CHAPTER 68 - APPROVAL EVALUATION OF ANIMAL DRUGS

Pre-Approval Inspections: New Animal Drug Applications (NADA) Abbreviated New Animal Drug Applications (ANADA) Investigational New Animal Drug Applications (INADA)	**IMPLEMENTATION DATE** UPON RECEIPT
	COMPLETION DATE Continuing
DATA REPORTING	

PRODUCT CODES	PROGRAM/ASSIGNMENT CODES
Industry Codes 56, 67, 68	68001-Domestic and Foreign Pre-Approval Inspections, Sample Collections, and Analytical Analysis

FIELD REPORTING REQUIREMENTS

A. When a pre-approval inspection request is received by a District Office, the District Director or their designee must evaluate the request within 10 calendar days of the original request date. Within 10 days of the original request, the District Director must submit a written statement to the Center for Veterinary Medicine's (CVM's) New Animal Drug Evaluation (NADE) current Good Manufacturing Practice (cGMP) Pre-Approval Program Manager (HFV-142) indicating his/her evaluation of the inspection request. If the District Director determines that there is sufficient inspection history to recommend 'approval' without an inspection, the written response should provide both a justification why an inspection will not be conducted and he/she should provide in writing an Approval Recommendation indicating their concurrence "based on cGMPs" of the pending NADA/ANADA/INADA application. Investigational New Animal Drug Applications (INADA) in the context of this document refers to the Chemistry, Manufacturing, and Control (CMC) component. If the District Director concurs that the facility needs a current inspection, the written response statement should indicate a current "Pending" cGMP status. Thus, indicating to CVM to withhold approval of the respective application(s) pending a current pre-approval inspection by the District Office. If a "Pending" status is assigned to a Pre-approval inspection

request, the inspection should take place within the following 30 days of the date of the District's written status response. Upon completion of an inspection, the District Director should provide a written response to the pre-approval inspection request indicating acceptable cGMP status for the facilities listed in the NADA/ANADA/INADA or stating the reasons why the cGMPs are not currently acceptable. A copy of this final response should be sent to the NADE cGMP Pre-Approval Program Manager (HFV-142) and to DMPQA (HFC-240).

1. Forward all violative and non-violative Establishment Inspection Reports (EIR's) within 30 days of completion of the inspection to the NADE cGMP Pre-Approval Program Manager (HFV-142), with the District's recommendation regarding the pending NADA/ANADA/INADA application(s). Include full documentation of all cGMP regulation violations. Districts must not wait for final completion of violative and non-violative inspection reports and final classification before notifying the Center of the District's recommendation.

2. A reference number (GMP#___) is assigned to all CVM pre-approval inspection requests. This reference number should be included in all correspondences regarding the respective inspection request.

B. Districts are required to promptly update the firm profile in accordance with Chapter 15, GWQAP Manual. As soon as the District becomes aware of any significant adverse inspectional, analytical, environmental, or other information which could affect the Agency's product approval decisions with respect to a firm, the District should immediately notify the NADE cGMP Pre-Approval Program Manager (HFV-142), DMPQA (HFC-240), and CVM's Division of Compliance (HFV-230).

C. Copies of worksheets pertinent to any violative samples analyzed under this program should be sent to the NADE cGMP Pre-Approval Program Manager (HFV-142).

D. Forward copies of all laboratory reports conducted under the program on NADA/ANADA method evaluations to the NADE cGMP Pre-Approval Program Manager (HFV-142).

E. Forward copies of all laboratory reports of tissue residue method trials conducted under the program to CVM's Division of Human Food Safety, HFV-150.

ORA HEADQUARTERS REPORTING REQUIREMENTS

In response to pre-approval inspection requests submitted by the NADE cGMP Pre-Approval Program Manager (HFV-142) for evaluation of a foreign establishment, ORA Division of Emergency and Investigational Operations (HFC-130) will respond to the inspection request within 10 calendar days and will submit a written statement to HFV-142 indicating an estimated inspection date. In some cases, CVM may be unaware of a recent foreign inspection that is currently being initiated or evaluated in another Center. If this is the case, ORA should inform CVM within 10 calendar days, so that CVM can evaluate the additional information prior to ORA initiating the inspection. The response from the Director of the ORA Division of Emergency and Investigational Operations (or his/her designee) may be based on results of previous inspections or other information that should be considered by CVM.

When an assessment results in an inspection, every effort should be made to have the inspection completed within 90 calendar days of the initial assessment response. The Director should notify CVM when the inspection is scheduled and include the name, location, and telephone number of the investigator assigned to the inspection. In many cases, it is necessary for the reviewer to contact the investigator, or to provide additional material, prior to the inspection.

Upon completion of an inspection the investigator should fax a copy of the FDA 483 to both ORA and CVM. Within 30 days after return to the U.S., the investigator should forward the original report with exhibits to the NADE cGMP Pre-Approval Program Manager (HFV-142), with a copy to ORA (HFC-130). Recommendations to withhold approval of an application must include specific justification for CVM consideration. CVM will not withhold approval where there is insufficient justification presented.

REGULATORY ACTIONS

Recommendations for regulatory actions shall also be forwarded to CVM's Division of Compliance, HFV-230.

PART I - BACKGROUND

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

This program is designed to ensure that attention is focused on all aspects of the manufacturing and control procedures listed in the application[1], on the product formulations proposed in the applications, and on any unapproved changes in formulating and manufacturing procedures. Such coverage is necessary to assure that the processes and procedures identified in the application have been followed for the products used in the clinical studies to generate the data in support of the application, and to assure that any modifications required for full-scale production have been validated.

During the pre-marketing review of proposed new animal drug products, it is necessary to determine whether or not a foreign or domestic establishment designated as a manufacturer, packager, labeler, or quality control facility can operate in conformity with current Good Manufacturing Practice (cGMP) regulations, and in accordance with NADA/ANADA/INADA or related Veterinary Master File (VMF) or Drug Master File (DMF) commitments.

Compliance determinations will be made through establishment inspections, product sampling and analysis, and appropriate document review.

This compliance program attempts to provide requirements that are compatible with those found in the Center for Drug Evaluation and Research (CDER) compliance program for new drug evaluation under CP 7346.832. Any differences in the animal drug program are related to the uniqueness of the types of products.

Because of the activities required under the investigational new animal drug (INAD) portion of a proposed new animal drug product, various references are made to the Agency's Bioresearch Monitoring Program and its relationship to this pre-approval program. Also satisfactory cGMPs are necessary prior to issuing a "Component Complete Letter" for the Chemistry, Manufacturing, and Control (CMC) Section of an INADA.

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[1] "application" as used in this program means NADA, ANADA, or INADA.

This program was previously revised to expand the number and scope of pre-approval inspections, thereby improving surveillance and enforcement activities related to pending applications. Inspections are now conducted not only with reference to cGMPs but also with reference to the specific requirements/commitments of the appropriate application. This current revision corrects numerous inconsistencies in the program, deletes obsolete areas, and provides additional instructions and clarifications for the current areas of emphasis. The program provides for bio-batch sampling and analysis, including samples collected from bioequivalence testing laboratories. Analysis may involve direct comparison of bio-batches and marketed products. The program also provides for an increased sampling plan for "forensic" samples.

Activities conducted under this compliance program are applicable to animal drug pharmaceutical dosage forms, Type A Medicated Articles, and the new drug substances that are listed in original NADAs, ANADAs, and INADAs, and supplements to the respective applications. Information in related VMFs and DMFs are also considered under this program.

Evaluation of analytical methods proposed in an application for drug residues in tissues from food-producing animals and Type C medicated feeds are also conducted under this program.

PART II - IMPLEMENTATION

A. OBJECTIVE

This program is applicable to submissions of original new animal drug products under a NADA, submissions for generic new animal drug products under an ANADA, or component CMC submissions for investigational new animal drug applications under an INADA. The program is also applicable to new drug substances, finished pharmaceutical dosage forms, and Type A Medicated Articles and related information provided in master files.

The objectives of this compliance program are:

1. to assure that establishments listed in a NADA, ANADA, INADA, or VMF/DMF have the requisite capabilities to fulfill the product specific commitments to manufacture, process, control, package and label new drug substances and new animal drug products (pharmaceutical dosage forms and Type A Medicated Articles);

2. to ensure adequacy of analytical methods used in manufacturing control and finished product specifications;

3. as directed by headquarters, to collect samples or assess data pertinent to FDA's NADA/INADA method trial review and evaluation process for analytical methods for tissue residues of animal drugs and medicated Type C medicated feeds.

This program provides for coverage of both domestic (U.S.) and foreign plant facilities. Such coverage is intended to be consistent to the extent possible.

Activities under this program are also applicable to changes proposed in supplemental submissions to the various applications.

B. PROGRAM MANAGEMENT INSTRUCTIONS

Before any NADA or ANADA is approved by the Center for Veterinary Medicine (CVM), or before a CMC "Component Complete Letter" is issued for an INADA, a determination will be made whether all establishments that will participate in the manufacture,

packaging, labeling or testing of the finished drug dosage form, new drug substance, or Type A Medicated Article are in compliance with the appropriate current Good Manufacturing Practice (cGMP) regulations and application commitments.

To start this process, reviewers in the Division of Manufacturing Technologies (HFV-140) will request an evaluation of the establishment to determine whether it can operate in conformity with cGMP regulations. The NADE cGMP Pre-Approval Program Manager (HFV-142) will evaluate the cGMP status of the requested establishment within 10 working days of the initial request. The Pre-Approval Program Manager will also indicate if there are any other compliance issues that may directly affect the current cGMP status of the facility. If no establishment inspection is necessary at this time, the Pre-Approval Program Manager will return the cGMP status request to the reviewer with a written response that the cGMP status is currently acceptable for the profile class indicated on the original inspection request.

If the NADE cGMP Pre-Approval Program Manager (HFV-142) determines that it is necessary for the facility to be inspected, the evaluation that is returned to the reviewer will indicate "Inspection Request Issued" and a reference number (GMP#___) is assigned to the inspection request. A pre-approval inspection request will be issued, if the current cGMP status is not acceptable, if the assignment requires a "10 day assessment", or if CVM does not have adequate documentation to determine the status within the information in NADE files. CVM will request inspections in accordance with the pre-established criteria that will be outlined in this compliance program. Optional pre-approval inspections may be performed where circumstances warrant. Every effort should be made to assure that the inspections are completed and reported within the timeframes required by this program so that an Agency decision can be made on the approvability of the application.

Before any NADA or ANADA is approved or any CMC section is found to be complete in an INADA by CVM, it must be determined whether or not:

1. any establishment that will participate in the manufacture, packaging, labeling or testing of the finished dosage form (pharmaceutical or Type A Medicated Article) or a new drug substance is in compliance with the appropriate cGMP regulations;

2. each application is accompanied by appropriate validated methods for testing the specific manufacturer's finished product and raw materials;

3. samples collected are authentic representatives of production lots;

4. the information filed in the application, accurately represents and completely supports the manufacturing and control processes that have been proposed;

5. validated methods should be available for the control of tissue residues from animal drugs and medicated feeds.

Assignments: A NADA/ANADA/INADA cannot receive an acceptable cGMP recommendation from the NADE cGMP Pre-Approval Program Manager (HFV-142) unless there has been a recent in-compliance cGMP inspection of the establishment for the specific profile class represented in the application. The NADE cGMP Pre-Approval Program Manager (HFV-142) will issue inspection assignments for both domestic and foreign facilities, requesting an assessment of the capability of a proposed establishment to operate in compliance with cGMP regulations. An audit of the NADA, ANADA, or INADA and of the cGMPs as applied to the specific drug product must be performed when an inspection assignment is received, unless sufficient, appropriate justification is provided for not doing the inspection at this time.

To make the most effective use of agency resources, an inspection will not be assigned until the applicant confirms to CVM that it is ready to be inspected (e.g., major pieces of equipment are all in place, firm has qualified and validated the equipment). The District and Foreign Program Managers will recommend action on each proposed specific drug product or proposed change, and not simply on the basis of the firm's overall compliance status.

Supplements: Supplements to approved original NADA and ANADA applications providing for changes in facilities or other related application commitments will also undergo a review to determine the cGMP compliance and conformance with commitments made in the respective supplement(s). The same procedures developed for the pre-approval process of an original application will be followed.

Investigational New Animal Drug: The Division of Manufacturing Technologies, HFV-140, reviews the Chemistry, Manufacturing, and Controls (CMC) section of the investigational new animal drug (INAD) submission. Before a component complete letter can be issued, the reviewer must receive an acceptable cGMP status from CVM's NADE cGMP Pre-Approval Program Manager (HFV-142) for all facilities, personnel, equipment, processes, controls and testing facilities listed in the application. Activities related to the inspection of facilities manufacturing a product under an INAD will be conducted only on assignment from CVM's NADE cGMP Pre-Approval Program Manager (HFV-142). Research facilities which are not otherwise required to register under Sec. 510 of the Act,

but are involved in the manufacture of investigational drug products will be inspected only upon assignment from the NADE cGMP Pre-Approval Program Manager (HFV-142).

Ten Day Assessment: In addition to the routine pre-approval inspection requests as outlined above, CVM will request a written assessment and/or a pre-approval inspection for all pending applications which request approval of a finished product Contract Manufacturer, a finished product Control Testing Laboratory, or if the application contains a new molecular entity active pharmaceutical (regardless of current profile status or date of previous inspection). This is based, in part, on the understanding that these types of facilities may have limited knowledge and experience in product specific manufacturing or testing.

For domestic facilities, the District Director (or his/her designee) should respond within 10 days to these requests with a recommendation relating to such approval. **The response should be either recommend "Approval", recommend "Withhold" approval, or recommend "Pending" until a pre-approval inspection can be conducted.** When an assessment results in an inspection, the inspection should be completed within an additional 30 calendar days of the initial assessment response. The District Director (or his/her designee) response may be based on results of previous inspections or other information that should be considered by CVM before approval. Recommendations to withhold approval of an application must include specific justification for CVM consideration. CVM will not withhold approval where there is insufficient justification presented.

For foreign facilities, the NADE cGMP Pre-Approval Program Manager will review the previous EIR and assess the firm's ability to perform the activities in the pending applications. If CVM determines that the current inspection has expired or if CVM does not have the files to make this assessment, an assignment will be sent to the Director of the Division of Emergency and Investigational Operations (or his/her designee), who should respond within 10 days to these requests by submitting a written statement to HFV-142 indicating an estimated inspection date. In some cases, CVM may be unaware of a recent foreign inspection that is currently being initiated or evaluated in another Center. If this is the case, ORA should inform CVM within 10 calendar days, so that CVM can evaluate the additional information prior to ORA initiating the inspection.

Every effort should be made to have the inspection completed within 90 calendar days of the inspection request. The Director (or his/her designee) should notify CVM when the inspection is scheduled and include the name, location, and telephone number of the investigator assigned to the inspection. In many cases, it is necessary for the reviewer to contact the investigator, or to provide additional material, prior to the inspection.

Profile Samples: Profile samples should be collected during both foreign and domestic pre-approval inspections for veterinary products when the inspection assignment request indicates that such samples should be collected. These samples should be forwarded to the National Forensic Chemistry Center (FCC), Cincinnati District (HFR-MA500)

Additional Profile Samples: The FCC is also conducting tests to identify the characteristics of all foreign bulk pharmaceutical chemicals that are exported to the U.S. This pre-approval program serves as a mechanism to increase the coverage of FCC's profiling program. The intent of these tests is to enable the FDA to detect whether other parties have substituted bulk drugs from other manufacturers and declared them as having been made by the facility being inspected. The FDA is developing profiles of all products manufactured at foreign facilities that are exported to the U.S.; therefore, the investigator should request that the firm provide three 10-20 gram samples of each product that it manufactures for export to the U.S. The samples should be taken from lots produced at various times during the past year. Note that this is not necessary, if the foreign facility has submitted samples to this program within the last five years for all bulk pharmaceuticals that are currently exported to the U.S. If samples have been previously submitted under this program within the last five years, then the firm should only submit bulk pharmaceuticals that were not previously submitted or ones that have had significant changes in their manufacturing process.

When transferring samples, take the necessary precautions to protect the samples from the contamination of human hands, dust, etc. Small plastic or glass container or plastic bags would be appropriate as sample containers. Please include a Material Safety Data Sheet for each product.

To assist in establishing a profile of each product, a flowchart and a brief description of the manufacturing process should be provided to FCC. Also obtain any impurity test methods and impurity limits for the product(s). Per Agency requirements, this information will be kept completely confidential.

For additional information regarding profiling of foreign bulk pharmaceutical chemicals, please refer to CP 7356.002F or contact the FCC at (513) 679-2700.

Method Validation Samples: Method validation samples may be requested to be collected by CVM on a "for cause" basis. When a method validation has been requested by CVM in a pre-approval inspection assignment, the application will remain incomplete until CVM receives both the cGMP status and the method validation results. The pre-approval inspection assignment request will indicate when such a sample is requested by CVM. The

respective methods and specifications should also be obtained during the inspection. (If the investigator and firm agree, the samples, method, and specifications may be forwarded directly to the servicing lab by the firm). The servicing lab representative for the respective District should contact the reviewer listed on the pre-approval request form to obtain the approved method and specifications to compare to those obtained from the firm. CVM's Pre-Approval Inspection Manager should be updated as to the current status of the analysis and results. **Note:** Every effort should be made to have the analysis completed and reported to CVM within 30 calendar days following the inspection date.

Any other samples collected on a discretionary basis (by District management) and any analysis conducted are the responsibility of the District involved.

Due dates

Two due dates are now being included on all CVM Pre-Approval Inspection Requests that are sent to the District Offices.

> The first date is the time-frame within which the District should provide a written response (10 (ten) calendar days of the request) as to their plan of action regarding the request (i.e. recommend "Pending" the inspection is scheduled to start on... or recommend to "Approve" no inspection necessary as this time because...). If a Pending status is assigned to a Pre-approval inspection request, the Pre-approval Inspection should take place within 30 calendar days of the date of the District's written status response. If there are reasons that an inspection should not be performed and an application should not be approved at this time, a "Withhold" status is assigned to the Pre-approval inspection request. If a Withhold status is assigned to the pre-approval request without a pre-approval inspection, then sufficient justification should be provided in the written response.
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> The second due date on the inspection request is when the District Director should provide to CVM a written response to the pre-approval inspection request indicating their concurrence for acceptable cGMPs for facilities listed in the NADA/ANADA/INADA or a written response with sufficient justification why the facilities are not acceptable. This should be within 30 calendar days after the completion of an inspection.

PART III - INSPECTIONAL

A. PRE-APPROVAL INSPECTION

1. NADA/ANADA/INADA Inspections

a. Domestic Establishments

Inspections will be conducted on assignment from the NADE cGMP Pre-Approval Program Manager (HFV-142). To ensure that District offices are aware of manufacturing information involving NADAs\ANADAs\INADAs, CVM will provide (upon request) the District(s) with a copy of the pertinent sections of the application or master file under Center review involving establishments in their respective areas. Upon completion of the inspection, instructions will be provided as to whether the documentation needs to be returned to CVM or whether it should be shredded at the District level.

b. Foreign Establishments

Inspections will be conducted on assignment from the NADE Pre-Approval Program Manager (HFV-142). ORA, DEIO will select an investigator and make travel arrangements for the foreign inspection. Once the investigator is identified, ORA will notify CVM and include an estimated date of inspection. The investigator may contact the reviewer that is indicated on the inspection request to obtain copies of manufacturing information involving NADAs/ANADAs/INADAs or master file under Center review. If both the reviewer and the investigator feel that copies of pertinent manufacturing information would be valuable information to the investigator prior to the inspection, then CVM will provide the information to the investigator. Upon completion of the inspection, instructions will be provided as to whether the documentation needs to be returned to CVM or whether it should be shredded by the investigator at the District level.

c. Inspection Coverage

Inspections will cover facilities, personnel, equipment, processes, controls and testing to assure compliance with appropriate cGMP regulations that are

used for the products specified in the assignment. In addition, product specific commitments will be audited using documentation in the appropriate NADA, ANADA, INADA, VMF, or DMF.

2. Bioequivalence Testing Facility Inspection

Inspections of facilities conducting bioavailability/ bioequivalence studies will be conducted on a "for cause" basis as a follow-up to discrepancies discovered from FDA laboratory examination of bioretention samples and from the Districts' pre-approval inspectional coverage of the applicants' bio-batch[2] manufacture and testing which show discrepancies or suggest fraudulent activity.

Inspections of such facilities under this pre-approval program should generally follow reporting and inspectional instructions in the Bioresearch Program specified in the assignment. Resource expenditures will be charged to the pre-approval program assignment code 68001.

Before initiating a pre-approval inspection of a bioavailability/bioequivalence study or facility, the District should consult with the NADE cGMP Pre-Approval Program Manager (HFV-142) for instructions. These inspections are specialized and need careful direction to ensure that inspectional efforts are maximized.

B. INSPECTION APPROACH

In general, the approach for inspection of a facility listed in an application (NADA, ANADA, INADA) or master file should be the same.

The inspectional information presented in the Investigations Operations Manual (IOM) Chapter 540 should be followed. The basic concepts of inspection as presented in Compliance Program 7356.002 should also be referred to for guidance. Parenteral drug products should be evaluated per inspectional instructions under CP 7356.002A. Bulk pharmaceutical substances (new drug substances) should be evaluated under the inspectional guide in CP 7356.002F. Type A Medicated Articles should be evaluated under CP 7371.005.

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[2] "Generic product bio-batches" are ANADA batches that are compared to the originator/reference product to establish their equivalence. "NADA bio-batches" are NADA batches used in safety or clinical trials to establish the safety and effectiveness of the proposed product. Bio-batch, pilot batches, and clinical supplies are generally considered synonymous.

1. Inspection Team

Inspection teams, where necessary, should consist of investigators, analysts, engineers, application reviewers and/or computer experts. Headquarters reviewers and scientists should be used as required. The inspection team leader is responsible for the overall scheduling and coordination of the inspection, as well as the preparation of the inspection report.

2. General Approach

An in-depth evaluation should be conducted of the data, including research and development data, to assure that the manufacturer uses the proposed manufacturing processes and controls.

The inspection should include a review of the production and control data from batch(es) used for clinical and/or bioavailability studies, if applicable. A similar review should be conducted for batches used to conduct stability studies since there can be problems if such information utilized in pilot batches differs significantly from production batches. If possible, a comparison should then be made of production and control procedures submitted in the filing to those procedures used for the manufacture of actual production batches.

The investigator(s) should determine whether or not the applicant has scientific evidence that supports full-scale production procedures and controls and that these processes and controls provide assurance that the process will perform adequately. Because of the volume of validation data associated with manufacturing and control processes (including laboratory procedures), complete review at a headquarters level is neither practical nor possible. Manufacturing process validation data (other than for sterile facilities) is rarely submitted in applications.

General aspects of an inspection should provide the following:

a. An in-depth review of the manufacturing facilities and practices as requested.

b. An evaluation of the facility's capability to perform requested operations.

c. A determination of compliance with existing cGMPs applicable to the proposed NADA/ANADA/INADA product.

d. A report of any deviation from NADA/ANADA/INADA and accompanying master file commitments and applicable cGMP regulations.

3. Manufacturing Process

The manufacturing process may cover the procedures for the manufacture of new drug substances or the new animal drug products (pharmaceutical dosage forms or Type A Medicated Articles) submitted in the NADA, ANADA, INADA or in a related drug master file.

The batch record as submitted in the application should be reviewed as a basic part of the inspection to assure that the proposed production process is actually the process that was used for the manufacture of the drug substance or new animal drug product.

Generally, manufacturers prepare reports which outline the experiments and data generated to develop the manufacturing process and select and identify the source and purity of the drug substance. This report should support the manufacturing process. It is normally not filed with the application.

Because the preliminary products are manufactured during the investigation stage as pilot or clinical supply batches, an evaluation of the facilities and controls used for the manufacture of the bio-batch/clinical batch should be made. Although complete process validation may not be an issue for pilot or clinical batches, accurate documentation is essential so that the process can be defined and related to the batch(es) used for any significant study.

The investigators should refer to a document published by FDA providing guidance for compliance with cGMPs for the production of investigational drugs. The "Guideline on Preparation of Investigational New Drug Products", published September 1990 (by CDER) states that drugs produced for clinical trials must comply with the cGMP regulations. For example, the drug product must be produced in a qualified facility using qualified equipment and adequately documented processes.

In many cases, clinical production or trial runs of new animal drug products are conducted in facilities other than the ones used for full-scale production. These facilities may have greater or lesser controls than the full-scale production processes. It is essential to determine if there will be or has been any difficulty in transferring the technology from clinical production or trial runs to full-scale production.

Many manufacturers frequently scale-up from the batch size used for clinical and/or bioavailability studies. The report that the manufacturers generate that assures the equivalency of the two different size batches should be reviewed. Some of the smaller manufacturers may lack the in-house expertise to be able to assure equivalency. It is not unusual to have this report prepared by a recognized expert in the area of biopharmaceuticals.

The bio-batch size must be justified showing the equivalency of the production batch size to the bio-batch size. The "Animal Drug Manufacturing Guideline I: Pilot Manufacturer, 1994," also provides guidance on pilot batch size in-relation to production batches.

For minor use or minor species products, CVM may allow for limited validation lots to be produced during the post-approval validation of production lots. For questions regarding the pre-approval inspection of facilities manufacturing minor use or minor species products, please contact the NADE cGMP Pre-Approval Program Manager (HFV-142), or Dr. Dennis M. Bensley, (HFV-143), 301-827-6956. Additional information may be found in CPG 7132c.08, Process Validation Requirements for Drug Products Subject to Pre-Market Approval.

FDA has determined that it is no longer necessary to routinely review a company's compliance with Federal, State, and local environmental laws and has deleted the requirements for the submission of emission information for manufacturing sites. However, if information available to the agency or the applicant establishes that general or specific emission requirements, promulgated by Federal, State, or local environmental protection agencies, do not address unique emission circumstances or if there is information available to indicate that an action threatens a violation of a Federal, State or local law or requirement for the protection of the environment, this could be sufficient grounds for withholding approval and requesting manufacturing information in an environmental assessment. If unique emission circumstances are found or there is a threat of violation of the local, State or Federal environmental requirement, the incidence should be reported to the NADE Pre-Approval Program Manager (HFV-142). For clarification, please contact Mr. Charles Eirkson, Environmental Assessment Team (HFV-145) 301-827-6958.

4. Reprocessing/Reworking/Reconditioning

If a reprocessing, a reworking, or a reconditioning of a veterinary drug product results in a supplemental application, CVM may issue a pre-approval inspection

request to verify the firm's ability to make the proposed correction to the product. With more complex issues, the District may choose to have an investigator present during the reprocessing, reworking, or reconditioning process.

The cGMP regulations require reprocessing procedures to be written. It is customary for applications to contain procedures covering foreseeable deviations from specifications (e.g., weight variation, content uniformity, unacceptable tablet coating, etc.). Reprocessing due to deviations not anticipated in the original application must be covered by a supplemental application. Approval of such reprocessing procedures is required by 21 CFR 514.8(a)(2) and 21 CFR 211.115. Approval must be obtained before release of the reprocessed drug product. If the application contains a reprocessing provision, the applicant must provide data to establish that the procedure will result in a product that is equivalent to the originally approved product. The firm must prove that the reprocessing procedures will have no adverse impact on the reprocessed finished drug product.

Request for the reworking or relabelling of a specific lot/batch due to an error in the manufacturing process is a Compliance issue and should be coordinated between the Division of Compliance (HFV-230) and the appropriate Field Office.

Compliance Program 7153.14 provides for reconditioning of drug and device products that have been produced or held by methods or under conditions not in accordance with cGMP regulations. Reconditioning a product is a Compliance issue and should be coordinated between the Division of Compliance (HFV-230) and the appropriate Field Office; however, the review of the proposed reconditioning plan may require a supplemental application. No product shall be released until all reconditioning commitments are fully met as verified by FDA.

5. Laboratory Units

Every NADA/ANADA/INADA inspection must include an evaluation of laboratory controls and procedures and a review of the raw data used to generate results. This data may be located in research and development test logs which, once a filing is made, is considered by the Agency to be data to which it has access.

The authenticity and accuracy of data used in the development of a test method should be reviewed.

Laboratory equipment and procedures must be qualified and validated.

6. Components

The supplier and source of the active drug substance(s) used must be identified. The physical characteristics of the drug substance are reviewed along with the physical specifications for the substance.

When a manufacturer changes suppliers of a drug substance from that used for the manufacture of the bio-batch or clinical batches, there should be data demonstrating that the dosage forms produced from the drug substances from the two different suppliers are equivalent.

New suppliers or sources of new drug substances must be approved under a supplement to the application.

7. Buildings and Facilities

The addition of a new drug product to a production environment must be carefully evaluated as to its impact on other products already under production and changes that may 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 cGMP, and application requirements. For example, new products, such as cephalosporins, would require that the firm assure and be able to prove that cross-contamination does not occur in regard to other products being made in the same facility. Such alterations to existing facilities will require a supplement to the approved NADA/ANADA to provide for current operations.

8. Equipment

Manufacturers must qualify their equipment to perform its intended function. They must also validate the cleaning processes for any new drug substance and dosage form.

9. Packaging and Labeling Controls

Packaging and labeling control procedures are to be evaluated. Poor label control and accountability may indicate a firm's inability to guarantee that a product will always be properly labeled.

Past practices of a firm relative to any label mix-ups should be reviewed. Label and packaging controls should be reviewed for violations of cGMP regulations.

C. INSPECTION SCHEDULING

The scheduling of inspections is left to the discretion of the District. Every reasonable effort should be made, however, to conduct pre-approval inspections at the earliest possible opportunity, but within 30 calendar days of the date of the initial 10 day assessment. The District has the discretion of contacting the firm prior to the inspection to ensure that all necessary facilities, equipment, personnel, and materials are available and operational. The completion of manufacturing process validation, while not a requirement for approval, is a GMP requirement that must be met before any shipments of product are made. Manufacturing process validation is normally based on the documented successful evaluation of multiple full-scale batches (usually at least (3)) to provide assurance that the process will reliably meet predetermined specifications. This information may be available for evaluation by the FDA District Office during the pre-approval inspection and may be found acceptable. However, if this information is not available at that time or process validation deficiencies are noted by the FDA Investigator during the pre-approval inspection, then the FDA District Office may wish to evaluate manufacturing process validation prior to shipment of the drug product. This will provide the FDA District Office the opportunity to inspect and verify the validation of the manufacturing process. Regulatory action, such as seizure, will be considered in instances where there is shipment of the drug product prior to completion of the process validation data. However, the respective District Office may decide that a re-inspection is not necessary at the completion of the manufacturing process validation. The re-inspection is left totally to the discretion of the respective district office.

D. NEW FACILITY REVIEWS

For the inspection of major new facilities, or major changes to existing facilities, 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

Investigators should be alert to the use of unapproved facilities, unapproved raw material suppliers, or other areas of flagrant cGMP violations during these inspections. Use of unapproved facilities should be reported immediately to the NADE cGMP Pre-Approval Program Manager, HFV-142. Inspections of these facilities are not required unless an assignment has been received from headquarters. The investigator should report other cGMP violations to appropriate District Investigations and Compliance Branches.

F. APPLICATION REVIEW

When pre-approval inspections are requested by CVM, pertinent application information will be available for the investigator to review; however, the investigator must request this type of information from the NADE cGMP Pre-Approval Program Manager (HFV-142). The investigator may wish to have copies sent to them, or if they wish to make arrangements to review the information at headquarters. The information may include a copy of the manufacturing and controls section of the application and/or appropriate DMF and any pertinent information relating to batches used to conduct any bioequivalence, bioavailability and stability studies. A copy of the headquarters Chemist/Microbiologist review may also be available for the investigator to review.

An audit of this information is essential to determine that commitments by the firm in the application are reflected in actual practice. A copy of the pertinent sections of the application or the DMF will be available (upon District request) for the investigator's use before and during the inspection. Review of application information is especially important in preparing for inspection of firms or processes with which the investigator is unfamiliar.

G. SAMPLE COLLECTION

This program will provide coverage of samples for original NADA, generic ANADA, and investigational INADA submissions. Samples required under supplements to approved applications will also be collected and analyzed under this program.

All NADA/ANADA/INADA samples that are to be collected under this program will be requested by Center assignment memo or at the discretion of the District office. The assignment memo will designate when samples(s) are to be sent to the National Forensic Chemistry Center, Cincinnati District (HFR-MA500) for product profile (fingerprinting) analysis.

Any "for cause" samples collected by the investigator at his/her discretion during a pre-approval inspection are the responsibility of the home District. The latter are normally collected because of some problem existing at the site, to detect the existence of a potential problem or document violative inspectional findings. Discretionary samples may also be related to information that is pertinent to the history of the site during previous inspections.

1. Original NADA Submissions

An original NADA submission provides information for a proposed drug product (pharmaceutical dosage form, Type A Medicated Article and Type B & C medicated feeds) that has been studied under an investigational new animal drug application (INADA).

a. INADA Component

The Division of Manufacturing Technologies, HFV-140, reviews the Chemistry, Manufacturing, and Controls (CMC) section of the investigational new animal drug (INAD) submission. Before a component complete letter can be issued, the reviewer must receive an acceptable cGMP status from CVM's NADE cGMP Pre-Approval Program Manager (HFV-142) for all facilities, personnel, equipment, processes, controls and testing facilities listed in the application. Studies that are normally conducted under INADs and that are relevant to the submission of the NADA include toxicity, animal safety, food safety, stability, environmental safety, and effectiveness of the drug.

Activities related to the inspection and collection of samples of facilities manufacturing a product as an INAD will be conducted on assignment from CVM's NADE cGMP Pre-Approval Program Manager (HFV-142). "For Cause" samples may also be collected by the investigator; however, any chemical analysis will be at the discretion of the District management. Research facilities which are not otherwise required to register under Sec. 510 of the Act, but are involved in the manufacture of investigational drug products will be inspected only upon assignment from the NADE cGMP Pre-Approval Program Manager (HFV-142).

Any additional activities (sample collections, investigations, etc.) will be coordinated under the Center's Bioresearch Monitoring compliance programs:

7368.808 - Good Laboratory Practices
7368.810 - Sponsors, Contract Research Organizations, Monitors
7368.811 - Clinical Investigators

b. NADA Submissions

Sample collection, for method validation and/or specification verification, will be performed only on assignment from CVM. Any discretionary sampling will be on a "For Cause" basis at the option of the investigator at the time of inspection. Information regarding types of analysis required may be obtained either from the firm's specification sheets or may be obtained from the reviewing Chemist/Microbiologist. These samples should have been produced using commercial scale equipment using the proposed manufacturing operational procedures. The "Animal Drug Manufacturing Guideline, 1994" may be referenced by the investigator for additional guidance.

NOTE: When a request for sample collection has been made and no samples are available, a follow-up inspection should be scheduled as soon as possible and samples collected at that time.

When required by assignment, method validation and/or specification verification samples should be forwarded to the respective District's servicing laboratory as specified by DFS. The assignment memo will also indicate whether samples should be sent to FCC (HFR-MA500).

2. Generic ANADA Submission

Under the Generic ANADA submission, three types of samples are available for collection and analysis. These are the bio-batch samples, the proposed generic product, and the innovator or pioneer product.

Any planned sample collection will be performed only on assignment from CVM. Information regarding types of analysis required may be obtain either from the firm's specification sheets or may be obtained from the reviewing Chemist/Microbiologist.

Any discretionary sampling will be on a "For Cause" basis at the option of the investigator at the time of inspection.

a. Bio-Batch Samples

Samples of the product used to conduct any bio-batch study may be collected. Bio-batch samples may be produced from a pilot scale operation.

The corresponding batch production record should be obtained and reviewed.

The methods(s) and any reference standards used for analysis of the bio-batch sample should be obtained. (At a minimum, identification and potency tests should have been conducted.)

The investigator should carefully review all records (production, analysis, results, etc.) concerning the bio-batch samples to assure proper quality control has been exercised.

b. Innovator or Pioneer Samples

In order to properly document the bio-batch sample and the results, the innovator or pioneer product relative to the proposed generic product should also be collected. If samples of the pioneer product are not available, it should be purchased from a commercial outlet.

c. Commercial Scale Production Samples

Samples of the proposed generic product will be collected by the investigator at the time a pre-approval inspection is conducted. These samples should have been produced using commercial scale equipment using the proposed manufacturing procedures. The "Animal Drug Manufacturing Guideline, 1994" may be referenced by the investigator for additional guidance.

NOTE: When a request for sample collection has been made and no samples are available, a follow-up inspection should be scheduled as soon as possible and samples collected.

Samples should be forwarded to the respective District Servicing Laboratory (assigned by DFS) and/or headquarters laboratories as specified in the CVM (HFV-142) assignment memo.

NOTE: When samples have not been requested for testing, the investigator may wish to collect samples for physical analysis. Chemical analysis will be at the discretion of the District management.

3. Supplements to Approved NADAs or ANADAs

Certain supplements to either type of application may require inspection of manufacturing facilities. Requests for these inspections and any sample collections will be made upon assignment by the CVM NADE cGMP Program Manager (HFV-142) for domestic facilities and foreign facilities.

4. Samples from Foreign Establishments

If samples are to be collected at foreign facilities, the NADE cGMP Pre-Approval Program Manager (HFV-142) will so indicate in the assignment memo. Samples should be air-shipped to the servicing laboratory as soon as possible prior to departure from the location.

NOTE: Samples from foreign manufacturers may be collected in the U.S. at distribution centers.

5. Sample Sizes

Unless specified in the assignment memo, the amounts of samples should be collected according to CP 7346.832 and its 7/8/96 supplement.

NOTE: The investigator should consult with their respective servicing laboratory and/or FCC with any other questions regarding appropriate sizes or method of shipment to the laboratory.

When instructed in the assignment memo, a sample shall be collected and forwarded to the FCC (HFR-MA500) for fingerprinting analysis. Also refer to CP 7356.002F for additional instructions.

H. DISTRICT RECOMMENDATIONS

In those cases where the District conducts routine inspections, they should advise the respective headquarters units of any information obtained which could affect an existing application under the NADA/ANADA/INADA review process. This is especially important in those cases when significant cGMP deficiencies or violations occur.

When a pre-approval inspection request is received by a District Office, the District Director (or his/her designee) must evaluate the request within 10 calendar days of the original request date. Within 10 days of the original request, the District Director must submit a written statement to the NADE cGMP Pre-Approval Program Manager (HFV-142) indicating his/her evaluation of the inspection request relating to the pending NADA/ANADA/INADA. **The response should be either recommend "Approval", recommend "Withhold" approval, or recommend "Pending" until a pre-approval inspection can be conducted.** The District Director's (or his/her designee) response may be based on results of previous inspections or other information that should be considered by CVM before approval. Recommendations to withhold approval of an application must include specific justification for CVM consideration. CVM will not withhold approval where there is insufficient justification presented. When an assessment results in an inspection, the inspection should be completed within an additional 30 calendar days of the initial assessment response. Within 30 calendar days after the completion of an inspection, the District Director should provide a written response to the pre-approval inspection request indicating their concurrence for approval of the of the NADA/ANADA, their concurrence for recommending a "component complete letter" for the INADA, or stating the reasons why the cGMPs are not acceptable. A copy of this final response should be sent to the NADE cGMP Pre-Approval Program Manager (HFV-142) and to DMPQA (HFC-240).

- The following information constitutes reasons for recommending a delay in the acceptance of the proposed facility and for not recommending the approval of the application:

  1. An inspection of the subject establishment is currently 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 cGMP and application 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 has the ability to manufacture products in compliance with cGMP and application requirements and commitments.

- **No application should be recommended for approval if the facility is found to be in a state of non-compliance with the cGMP regulations until satisfactory correction is made.** However, cGMP deviations not warranting any Agency action should not result in a recommendation to withhold approval of applications.

NOTE: Whenever the District recommends that approval be withheld, the District must send a letter to the applicant informing them of the District's recommendation. The letter should also ask the firm to advise the District as to what corrective actions, if any, will be taken and of the timetable for these corrections.

The investigator should inform the facility management of significant cGMP and other issues that need to be resolved to gain NADA or ANADA approval, or to complete the INADA. The investigator should also advise the facility management that responses to FDA-483 items must be directed to the District for resolution. The District should follow-up responses to FDA-483 items as soon as possible, since there is a pending application.

EIRs must report adverse findings in full regarding both cGMP and application deficiencies. If a non-approval recommendation is made, the EIR must be submitted to HFV-142 within 30 days of completion of the inspection. EIRs and FDA 483s, will be reviewed by CVM's cGMP Pre-Approval Program Manager. If the Program Manager determines that there is a potential regulatory concern, then the inspectional package is forwarded to CVM's Division of Compliance, HFV-230 for follow-up.

A notification should be submitted to DMPQA, HFC-240, whenever an ongoing inspection finds cGMP deficiencies that may make the inspection OAI.

Due dates: Two due dates are now being included on all CVM Pre-Approval Inspection Requests that are sent to the District Offices. The first date is the timeframe within which the District should provide a written response, (10 (ten) calendar days of the request) as to their plan of action regarding the request (i.e. recommend to "Approve" no inspection necessary at this time, recommend "Withhold" due to current action, or "Pending" until a pre-approval inspection can be conducted). If a Withhold status is assigned to a Pre-approval inspection request, the response should include a detailed justification. If a Pending status is assigned to a Pre-approval inspection request, the Pre-approval Inspection should take place within the following 30 calendar days of the date of the District's 10-day written status response.

The second due date is when the District Director should provide a written response to the pre-approval inspection request either indicating their concurrence for approval of the of the NADA/ANADA, or stating the reasons why the approval should not be granted. This final

report should be received by CVM within 30 calendar days after the completion of an inspection.

I. FOREIGN OFFICE RESPONSE

For foreign facilities, the NADE cGMP Pre-Approval Program Manager will review the previous EIR and assess the firm's ability to perform the activities in the pending applications. If CVM determines that the current inspection has expired or if CVM does not have the files to make this assessment, an assignment will be sent to the Director of the Division of Emergency and Investigational Operations (or his/her designee), who should respond within 10 days to these requests by submitting a written statement to HFV-142 indicating an estimated inspection date. In some cases, CVM may be unaware of a recent foreign inspection that is currently being initiated or evaluated in another Center. If this is the case, ORA should inform CVM within 10 calendar days, so that CVM can evaluate the additional information prior to ORA initiating the inspection.

Every effort should be made to have the inspection completed within 90 calendar days of the inspection request. The Director (or his/her designee) should notify CVM when the inspection is scheduled and include the name, location, and telephone number of the investigator assigned to the inspection. In many cases, it is necessary for the reviewer to contact the investigator, or to provide additional material, prior to the inspection.

Upon completion of an inspection the investigator should fax a copy of the FDA 483 to both ORA and CVM. Within 30 days after return to the U.S., the investigator should forward the original report with exhibits to the NADE cGMP Pre-Approval Program Manager (HFV-142), with a copy to ORA (HFC-130). Recommendations to withhold approval of an application must include specific justification for CVM consideration. CVM will not withhold approval where there is insufficient justification presented.

PART IV - ANALYTICAL

When samples are requested to be collected, the respective District's servicing laboratory will perform the analysis. When discretionary physical samples are collected to document violative conditions, they should also be analyzed by the District's servicing laboratory.

A. ANALYZING LABORATORIES

1. Servicing Laboratories

The field laboratories to be used for conducting testing will be identified by Division of Field Science, ORA, (HFC-140).

The analysis of discretionary samples collected (for cause) by the investigators during the course of a pre-approval NADA/ANADA/INADA inspection will be conducted by the servicing laboratory or special laboratory as needed.

Laboratories may be requested to test for finished product specifications or other discretionary physical sample testing, method validations for evaluating finished product/in process procedures (this may be requested, although CVM does not routinely perform method validations), or laboratory participation in a method trial for drug residue in animal tissues, eggs, milk or other products. DFS will identify laboratories for all field testing required under this program.

Analysis of samples for product profiling (fingerprinting) will be conducted by the National Forensic Chemistry Center in the Cincinnati District.

2. Headquarters Laboratories

All headquarters laboratory analytical work will be handled by the Division of Residue Chemistry (Analytical Methods Team, HFV-511). Appropriate CDER, CFSAN or headquarters laboratory units will be used for special analysis should the need occur.

B. ANALYTICAL TESTS

When samples are requested, all proposed NADA/ANADA/INADA products will be tested according to the proposed NADA/ANADA/INADA methods. A copy of the proposed methods may be obtained from the sponsor, from the reviewer listed on the pre-

approval inspection request, or from the NADE cGMP Pre-Approval Program Manager (HFV-142). Only product release methods will be evaluated.

Normally, release tests, such as sterility, pyrogens, and particulate matter, on pharmaceutical preparations, need not be performed unless the investigator has cause for such to be done. The investigator should indicate on the collection report if these or other tests are to be done.

If the product is listed in the current USP, the applicable USP monograph tests will be used. If the product is found to be compounded in such a way that it cannot be accurately analyzed by applicable USP methods, then it is not in compliance with the FD&C Act. Excipient samples may be used to perform recovery and interference studies to confirm the validity and applicability of the methods provided by the firm.

NOTE: Any questions regarding the types of tests to be conducted should be directed to either the NADE cGMP Pre-Approval Program Manager (HFV-142) or the HFV-140 Reviewer that was designated on the original pre-approval inspection request.

C. SAMPLE ANALYSIS

When samples are collected during a pre-approval NADA, ANADA, or INADA inspection, they will be handled as described below:

1. Bio-batch Samples

Unless directed by a Center assignment memo, analysis of bio-batch samples will be on a "for cause" basis. Samples will be analyzed by the assigned laboratory.

Where applicable, the bio-batch samples should be tested for dissolution characteristics and compared physically and chemically with the production sample and with the sample of the innovator's product. A report on the physical and chemical profile of the firm's bio-batch sample should be prepared. This report may be used in the future to identify any deviation by the firm from the approved formulation or production.

2. NADA/ANADA Commercial Sample Comparison

If available, the finished product (commercial batch-size) sample collected at the time of the pre-approval inspection should be compared physically with the bio-batch sample and be evaluated and tested using the application test methods.

3. Finished Dosage Form Samples

Samples may be requested of finished products for verification of specifications or other discretionary physical sample testing.

4. Method Validation Samples

Samples may be requested for method validation for evaluating finished product/in process procedures (these samples may be requested, although CVM does not routinely perform method validations). The pre-approval inspection assignment request will indicate when such a sample is requested by CVM. The respective methods and specifications should also be obtained during the inspection. (If the investigator and firm agree, the samples, method, and specifications may be forwarded directly to the servicing lab by the firm). The servicing lab representative for the respective District should contact the reviewer listed on the pre-approval request form to obtain the approved method and specifications to compare to those obtained from the firm. CVM's Pre-Approval Inspection Manager should be updated as to the current status of the analysis and results. **Note:** Every effort should be made to have the analysis completed and reported to CVM within 30 calendar days following the inspection date.

5. Forensic Samples

Samples may be requested for product profiling (fingerprinting) that will be conducted by the National Forensic Chemistry Center (FCC) in the Cincinnati District (HFR-MA500). To assist in establishing a profile of each animal drug product tested, a flowchart and a brief description of the manufacturing process should be provided to FCC. The investigator should also obtain any impurity test methods and impurity limits for the product(s). Per Agency requirements, this information will be kept completely confidential. For additional information regarding profiling of foreign bulk pharmaceutical chemicals, please refer to CP 7356.002F or contact the FCC at (513) 679-2700.

6. Tissue Residue Samples

District laboratory participation in method trial for drug residue in animal tissues, eggs, milk or other products may also be conducted under this compliance program. Method trials for tissue residue methods are conducted according to the specifications of the CVM Sponsor Monitored Method Trial procedures. Requests

for field laboratory participation in tissue residue method trials will issue from CVM, Division of Human Food Safety, HFV-150. All analytical method information and test samples will be coordinated by CVM, HFV-150. The detailed specifications for CVM's method trial procedures are available under separate cover. For further information regarding pre-approval method trials of these types contact Dr. John J. O'Rangers, HFV-150, (301) 827-6987. (Email: joranger@cvm.fda.gov)

7. Method Trial

Any analytical work required by FDA to validate sponsor methods for finished dosage forms (pharmaceutical or Type A Medicated Articles, Type B or C Medicated Feeds), as proposed in NADAs or ANADAs, shall also be conducted under this compliance program. For further information regarding pre-approval method trials of these types contact Mrs. Mary Leadbetter, HFV-143, 301-827-6964.

8. Analytical Report

According to the type of analytical evaluation that was requested, a report of the evaluation of the product and methods will be prepared by the laboratory, signed by the District Director or acting person, and forwarded to the NADE cGMP Pre-Approval Program Manager (HFV-142) with a copy to HFC-140 and a copy to the home District, where necessary.

The report may contain the following information:

a. Identification of the application (NADA/ANADA).

b. Description of the product tested.

c. An evaluation of each test performed by the laboratory.

d. Results of all tests performed.

e. Comparison of FDA laboratory results obtained with the applicant's data where available.

f. Confirmation that the product complies with that described in the application.

g. A copy of the signed Form FD-2187 original worksheet.

h. A recommendation in any combination of the following categories:

1. Methods are acceptable;

2. Methods are acceptable after specified modifications are made;

3. Methods unacceptable for regulatory purposes;

4. Product meets specification;

5. Product does not meet specifications.

i. A description of the reserve sample.

9. Reserve Samples

The reserve samples, associated documentation, and copies of the FDA laboratory reports should be stored in an orderly and retrievable system for five years, or less upon the concurrence of the NADE cGMP Pre-Approval Program Manager.

10. Sample Follow-Up

On a random basis, the servicing laboratory will notify the home District approximately one year after approval and request post-approval follow-up samples of the products for testing. This activity (collection and testing) should be conducted under compliance program 7371.001, Drug Process and NADA Inspections and 7371.005, Type A Medicated Articles. Copies of these requests should also be sent to the NADE cGMP Pre-Approval Program Manager (HFV-142).

D. SAMPLE AND DATA STORAGE

The laboratory responsible for the evaluation of methods in a given application is required to maintain a 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. All related written material and samples should be available to CVM and the home District on short notice.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

For Domestic facilities, the responsible District should recommend withholding approval when there are significant deviations from cGMP regulations, or other application commitments, even though it is not prepared to seek regulatory action at the moment. The investigator should discuss cGMPs, and other problems having a direct bearing on a NADA/ANADA/INADA application with the appropriate facility management and to obtain the firm's response to the discussion following issuance of the FDA-483. The Field Management Directive No. 145 "Procedure for Release of Establishment Report to the Inspected Establishment" should be followed at the conclusion of each inspection report.

For Foreign facilities, the investigator submits their recommendation directly to the NADE cGMP Pre-Approval Program Manager, HFV-142. The investigator should also discuss cGMPs, and other problems having a direct bearing on a NADA/ANADA/INADA application with the appropriate facility management. The firm's response following issuance of the FDA-483 should be submitted to the NADE cGMP Pre-Approval Program Manager, HFV-142 with a copy to the investigator. If the response is received by the investigator prior to their completion of their final report, then the investigator should provide their evaluation of the firm's response in the EIR. EIRs must report adverse findings in full regarding both cGMP and application deficiencies. If a non-approval recommendation is made, the EIR must be submitted to HFV-142 within 30 days of completion of the inspection. EIRs and FDA 483s, will be reviewed by CVM's cGMP Pre-Approval Program Manager (HFV-142). If the Program Manager determines that there is a potential regulatory concern, then the inspectional package is forwarded to CVM's Division of Compliance, HFV-230 for follow-up. In many cases a team approach (including CVM's cGMP Pre-Approval Program Manager, CVM's Compliance Consumer Safety Officer, the ORA Investigator, and the HFV-140 Reviewer), is utilized to resolve potential regulatory concerns.

When significant cGMP deviations are encountered, the firm profile should be updated as soon as the FDA-483 is issued. If these significant cGMP deviations also apply to commercially marketed products, a warning letter may be issued. However, do not issue a warning letter when the cGMP deviations do not apply to commercially marketed products.

Significant cGMP deviations that impact on products already approved must be corrected. The sponsor should be advised that in some instances a supplement to the NADA/ANADA/INADA would be necessary to provide current information. Appropriate regulatory and/or administrative action(s) should be recommended when, in the judgment of the responsible District or CVM's Division of Compliance, such action is necessary to gain compliance with cGMP requirements.

The investigating District compliance branch shall institute regulatory/administrative follow-up in accordance with the Type A Medicated Articles Compliance Program (7371.005) or the Drug Process and New Animal Drug Inspection Compliance Program (7371.001) as appropriate where violative cGMP practices are encountered or manufacturing practices do not comply with NADA/ANADA/INADA commitments.

Recommendations for regulatory or administrative follow-up for violative inspections of foreign facilities shall be received by and acted upon (e.g., issuance of letters to firms and preparation of Import Alerts) by the CVM's Division of Compliance (HFV-230).

If applications are withheld because of cGMP non-compliance and the cGMP deficiencies also apply to commercially marketed products, then the District should contemplate taking action to assure that the deficiencies are corrected. A copy of any warning letter should be sent to CVM's cGMP Pre-Approval Program Manager (HFV-142), CVM's Division of Compliance (HFV-230), DMPQA (HFC-240), and to the Division of Compliance Policy (HFC-230).

When significant deviations are encountered and the firm fails to make prompt corrections, the District should then recommend regulatory and/or administrative action against any other approved product manufactured under the same conditions.

When the inspection is considered "closed", the Field Management Directive No. 145 "Procedure for Release of Establishment Report to the Inspected Establishment" should be followed for the release of the EIR to the inspected facility.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. Investigations Operations Manual, Subchapter 540

2. Code of Federal Regulations, Title 21

   a. 21 CFR Part 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
   b. 21 CFR Part 211 - Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals
   c. 21 CFR Part 226 - Current Good Manufacturing Practice Regulations for Type A Medicated Articles
   d. 21 CFR Part 514 - New Animal Drug Application: Section 514.1(b)(4)(5)(6)
   e. 21 CFR Part 25 - Environmental Impact Considerations

3. Field Management Directive No. 135, "Pre-operational Reviews of Manufacturing Facilities"

4. CP 7132c.08 - Process Validation Requirements for Drug Products Subject to Pre-Market Approval

5. CP 7371.001 - Drug Process and NAD Inspections

6. CP 7371.005 - Type A Medicated Articles

7. CP 7368.810 - Sponsors, Contract Research Organizations, Monitors

8. CP 7368.811 - Clinical Investigators

9. CP 7368.808 - Good Laboratory Practices

10. CP 7356.002 - Drug Process Inspections

11. CP 7356.002A - Sterile Drug Process Inspections

12. CP 7356.002F - Bulk Pharmaceutical Chemicals

13. Current edition of United States Pharmacopeia/National Formulary and Supplements

14. Guideline on Preparation of Investigational New Drug Products, September 1990

15. GWQAP Manual, Profile System, Chapter 15

16. Regulatory Procedures Manual, Chapters 7 and 8

17. Biotechnology Inspection Guide, November 1991

18. Animal Drug Manufacturing Guideline, 1994

19. Field Management Directive No. 145 "Procedure for Release of Establishment Report to the Inspected Establishment"

B. PROGRAM CONTACTS

1. ORA Contacts

a. Investigational

1. Domestic Facilities

James Dunnie
Division of Emergency and Investigational Operations (HFC-130)
Phone: 301-827-5652

2. Foreign Facilities

Rochelle Kimmel
Division of Emergency and Investigational Operations (HFC-130)
Phone: 301-827-5663
FAX: 301-827-6685

b. Analytical

George Salem
ORO/Division of Field Science (HFC-141)
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2. Center Contacts

a. NADE cGMP Pre-Approval Program Manager

Michael Smedley
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b. NADE cGMP Pre-Approval Program Manager, Assistant

Robin Stone
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c. Regulatory Actions

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