

- Product Tests, Methods and Specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER is responsible for the scientific review of the associated data, and the ultimate approval of the tests, methods and

specifications established for the drug product in the application. The field will advise the Center when it finds a questionable specification.

- Product Stability: Inspection of the establishment to determine compliance with CGMP requirements and to conduct an audit of the data furnished to CDER in the application is a Field responsibility. This requirement applies to both the relevant preapproval batches, as discussed above, and the proposed commercial batches. CDER application review chemists are responsible for review of the proposed drug product stability protocol, specifications, and evaluation of the data submitted in support of the expiration dating period proposed for the drug product in the application.

- Comparison of the Relevant Preapproval Batch(es) and Proposed Commercial Production Batches: CDER chemists are responsible for the comparison of the formulation, manufacturing instructions and associated in-process and finished product tests and specifications established for the relevant preapproval batch(es) with the proposed commercial production batch to determine the acceptability of the firm's proposed scale-up procedure.

  The field will compare the process used to make the pre-approval batches with the actual process used to manufacture the validation batches. Significant differences in these processes will be evaluated by CDER's Office of Compliance to determine whether the differences constitute fraud, and by the reviewing officers to determine whether differences in the processes will affect the safety and effectiveness of the resulting product.

- Facilities, Personnel, Equipment Qualification: Review of the information and inspection of the establishment to determine compliance with CGMP requirements is a Field responsibility.

- Equipment Specification(s): Audit of the data submitted for CDER review in the application is a Field responsibility. CDER scientists are responsible for the review of equipment specifications furnished to the Center in the application.

- Packaging and Labeling (CGMP Controls): Review of the controls information and inspection of the establishment to determine compliance with CGMP requirements is a Field responsibility.

- Process Validation: Inspection of the establishment to determine compliance with CGMP requirements and adherence to application requirements is a Field responsibility. See Part V, "2. PROCESS VALIDATION." CDER may request data to support validation of sterile processing operations, e.g. environmental monitoring, equipment validation, sterile fill validation, and associated sterile operations.

- Reprocessing: Inspection of the establishment to

determine compliance with CGMP requirements and to conduct an audit of the data submitted to the Center in the application is a Field responsibility. CDER application review chemists are responsible for review of reprocessing protocols proposed in the application. All reprocessing procedures must be validated and/or scientific data must be available to justify the reprocessing procedure. The field will audit the validation of these procedures.

- Ancillary Facilities: Review of this information is a Field responsibility. Upon CDER request or in District management's judgement, ancillary facilities (contract testing laboratories and contract packagers and labelers) will be inspected to determine compliance with CGMP requirements. The name, address and function of each ancillary facility will be indicated in the drug application, and CDER will review biological and immunological test methods and results submitted. These facilities shall also provide a certification in the drug application regarding compliance with the conditions of approval of the application.

Agency management has determined that the CDER application review process, and the Districts' CGMP inspection and application data audit activities, can be coordinated to improve the efficiency of the preapproval process by encouraging CDER application reviewers, and District investigators and analysts to consult with each other in the course of carrying out their mutual responsibilities.

Accordingly, District investigators and analysts who have questions to discuss with CDER scientists assigned to applications should call the individual whose name appears on the District assignment, or when the CDER reviewer is unknown, to call the appropriate CDER contact who will locate the individual(s) assigned to the application(s) in question and arrange for them to return the call. Similarly, CDER application reviewers who wish to communicate with investigators and analysts performing inspections and laboratory investigations related to the application they have under review will call the preapproval program contact in the appropriate District for assistance in locating the assigned District investigator(s)/analyst(s). (See Part VI for a list of CDER and District program contacts.)

* *STRATEGY FOR ASSIGNING INSPECTIONS*

The strategy for assigning inspection requests for preapproval inspections has been divided into two categories, (1) categories that will regularly prompt an inspection request, and (2) categories when the district office may elect to perform an inspection.

A. The following categories will regularly prompt a preapproval or CGMP inspection request from CDER Office of Compliance. It is anticipated that the inspections will be conducted except when ORA Field offices recommend the inspection need not be completed:

1. *New molecular entities (NMEs) (includes finished drug product and the active pharmaceutical ingredient)*
2. *Priority NDAs*
3. *First application filed by an applicant*
4. *For-Cause inspection*
5. *For original applications, if the current CGMP status is unacceptable or greater than 2 years*
6. *For certain pre-approval supplements, such as site change or major construction, if the CGMP status is unacceptable*
7. *Treatment IND inspections*
8. *Information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients*

B. *The district office will have the opportunity to determine if a preapproval inspection is warranted for the following categories. ORA will be queried on the need to conduct a preapproval inspection via the "10 day status" request process in EES.*

1.
2. 1. *All original applications not listed above*
3. 2. *All preapproval supplements not listed above*

C. *Currently, CDER will request a 10-day status report for CBE supplements. Districts should use their knowledge of the firm to assess the need for a prompt inspection of the facility. Districts may also, at their discretion, assign and conduct inspectional audits above and beyond those for which they receive specific headquarters assignment.*

10 DAY NOTIFICATION

As specified under the strategy for assigning inspections, for firm's not assigned inspections by headquarters, CDER Office of Compliance, through EES, will consult the districts prior to approving each application. The districts will respond within 10 calendar days to these requests with a recommendation relating to such approvals. ***The response will be one of three options: recommend approval, recommend-withholding approval, or recommend delay until a pre-approval inspection can be conducted.*** *The responses will be based on results of any already completed district inspections or other information that should be considered by CDER before approval.*

Note: Recommendations to withhold approval of an application must include specific justification for CDER consideration. CDER will not withhold approval where sufficient justification is lacking. ***For NDAs, any decision to inspect must take into account the application's PDUFA date.***

INVESTGATIONAL DRUGS

Inspections will be requested by the Center when:

1. *The IND is a Treatment IND or Treatment Protocol (21 CFR 312.34 and 312.35.*

2. *There is information available to the Center for Drug Evaluation and Research indicating that inspection is warranted to protect the health of patients.*

For Treatment INDs and Treatment Protocols, treatment may begin 30 days after submission of the application unless placed on "clinical hold." In order to adequately protect patients' health, a comprehensive evaluation must be conducted within this 30-day period. Consequently, Districts must complete inspections and provide recommendations within 10 calendar days after receipt of assignments.

Districts should identify commercial manufacturing facilities that produce clinical supplies for use by other research facilities in the performance of clinical trials. These commercial facilities should be inspected periodically as resources allow, using CGGM 56002 as a guide, in order to assure global CGMP compliance. Manufacturing facilities that produce clinical supplies for their own use should be covered on a for cause basis only. Refer to the FDA's March 1991 "Guideline on Preparation of Investigational New Drug Products.
***

Bioequivalence Testing Facilities (Biolabs)

Samples of the test articles retained by biolabs will be collected routinely in accordance with the instructions in Part III Inspection - Section G., under the subsection on "Biotest Facility Samples". However, under this program, inspections of facilities conducting bioequivalence/ bioavailability studies will be initiated as a follow-up to

discrepancies discovered from FDA laboratory examination of such bioretention samples and/or from the District's pre-approval inspectional coverage of bio-batch manufacture and testing.

Specific guidance for conducting these for-cause inspections must be obtained through direct contact with the Division of Scientific Investigations, Clinical Investigations Branch, before initiating the inspection. These inspections are specialized and need careful direction to ensure that the inspectional efforts are maximized. The instructions under Compliance Program 7348.001 (In Vivo Bioequivalence) apply however, this coverage is distinct from that where inspections of facilities/studies are requested in conjunction with headquarters' reviews of biostudies. Those inspections are requested by headquarters to validate bioequivalence claims, or where the facility is unknown to the agency, or where there are gross problems, fraud, or suspected conspiracy.

While CP7348.001 should be reviewed, resources should be charged to the appropriate pre-approval program assignment code.

District Responsibilities

The Act requires the Agency to review applications within a certain period, and prescribes the specific grounds for withholding approval. District inspections and investigations are an inherent part of the agency's preapproval evaluation process, and must be conducted according to these statutory requirements. Therefore, Districts are responsible for timely responses to headquarters assignments, and District recommendations to delay, withhold or grant approval must provide adequate, documented grounds consistent with the Act, and must be fairly and equitably applied.

It is expected that any District conclusion or recommendation carries the approval of the District Director.

PART III - INSPECTIONAL

Operations

A. Inspection Team

At local District option, and/or CDER option, or where special expertise or other unique considerations warrant, inspection teams will be employed.

Inspection teams may consist of investigators, analysts, engineers, and/or computer experts, as appropriate. The individuals must be highly skilled in drug manufacturing and analytical technology. For example, these experts are typically the ones assigned to inspect new operations and to inspect highly complex systems that have produced products that failed specifications.

Investigators, or inspection teams, performing inspections/ data audits, and the analyst validating/verifying the proposed method should communicate with the CDER chemist or other scientist assigned to the application whenever issues or questions arise which may be of mutual concern. (See Part VI for CDER contacts.)

B. Inspections/Audits

1. Manufacturing Process

a) Drug Product (Dosage Form)

In many cases, clinical production or trial runs of a new drug are produced in facilities other than the ones used for full scale production. The facilities and controls used for the manufacture of the batch(es)[2] must be audited. For a generic drug product, the biobatch(es) are required to be manufactured in production facilities, using production equipment, by production personnel, and the facility is to be in conformance with CGMP's. Accurate documentation is essential so that the production process can be defined and related to the batch(es) used for the early clinical, bioavailability, or bioequivalence studies of new drug or generic drug products.

FDA has also published guidance for compliance with GMPs for the production of investigational drugs. Refer to this document for added assistance.

The batch records submitted in the application must be audited as part of the inspection to assure that the proposed production process is the process that was used for the manufacture of the bio/stability batches. Some

[2] Generic product biobatches are ANDA batches that are compared to the originator/reference product to establish their equivalence. NDA biobatches are NDA batches comparing the product planned for marketing with that studied during clinical trials to establish their equivalence.

manufacturers have historically made small batches that were used for biostudies and stability studies and misrepresented them as larger batches in submissions. Documentation sometimes has included R&D notebooks and/or batch records. Inventory records and/or receiving records of drug substances have been found to be of value in documenting the accountability of drug substances used in the early batches.

b) Drug Substance (Bulk Drug Chemical)

The "Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing" and Compliance Program 7356.002F covering Bulk Pharmaceutical Chemicals should be used for guidance for inspections covering bulk drug chemical manufacturing processes. Refer to Part V for a discussion of validation requirements.

2. Reprocessing

The GMP regulations require reprocessing procedures to be written, and it is customary but not required that NDAs/ANDAs contain procedures covering foreseeable deviations from physical specifications (e.g., color, capped tablets, deviations from hardness specifications, etc.).

If the NDA/ANDA contains a reprocess provision, the applicant must produce scientific data to establish that the procedure will result in a product that is equivalent to the original product.

3. Laboratory

Laboratory equipment and procedures must be qualified and validated. Every NDA/ANDA inspection will include an evaluation of laboratory controls and procedures, and an audit of some of the raw data used to generate results. This data may be located in research and development test logs. The authenticity and accuracy of data used in the development of a test method should be reviewed. Use the Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993, for inspectional criteria when covering laboratory operations.

4. Components

The supplier and source of the active drug substance used in the manufacturing of the biobatch and/or clinical batch should be identified.

When a manufacturer changes suppliers of drug substance from that used for the manufacture of the bio-batch or clinical batches, then the application should include data demonstrating that the dosage forms produced from the drug substances from the two different suppliers are equivalent in terms of conformance with established specifications, including those stated in the application. The data used to determine the adequacy of the physical specifications established for the

subsequent suppliers(s) of the drug substance should be audited for acceptability.

5. Building and Facilities

The addition of any new drug to a production environment must be carefully evaluated as to its impact on other products already under production and changes that will be necessary to the building and facility. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their impact on the overall compliance with GMP requirements. For example, new products, such as cephalosporins, would require that the firm demonstrate through appropriate separation and controls that cross-contamination can not occur with regard to other products being made in the same facility. Also, facilities that may already be operating at full capacity may not have adequate space for additional products.

6. Equipment

New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

7. Packaging and Labeling Controls

If warranted, packaging and labeling control procedures are to be evaluated. Poor label control and accountability for other products may have an adverse impact on the firm's ability to assure that the new drug will always be properly labeled.

Review the label and packaging controls, taking into account past label mixups and recalls.

C. Inspection Scheduling

The scheduling of inspections is left to the discretion of the District within any assigned time frames. This includes scheduling of inspections for which the district has received specific headquarters assignments. Every reasonable effort should be made, however, to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays are not supportive of the Agency's responsibilities to provide timely review of NDAs and ANDAs. Where no CDER assignment has issued, Districts are urged to coordinate with CDER reviewing offices when planning inspections to promote efficiency in the Agency's operations.

Such scheduling applies to biobatch facilities (if the biobatch is not required to be manufactured in production facilities) and production facilities, both of which must be covered with respect to conformance with CGMPs.

Districts may contact manufacturers to determine the readiness of facilities for inspections. In some cases facilities or the development of manufacturing processes

may not have been completed. In addition, there may have been changes in the status of an application, e.g., major application deficiencies or the deletion of an ancillary facility, that will affect the need for an inspection.

D. New Facility Reviews

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial. Field Management Directive No. 135 "Pre-Operational Reviews of Manufacturing Facilities," provides guidance in this area. Meetings or pre-operational inspections may be scheduled when such activities will contribute to the overall efficiency and effectiveness of the CGMP evaluation process.

E. Surveillance

Districts should be alert to the use of unapproved facilities or unapproved drug substance manufacturers during these inspections. If unapproved facilities are in use, they should be reported immediately to HFD-320. Inspections of these facilities are not required unless an assignment has been received from headquarters.

F. Application Audit

An audit of the drug application is essential to determine that commitments by the firm in the application are reflected in actual practice. An examination of application information is also important in preparing for inspections of firms or processes with which the investigator is unfamiliar.

A third (field) copy of pertinent application information is now required at the time of application filing for use in making audits. The applicant is required to submit the third copy directly to the applicant's home FDA district office (Foreign firms are required to submit the third copy to headquarters). The field copy of the application includes a copy of the manufacturing and controls section of the application, and information relating to batches used to conduct any bioequivalence, bioavailability and stability studies. Because trade secret or other confidential information is included in these copies, it is essential that the information be carefully protected to prevent its release to the public.

G. Sample Collection

This compliance program covers the collection of samples of the biobatches for forensic analysis. Such samples of biobatches will be collected at both the applicant and the biotest facility in association with each drug application where an in-vivo or in-vitro study has been submitted to FDA to demonstrate bioequivalence. In addition, the program requires the collection of two samples of the innovator product to which the ANDA biobatch is compared. To rule out substitution or other manipulations, one of the

samples must be collected at the biotest facility and the other from the innovator.

The above samples must always be collected even where adverse inspectional findings result in district recommendations to withhold application approvals. Instructions for collection of forensic samples at the applicant, the innovator, and biotest facilities are included in the subsections under the "Forensic Samples" section which follows.

The program also covers the collection of method validation samples for NDA products to confirm that applicants' proposed analytical methods are suitable for regulatory purposes. Similar coverage extends to ANDA and AADA products where non-compendial methods are proposed. The headquarters review chemist will issue an assignment for collection of methods validation samples for NDAs and ANDAs, and the Office of Compliance will inform the district to collect such samples for AADAs. (See instructions under "Method Validation Samples", below).

For ANDA and AADA products for which compendial test methods are proposed, samples will be collected for method verification purposes to ensure that the product as compounded can be assayed satisfactorily with the compendial method. Such analytical verification is not intended to "validate" the compendial (USP) method. Specific assignments will not issue from headquarters for collection of AADA and ANDA methods verification samples although the Office of Compliance will inform the district of the need to collect such samples (See instructions under "Method Validation Samples", below).

When possible, pre-approval inspections should be coordinated with the laboratory that is scheduled to perform the method validation so that they can participate in the inspection and in the collection of samples. Method validation samples are to be collected under this program on both foreign and domestic inspections.

In most cases, the home district is responsible for pre-approval sample collections. Such samples are collected at facilities in its area or through requests to other districts if samples are located elsewhere. However, headquarters is responsible for arranging sample collections in foreign countries. Therefore, districts should notify ITOB, HFD-324, and the assigned laboratory that samples need to be collected at the foreign firm. Foreign inspection staff will collect such samples in association with pre-approval inspections which they conduct. In countries with which FDA has bilateral inspection agreements (Canada, Sweden and Switzerland), the health authorities in those countries will collect or coordinate with HFD-320 for collection of all such samples.

The chart included as ATTACHMENT A summarizes pre-approval sampling operations, and the following narrative provides more detailed information.

Sample Definitions

Validation Sample- This is a single sample consisting of the product collected from the biobatch that is to be method tested in accordance with NDA, AADA, ANDA or USP specifications. It must be collected by FDA, not prepared and packaged by the firm for pick-up, and not forwarded to FDA by the firm. In some cases this may be a split sample going to two laboratories. In NO case should it be intermixed with subs that are properly part of the forensic sample. Report such sample collections under PAC 46832 (NDAs) or 52832 (AADA/ANDAs).

Forensic Sample- This is a single sample collected from the manufacturer, and it includes a sample of the finished dosage form (biobatch), a sample of the biotest portion sent to the biotest lab, a sample of the innovator's sample sent to the biotest lab, samples of excipients, and supporting documentation. The biotest portion and the innovator's portion, collected at the applicant firm, are part of the forensic sample and not "biotest" or "innovator" samples. Report such sample collections under PAC 46832B (NDAs) or 52832B (AADA/ANDAs).

Biotest Sample- This is a single sample that is collected at the contract biotesting laboratory consisting of the biobatch and innovator's product. Report such sample collections under PAC 52832C (AADA/ANDAs only).

Innovator Sample- This is a single sample that is an authentic sample collected by FDA from the innovator firm. Report such sample collections under PAC 52832C.

General Sampling and C/R Preparation Instructions

To the extent possible, use only one sample number for the validation/verification sample and one sample number for the forensic sample. Such numbers also should be cross-referenced. Carefully follow the PAC reporting instructions under the sections which provide detailed sampling instructions below.

Collect bulk substances (active ingredients, standards, impurities, excipients) in opaque, non-reactive containers, such as amber glass bottles, but not in Whirl-pak or other types of plastic bags. Also, Material Safety Data Sheets are required by OSHA under the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200) for all hazardous chemicals, and should be obtained for any new or unusual chemical compounds that are collected. In their absence, ask the firm to provide any safety or handling information that would be important to laboratory handling of these materials, and include such information under "Remarks" on the C/R.

Determine whether all equipment and supplies that are required for the tests are commercially available. If not, loan arrangements may have to be made. The analyst member of the inspection team may assist in making this

determination.

Include both the documentation and the sample material under seal in a single sample package. Avoid, where possible, using more than one collection report for each assignment, i.e., each forensic sample, each validation sample, each biotest facility sample, etc. Attach the FDA-525, containing the original collection report (or a good copy), to the outside of the sample package.

METHOD VALIDATION SAMPLES

1. NDA - These samples will be collected upon receipt by the home district of the Method Validation forms FDA 2871 and 2871A (and MV package). These forms are issued by the reviewing chemist when satisfied that adequate analytical information has been submitted by the applicant. They include information about the items and quantities to be collected and request the assignment of field testing laboratories and CDER validating laboratories. The laboratories will be identified in the assignment, and two validation samples normally are collected for NDAs.

   Laboratory policies and procedures for validating analytical methods, submitted to CDER with NDA's, is available in Staff Manual Guide 4831.3- Validation of NDA Analytical Methods.

2. ANDA - Samples for applications specifying non-compendial methods will be collected as for NDA's above. Where methods are compendial (USP), samples for methods verification, as discussed below, will not be specifically requested by the Office of Generic Drugs. These samples are collected on the initiative of the home district in association with the assigned pre-approval inspections (or the request for evaluation if a pre-approval inspection is not assigned).

3. AADA - Samples will be collected after the receipt of a request from the Office of Compliance. As part of the request for inspection, the Office of Generic Drugs will indicate in the "comments" section of the Establishment Evaluation Request (EER) that samples are to be picked up for methods validation or methods verification. The Office of Compliance will then inform the appropriate District. All methods (compendial and non-compendial) will be handled in this manner.

Where samples are located at a site outside the district, the home district will request their collection by the appropriate district. Samples should be submitted to the appropriate laboratory as indicated in Part IV (NDA's and ANDA's) or to the Division of Research and Testing (AADA's) unless otherwise assigned. Consult with the validating laboratory on appropriate sample sizes for dosage forms not listed below. The minimum sample size consists of enough material to conduct all required tests at least three times. Do not overlook microbiological testing when it is part of the application. The following are the requested sample sizes to be collected for each specific dosage form:

Sample Sizes:

Tablets and Capsules - 300 units
Injections, Single-dose - 100 units
Injections, Multi-dose - 10 units
0ral Liquids - 36 ounces
Oral Powders for reconstitution - 10 units
Metered-dose Inhalation Aerosols - 40 canisters
Inhalation Solutions and Powders - 40 vials
Transdermals - 50 patches
Suppositories - 50 suppositories
LVP's - 20 units (60 additional, if sterility testing is to be performed)
Topical, Ophthalmic and Otic Products - 40 units (60 additional, if sterility testing is to be performed)
Drug Substance - 10 x 300 mg.

Collect any non-compendial reference standards, including impurity and related compound standards, that are needed to test the samples. A non-compendial reference standard is one that is not available from USP.

Methods validation will be conducted where non-compendial analytical methods are included in the application. Methods verification may be conducted where the methods are compendial (USP). The latter will confirm whether the product as compounded can be analyzed satisfactorily with the USP method and is not intended to "validate" the USP analytical method.

Samples are to be collected for methods validation or verification for each application even if there is no requirement to establish bioequivalence with the innovator/reference product through in vivo or in-vitro studies, (e.g., oral solutions, injections). Where biostudies are required and have been submitted to the application, method validation/verification samples should represent the same batches used in such studies. Ideally, samples collected for method validation or method verification should be within expiration date. If the biobatch is beyond expiration date, an attempt should be made to collect a more recent pre-approval batch within expiration, if available. If unavailable, the out-of-expiration bio-batch would be acceptable for such studies.

Each sample collected for method validation or verification under this program should be flagged: "**Method Validation/Verification NDA/ANDA/AADA _____(application number of the product sampled).** Use PAC 46832 for NDA or PAC 52832 for AADA/ANDA sample reporting.

FORENSIC SAMPLES

1. NDA - Samples of the clinical production batch should be collected during pre-approval inspections. The following are the requested sample sizes to be collected for each specific dosage form:

   Sample Sizes:

Finished Dosage Form - 50 units†
Inactive Ingredients - 40 grams
Capsule Shells - 100 units
Colors and Dyes - 400 mg
Active Ingredients - 20 grams††
Impurity and related compounds - 50 mg††

†These samples should be from the batch(es) used to establish the bioavailability of the product. More than one batch should be sampled if the formulation/process for the batch used in pivotal clinical safety and efficacy studies is revised and the revised product is the subject of additional biostudies.

††If the sample size is inappropriate, check with the designated laboratory for instructions.

The firm may no longer have the inactives used to make the biobatch. If they are not available, collect other samples of the same inactives and indicate this on the collection report.

In addition, collect:

- a copy of the preapproval batch record;
- certificates of analysis (if applicable) received by the firm from suppliers for the specific batches of each active and inactive ingredient collected; and
- reports prepared by the firm of any tests performed by them on the batches of active ingredients collected. These reports should include methods,spectra, chromatograms and other charts.

All of the above should be collected under a single sample number whenever possible.

These samples and records should be forwarded to either the Philadelphia District Laboratory (for applicants in MA and SE Regions) or the Northeast Regional Laboratory (for applicants in all other regions) according to the location of the applicant.

2. ANDA - These samples should be collected during the pre-approval inspection when method validation or verification samples are collected. Collect the same lot number of the innovator and applicant product used in the biotesting as well as the same lot number of the ingredients used in the biobatch, if available. To rule out substitution or other manipulations, the innovator product must be collected from the innovator (and biotest facility) and <u>not</u> from the applicant. When the same lot number is no longer available at the innovator, collect a sample of the batch nearest in production time to the batch submitted to the biotest laboratory.

Applicant Samples

Sample Sizes:

Finished Dosage Form/Innovator - 20 units[†]
Finished Dosage Form/Applicant - 20 units[††]
Inactive Ingredients - 40 grams
Capsule Shells - 100 units
Colors and Dyes - 400 mg[†††]
Actives - 20 grams[†††]

[†]Obtain the lot number of the innovator product, and collect no less than six dosage units at the innovator firm. If the innovator is located in another district, use the memo format included as Attachment D to request such sample collections. Also submit a signed copy of the batch record showing the batch formulation and date of production.

[††]This sample should be collected from the retention sample of the applicant's product that was submitted to the bioequivalency testing laboratory.

[†††]If the sample size is inappropriate, check with the designated laboratory for instructions.

If special equipment or supplies were collected with the method validation samples, list this on the forensic collection report and indicate which laboratory received method validation sample.

In addition, collect:

- a copy of the preapproval batch record;
- a complete copy of approved testing method if other than USP(if USP, identify the edition and supplement, if applicable, for the test method used by the firm, e.g., USP XXII, First Supplement);
- certificates of analysis received by the firm from suppliers for the specific batches of each active and inactive ingredients collected;
- reports prepared by the firm of any tests performed by them on the batches of active and inactive ingredients collected. These reports should include methods, spectra, chromatograms, and other charts.
- analytical reports of the applicant's analysis of the lots of their product and the corresponding innovator product submitted to the private laboratory for bioequivalency testing; and
- a copy of reports received by the applicant from all bioequivalence laboratories for all in-vitro tests performed on the product covered by the ANDA. Ensure that the name and address of the biotest lab is included.

All of the above should be collected under a single sample number whenever possible.

In some cases, particularly for NDA products, clinical/biobatches may be beyond expiration date at the time of sampling. This is associated with the sometimes lengthy development and application approval times and does not preclude sampling for forensic purposes.

These samples and records should be forwarded to either the Philadelphia District Laboratory (for applicants in MA and SE Regions) or the Northeast Regional Laboratory (for applicants in other regions).

Each sample collected for forensic analysis under this program should be flagged: "**Applicant Forensic-NDA/ANDA/AADA_____"(application number of the product sampled).** Use PAC 46832B (NDAs) or PAC 52832B (ANDAs/AADAs).

Note: The innovator product, collected at the innovator firm, should be reported under PAC 52832C.

Biotest Facility Samples

This program directs the collection, at the biotest facility, of innovator and applicant products used by the biotest facility in determining bioequivalence. These samples will be tested and compared to the biobatch and innovator batches collected as directed above under "Applicant Samples" to rule out product substitution or other manipulations. The home district will collect such samples at biotest facilities within its own area. When the biotest facility is located outside the district, sampling assignments will be sent to the appropriate district (See Attachment E for the memo to use to assign such sample collections).

Samples at biotest facilities will be collected for each application when in-vivo or in-vitro bioequivalence studies have been conducted. Although such samples should be collected promptly, they need not be collected individually in association with each pre-approval inspection or evaluation. Districts may "batch" such sample collections or combine sampling with other inspectional coverage of biotest facilities as long as the period for such batching does not exceed two months. However, use only one sample number for each ANDA.

These samples, including the complete C/R and all attachments, should be forwarded to either the Philadelphia District Laboratory (for applicants in MA and SE Regions) or the Northeast Regional Laboratory (for applicants in other regions). In Item 21 on the C/R, record the amount of reserve of the biobatch. Identify the biotest samples with the manufacturer's batch number, date of receipt by the biotest lab, and any identification number assigned by the biotest laboratory. Include a copy of the laboratory's summary report that references these numbers and presents comparison data. The samples should each consist of 20 dosage units, but no less than 6, of the innovator and applicant products.

Each biotest facility sample collected for forensic analysis under this program should be flagged: **"Biotest Forensic-ANDA _____" (application number of the product sampled).** Use PAC 52832C for reporting sampling of biobatch and innovator products at biotest facilities and also for sampling of innovator product at the innovator firm.

H. Regional/District Recommendations

In those cases where CDER does not specifically assign a pre-approval inspection, districts will be requested to concur in approval, or to report information that would warrant delay of approval, such as the following:

1. An inspection of the subject establishment is underway, covering processes applicable to the product in question;

2. New information exists, such as an inspection, significant complaint or recall involving a health hazard, which casts doubt on the firm's ability to manufacture the product in question in compliance with GMP and NDA/ANDA requirements; or

3. Notwithstanding a lack of recent violations, the District believes that a special pre-approval inspection should be conducted to assure that the firm can manufacture products in compliance with GMP and NDA/ANDA requirements and to assure that commitments listed in the application have been met.

Districts will reply to CDER's notifications within 10 calendar days (with an information copy to MPQAS) with sufficient information to document the basis for delaying or withholding approval, if delay or withholding is recommended. A reply is required for each separate notification, and replies are expected to reflect concurrence by the District Director.

A CI/Potential OAI notification should be submitted to MPQAS, HFC-240, whenever an ongoing inspection finds CGMP deficiencies that pertain to marketed product.

In all of the cases, method validation, verification, and forensic samples should always be collected. The 10-day response should include a listing of all pre-approval samples collected, or if not collected, reasons for such non-collection. A copy of each response should be sent to both HFD-322 and the assigned analyzing laboratories. This sample collection is important since the testing of the NDA/ANDA product may further support the district's recommendation to delay or withhold application approval.

PART IV - ANALYTICAL

Two major types of analyses are conducted under this program. One involves testing samples of the biobatch/clinical batch for forensic purposes, including fingerprinting. The other involves analysis of method validation/verification samples to ensure, for regulatory purposes, that products can be tested adequately with methods proposed in drug applications. See Part III, Section G, for further information.

All field laboratory pre-approval assay work will be conducted by the following designated laboratories:

HOME DISTRICT of APPLICANT	LAB
Atlanta, Nashville, Orlando	SRL
New Orleans	NOL
Boston, Buffalo	WEAC
New York	NRL
Baltimore	BLT
Cincinnati	CIN
Newark, Philadelphia	PHI
San Juan	SJN
Chicago, Minneapolis, Detroit	DET
Dallas (ANDAs only), Kansas City (ANDAs only)	DAL
Dallas (NDAs only), and Kansas City (NDAs only)	DEN
Denver	DEN
Los Angeles, San Francisco, Seattle	SEA
Foreign	NRL ††

††Unless Otherwise Assigned (Where the foreign firm has a related U.S. site, the servicing lab for the U.S. site may be assigned)

Headquarters laboratory work will be handled by the Division of Drug Analysis (HFH-300).

AADA laboratory evaluation work will be handled by the Division of Research and Testing (HFD-470).

Division of Drug Analysis (DDA) will be the designated laboratory for all pre-approval samples from bilateral inspection agreement countries (MOUs with Canada, Sweden, Switzerland). This includes both forensic and methods validation/verification work involving dosage forms, drug substances and excipients. An exception to this policy will be for antibiotic drug products, where the methods validation/verification will be performed by the Division of Research and Testing (HFD-470). Forensic analysis of antibiotics will be performed by DDA.

A. Forensic Analysis

The Northeast Regional and Philadelphia District Laboratories will be responsible for most biobatch sample analyses under this program using methods such as FTIR to produce "fingerprints" for comparison with marketed

products. An exception to this policy includes samples from countries with which the agency has bilateral agreements; these samples will be analyzed by DDA.

For each product that consists of a solid dosage form (tablets or capsules), and each dosage level, under a given NDA or ANDA, the laboratory will initially prepare a Physical Description Report and make color photographs. The photographs should show top, side, and end views, bottom views if there are distinctive markings, and a picture of the broken surfaces of a tablet or the contents of a capsule. In order to document standard photographic conditions, include in all photographs the Pantone color guide that matches the outer surface of the tablet or capsule. These photographs will be filed for later use in comparisons with innovator product or with later batches of the applicant firm's product.

The results of forensic analyses will also be utilized for comparison with the post-approval samples collected under the Post-Approval Audit Compliance Program (CP 7346.843).

B. Methods Validation

Detailed instructions about assigning, conducting, and reporting methods validation work is contained in Staff Manual Guide 4831.3. This guide should be consulted for details about proper procedures for validating NDA analytical methods. In general, the following procedures apply:

1. When an application is ready for analytical methods validation, the reviewing chemist within the appropriate Division of the Office of Drug Evaluation (NDAs) or the Office of Generic Drugs (ANDAs) will send an assignment to the home district office notifying them of the need to conduct the methods validation. Such assignments will include the validation package submitted by the applicant. Copies of the requests for validation will be sent to the ORA/ORO/Division of Field Science (HFC-140). The field investigator/chemist then will collect samples of the batches for assay and methods validation testing and verify that the methods used by the firm are the same as those filed in the application.

2. Upon receipt of the notification to conduct a methods validation, the district will promptly collect appropriate samples of the biobatch/clinical production batch for method validation, verify that the methods used by the firm are the same as those filed in the application, and forward samples to the appropriate assigned laboratories.

3. If the assigned field laboratory will be unable to complete the methods validation and other assays within 45 days, the laboratory should contact the Division of Field Science for assistance in assigning the work to another laboratory. The home district is responsible for collection of samples and for shipment of the samples to the testing laboratories.

4. Methods are to be run as described in the application. A 45 day period will normally be allowed for methods validation and the clock will start when the laboratories have received all the necessary samples, information, and equipment.

5. If a laboratory encounters problems in the methodology that require additional information from the applicant, the laboratory director will review and approve the need to contact the applicant for the information. The information will be requested in writing or confirmed in writing, if requested by telephone, and this written request will be included in the documentation submitted to the review chemist.

6. The laboratory will not advise the applicant of the final conclusion with respect to methods validation, but may tell them when a study is completed and submitted to headquarters.

7. While validation is in progress, validating laboratories are not to communicate with each other regarding test results or observations that may bias recommendations. However, purely technical or analytical problems may be discussed without revealing results. The review chemist and DFS are to be kept informed of all such communications. Any such communication should be documented by memo with copies provided to the review chemist and DFS.

8. When each laboratory has completed its portion of the methods validation, a final report should be compiled. Headquarters and field laboratory reports will be forwarded directly to the review chemist by the Laboratory Director with a copy to the appropriate District Director.

9. Each validation report will contain the following information:

   (a) Identification of the application and test samples received and description of the product tested including confirmation that it complies with the product described in the application.

   Use Attachment C to describe the product undergoing testing. Submit the completed Attachment C form with the worksheets to the review chemist. Send a copy of the Attachment C, collection report, and a copy of the Review Chemist's request memo to the laboratory who is performing the forensic analysis.

   (b) Original worksheets with calculations, results, comments by the analyst(s), associated spectra, chromatograms, etc. that include results of all tests performed and comparison of results obtained with the applicant's data and with the applicable specifications.

   (c) An evaluation of each test provided by the firm and performed by the laboratory, accompanied by the

original signed form FDA-2871.

(d) A recommendation as to whether the methods are acceptable, acceptable after specified changes are made, or not acceptable.

Note: If the product is found to be compounded in such a way that it cannot accurately be analyzed by applicable USP methods, the product is not in compliance with the FD&C Act.

10. The Office of Generic Drugs or the Office of New Drug Evaluation is responsible for all correspondence with the applicant including approval/disapproval of methods. The review chemist will forward a copy of the letter of approval accompanied by any approved NDA or ANDA method modifications to the laboratories that conducted the methods validation. Copies of all disapproval letters, subsequently approved changes, and similar correspondence with the firm will also be sent to the laboratories.

11. The laboratory responsible for the evaluation of methods in a given firm's NDA or ANDA application is required to maintain an orderly sample and data storage system that completely documents the materials received, as well as reserve samples, related to the application evaluation and the pre-approval inspection of the firm. This file will be up-dated with CDER approved changes after the initial approval. All related written material and samples will be available to CDER and the home district on short notice.

    The reserve samples, associated documentation and copies of the FDA laboratory reports will be stored in an orderly and retrievable system for a minimum of five years.

PART V – FOLLOW-UP: REGULATORY/ADMINISTRATIVE STRATEGY

1. GENERAL

The plant should be in substantial compliance with GMP regulations and should have the necessary facilities and equipment in place to manufacture the specific product in the pending application. District Directors should recommend withholding approval until these conditions are met.

The district should recommend withholding approval when there are significant deviations from GMP regulations or other application commitments that may adversely impact on the products(s) covered by the pending applications. Some significant problems include, but are not limited to:

- Application misrepresents data or conditions relating to pre-approval batches
- There are other inconsistencies and/or discrepancies raising significant questions about the validity of records
- Pre-approval batches are not made in accordance with GMPs
- There is a failure to report adverse findings or test data without adequate justification

Districts are encouraged to discuss GMP and other problems having a direct bearing on the district's recommendation for NDA/ANDA approval and to obtain the firm's response to the discussion following preparation and issuance of the FDA-483.

If applications are withheld because of significant CGMP non-compliance, and the GMP deficiencies also apply to commercially-marketed products, then action must be taken to assure that the deficiencies are corrected.

Refer to the Regulatory Procedures Manual for consideration of actions that may be indicated.

The district director is expected to send a letter advising the plant officials (or the sponsor when appropriate) that the district has recommended withholding approval of the application and shall state the reasons for this recommendation. This letter must be issued quickly and should be issued at the same time the district informs the Center of its recommendation to withhold approval. This letter shall not be titled "Warning Letter" unless the documented conditions affect an approved and marketed product(s) and meets the requirements for a Warning Letter listed in the RPM.

No application should be recommended for approval if the applicant is found in a state of non-compliance with the CGMP regulations that may adversely impact on the

product(s) covered by the pending applications until satisfactory correction is made. However, insignificant deviations should not result in a recommendation to withhold approval of applications.

2. PROCESS VALIDATION

Districts must not recommend withholding approval of applications based on lack of complete full scale, multiple batch process validation.

Although the agency does not require the manufacturer to fully validate the manufacturing process and control procedures of the commercial batch production prior to approval, the Center reviewing offices will require that certain data be filed to demonstrate that a plant's sterilization and aseptic fill process has been qualified. These filing issues are under the control of the Center's reviewing divisions. Manufacturers' questions about these filings should be directed to the reviewing division and should not be discussed by the inspection team.

Since complete process validation is not required prior to approval, the field is not required to audit complete process validation for sterile and non sterile processes until the application has been approved. However, if the plant has already validated the process prior to the pre-approval inspection, the validation should be evaluated during the pre-approval inspection. The inspection team should list deficiencies in the validation process on the FDA-483 and advise the plant official that complete validation must be completed prior to shipment.

Do not recommend withholding approval based solely on absent/incomplete process validation, unless available data are of questionable validity.

Sponsors must be able to justify filed specifications with scientific data. In other words, the sponsor should have conducted sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data form the basis for the review and evaluation of the application and these specifications form the basis of the validation protocol which may be developed following the approval of the application. The final step in the product development process is validation that the process will perform consistently. Companies are expected to validate the process using the specifications listed in the filing.

Process validation requirements for the manufacture of bulk pharmaceutical chemicals (BPCs) differ somewhat from those involving dosage forms. The Guide to Inspection of BPCs issued in 1991 states that BPC manufacturers are expected to adequately determine and document that significant manufacturing processes perform consistently. The type of BPC, the range of specifications and other factors determine the extent of the process development and documentation required. The documentation system required for early process steps must provide a chain of documentation, and while it need not be as comprehensive as

in the later parts of the process, the manufacturer is required to identify and control the key steps in the process.

Many BPC manufacturers have recently initiated validation programs and we recognize that not all BPCs can be validated simultaneously. Therefore, we do not anticipate taking legal action where a firm has an adequate program in place, including reasonable milestones. Regulatory action should be recommended where there is a lack of validation and evidence of a significant number of failed batches.

District offices are responsible for the implementation and management of a program to assure that manufacturing processes and laboratory control procedures have been validated prior to the shipment of recently approved dosage form drugs. No assignments will issue from CDER. Districts may recommend seizure of a drug product shipped prior to substantial compliance with validation requirements.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

References

A. Code of Federal Regulations, Title 21

Part 210 and 211, Drugs: Current Good Manufacturing Practice
Part 310, New Drugs
Part 314, New Drug Applications
Part 429, Drugs Composed Wholly or Partly of Insulin
Part 431, Certification of Antibiotics

B. Code of Federal Regulations, Title 29

Part 1910, OSHA Hazard Communications Standards

C. CP 7356.002 - Drug Process Inspections
CP 7346.843 - Post Approval Audits
CP 7348.001 - In-vivo Bioequivalence Inspections

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

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

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

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

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

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

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

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

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

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

N. GWQAP Manual, Profile System, Chapter 15.

O. Regulatory Procedures Manual, Chapters 7 and 8.

P. Staff Manual Guide 4831.3, Validation of NDA Analytical Methods.

ATTACHMENTS

Attachment A - Pre-approval Samples
Attachment B - List of Narrow Therapeutic-Range Drugs
Attachment C - Characterization of Dosage Forms
Attachment D - Innovator Sample Request Form
Attachment E - Biotest Facility Request Form

CONTACTS

A. Center for Drug Evaluation and Research

Laboratories:

*Division of Pharmaceutical Analysis (HFD-920)
1114 Market St., Room 1002
St. Louis, MO 63101
Director: Lucinda Buhse (314)-539-2134
Deputy Director: Nick Westenberger (314)-539-3869*

New Drug Applications:

Contact Offices for NDAs (General):

*Application Receipt and Filing Questions:
Business Information Staff (HFD-141)
Anna M. Myers (301)-594-1993*

*Application File Management Questions:
The Division of Records Management (HFD-143)
Mia Prather (301)-827-3949*

Questions about NDA content:
Refer to contacts in EES listed in Contact folder of the

Application in question.

Abbreviated New Drug Applications:

Office of Generic Drugs (HFD-600)
*Peter Rickman (301)-827-0507
Tim Ames (alternate) (301)-827-5844*

Compliance Issues:

Office of Compliance
Division of Manufacturing and Product Quality
Investigations and Preapproval Compliance Branch, (HFD-322)
*Edwin Rivera-Martinez (301)-827-9012
Concepcion Cruz (301)-827-9013*

*Foreign Inspection Team
John Dietrick (301)-827-9021*

Bioequivalence Study Issues:

Office Medical Policy
Division of Scientific Investigations (HFD-48)
C.T. Viswanathan, Ph.D. (301)-594-0163

*B. Therapeutic Drug Products recently transferred from CBER to CDER

For questions relative to the Therapeutic Facilities Review Branch, please see CPGM 7356.002M for contact information.*

C. ORA HEADQUARTERS

Division of Field Investigations/ORO

Domestic:

Operations Branch (HFC-130)
*Gerald Miller
Division of Field Investigations
(301)-827-5655*

Foreign:

International Operations Branch (HFC-130)
*Rebecca Hackett (301)-827-3777
Division of Field Investigations*

Division of Field Science/ORO (HFC-140)
Donald Lech (301)-827-4603

D. ORA FIELD (Program Coordinators)

See IOM for a listing of NDA/ANDA Preapproval Drug Managers, or contact DFI for a current listing as included in the ORA biannual telephone and address directory.

PART VII - CENTER RESPONSIBILITIES

A. The Division of Manufacturing and Product Quality will:

1. Monitor the compliance status of the drug industry.

2. Issue inspection assignments in accordance with CDER Policy.

3. Assure that Districts are notified in writing of applications under Center review involving establishments in their respective areas, when a pre-approval inspection is not specifically assigned.

4. Develop and communicate compliance evaluations to the appropriate reviewing division within the Center; application deviations and CGMP deficiencies will be cited with specificity.

5. Notify reviewing divisions of violations associated with inspections or sample analyses so that application approvals can be withheld as appropriate from these establishments.

B. The Offices of Drug Evaluation will:

1. Request compliance evaluations in accordance with CDER Policy.

2. Issue NDA method validation assignments. They will also communicate with laboratory personnel as necessary to complete the validation process.

3. Evaluate Method Validation reports from each laboratory and inform the applicant of their conclusions.

4. Provide copies of all approval, deficiency and nonapproval letters to appropriate field and headquarter offices.

5. Consult with District investigators and analysts on issues of mutual concern.

~~B.~~C. The Office of Generic Drugs will:

1. Request Compliance Evaluations in accordance with CDER policy.

2. Issue ANDA method validation assignments for non-USP methods. They will communicate with laboratory personnel, as necessary to complete the validation process.

3. Evaluate laboratory method validation/verification reports and inform the applicant of the approval/nonapproval of the method conclusions.

4. Provide copies of all approval, deficiency and

nonapproval letters to appropriate field offices.

5. Consult with District investigators and analysts on issues of mutual concern.

D. The Division of Drug Analysis - St. Louis

1. Analyze samples assigned under this program.

2. Provide the Division of Manufacturing and Product Quality with analytical results for forensic samples analyzed where fraud or other discrepancies are discovered.

3. Provide the appropriate OGD and ODE review units with analytical results associated with methods validation/verification work.

4. Provide consultative services to headquarters and field offices for on-going investigations.

Pre-approval Samples

[Not available electronically]

List of Narrow-Therapeutic Range Drugs

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[Deleted due to changes in Part II which remove this category as one of the reasons for assigning a PAI inspection.]

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Characterization of Dosage Forms

[Not available electronically]

Innovator Sample Request Form

[Not available electronically]

Biotest Facility Request Form

[Not available electronically]