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 (INAD) Applications Generic Investigational New Animal Drug (JINAD) Applications Conditional New Animal Drug Applications (CNADA)	IMPLEMENTATION DATE UPON RECEIPT COMPLETION DATE Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM / ASSIGNMENT CODES
All Animal Drugs Use appropriate product codes.	68001-Innovator Domestic and Foreign Pre-Approval Inspections, Sample Collections, and Analytical Analysis 68001G-Generic Domestic and Foreign Pre-Approval Inspections, Sample Collections, and Analytical Analysis

FIELD REPORTING REQUIREMENTS

Reporting requirements both prior to and after pre-approval inspections (PAI) are outlined in the March 26, 2010 Memorandum of Understanding: ADUFA and AGDUFA Pre-Market Applications Assignment Tracking Procedures Between CVM and ORA, which is provided in the Attachment to this document. CVM's PAI program is managed by the Division of Manufacturing Technologies (DMT) at the Office of New Animal Drug Evaluation (ONADE) at the Center for Veterinary Medicine (CVM).

Prior to the inspection, it is recommended that the investigator assigned to an animal drug pre-approval inspection and the appropriate staff at DMT discuss any necessary background information including possibly identifying specific critical areas to be covered during the investigation.

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PART I - BACKGROUND

The Food, Drug, and Cosmetic Act provides that FDA may approve an animal drug application 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.

The Center's determination of the adequacy of these pre-market applications includes inspectional requirements in addition to filing requirements as set forth in pertinent sections of the Code of Federal Regulations.

In response to the FDA Initiative, *Pharmaceutical cGMP's for the 21st Century: A Risk Based Approach,* the pre-approval inspection program in the Office of New Animal Drug Evaluation (ONADE) utilizes the Pre-Approval Inspection Decision Support System (PAIDSS). This risk based module is used to support inspection request decisions. The following principles outlined in these Agency initiatives serve as the foundation for PAIDSS:

- the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality;
- the latest scientific advances in pharmaceutical manufacturing and technology are encouraged;
- the submission review program and the inspection program operate in a coordinated and synergistic manner;
- regulation and manufacturing standards are applied consistently;
- management of the program encourages innovation in the pharmaceutical manufacturing sector; and
- FDA resources are used most effectively and efficiently to address the most significant health risks.

These risk based principles are consistent with section 705 of the "Food and Drug Administration Safety and Innovation Act", as amended July 9, 2012.

In addition, DMT strongly encourages communication and collaboration between investigators and DMT review staff prior to the pre-approval inspection in order to identify critical aspects of the manufacturing and control procedures for the facility. Information provided in the manufacturing applications to CVM is used to prioritize inspection resources towards areas of concern or criticality whenever possible.

During the pre-marketing review of proposed new animal drug products, FDA must determine if a foreign or domestic establishment designated as a manufacturer, packager, labeler, or testing laboratory can operate in conformity with current Good Manufacturing Practice (cGMP) regulations, and in accordance with NADA/ANADA/INAD/JINAD/CNADA or related Veterinary Master File (VMF) or Drug Master File (DMF) filing requirements. Also, satisfactory cGMPs are necessary prior to issuing a *Technical Section Complete Letter* for the Chemistry, Manufacturing, and Controls (CMC) Technical Section of an INAD/JINAD or approving certain CMC supplements. As stated in CVM's Program Policy and Procedures Manual 1240.3622

Good Manufacturing Practice Compliance Status, no new animal drug application or medicated feed license will be approved for firms that are not in compliance with cGMPs. Exceptions based on degree of non-compliance will be determined on a case-by-case basis. An example of an exception is where existing GMP violations at a firm involve a process or area not relevant to the product under consideration, e.g., an NADA for a tablet when the firm may have GMP problems only in its sterile production area. Approval for the application may be granted if Center personnel and Field District Offices concur.

Compliance determinations will be made through establishment inspections, appropriate document review, and product sampling, where applicable. This compliance program provides requirements that are compatible with those found in the Center for Drug Evaluation and Research (CDER) compliance program for new drug evaluation under CPG 7346.832.

Activities conducted under this compliance program are applicable to animal drug pharmaceutical dosage forms, Type A Medicated Articles, and their components including new drug substances listed in NADAs, ANADAs, INADs, JINADs, CNADAs and related VMFs and DMFs.

The Animal Drug User Fee Act (ADUFA) and Animal Generic Drug User Fee Act (AGDUFA) authorize FDA to collect fees. Under the user fee legislation, FDA agreed to pursue a comprehensive set of review performance goals to improve the timeliness and predictability of the review of animal drug applications and investigational animal drug submissions. The types of premarket applications and required inspection timeframes are covered by the MOU in the Attachment "ADUFA and AGDUFA Pre-Market Applications Assignment Tracking Procedures Between CVM and ORA."

PART II - IMPLEMENTATION

A. OBJECTIVE

The objectives of this compliance program are:

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

2. to assure that the CMC information in an application corresponds to actual cGMP manufacturing and control procedures in a facility.

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

In an effort to facilitate the mutual exchange of information, CVM will provide a bi-weekly Foreign Inspection priority list and ORA will provide a bi-weekly update to this list as described by the CVM/ORA MOU in the Attachment.

B. PROGRAM MANAGEMENT INSTRUCTIONS

Before any NADA or ANADA is approved by CVM, or before a CMC Technical Section Complete Letter is issued for an INAD/JINAD, 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 must be in compliance with the appropriate current Good Manufacturing Practice (cGMP) regulations and application requirements. After receipt of a submission, DMT review staff assess the cGMP status of all relevant facilities.

Assignments: The CVM cGMP Pre-Approval Program Manager in HFV-140 designates a status for a facility identified in applications based on the current cGMP inspection history for the specific profile class. The decision to issue a pre-approval inspection request for a facility is based on a combination of risk factors including the CMC content in an application, facility inspection history, and complexity of process.

Priority Pre-Approval Inspection Risk Considerations:

1. Establishment is named in an application to FDA for the first time, including establishments that have never been inspected or have been inspected only for non-application drugs;
2. Finished product or API is manufactured by a substantially different manufacturing process or dosage form than previously covered at the establishment
3. Complexity of manufacturing process performed at the establishment

4. Numerous application submissions or certain site/process/product changes that are expected to pose significant challenge to the state of control of the facility or process
5. Compliance and recall history
6. Facility inspection history
   a) If the facility status for the profile class of interest has not been updated via a site inspection within the past 2 years, the facility will be considered for inspection. Facilities which have not been inspected within the last 4 years or which have an "unacceptable" status are designated highest priority.
   b) Facility has undergone significant modifications or renovations since last inspection.
   c) Inspections performed by foreign governments or entities are considered as factors, where appropriate.
7. Other submission content factors such as:
   a) Finished product containing a New Molecular Entity (NME)
   b) Finished product content assay with a narrow range (e.g., 95-105% labeled strength for narrow therapeutic index drugs)
8. Risk mitigating factors from submission content such as:
   a) Risk management programs at facility
   b) Use of advanced technologies and controls such as quality by design and real time monitoring
   c) Submission of pharmaceutical development reports

The CVM cGMP Pre-Approval Program Manager issues pre-approval inspection assignments for both domestic and foreign facilities. An inspection request is issued in accordance with the timelines described in the CVM/ORA MOU in the Attachment. An audit of the cGMPs as applied to the specific drug product or component must be performed when an inspection assignment is received, unless appropriate justification is provided by the Field Office that the facility is currently acceptable.

Investigational Animal Drug and Original Applications: DMT reviews the CMC section of the INAD/JINAD/NADA/ANADA/CNADA submission. Before a technical section complete letter or an approval letter can be issued, the reviewer must receive an acceptable cGMP status from the CVM cGMP Pre-Approval Program Manager for all facilities listed in the application. Research facilities which are not otherwise required to register under Sec. 510 of the Act, but are involved in the manufacture of investigational new animal drug products will be inspected only upon assignment from the CVM cGMP Pre-Approval Program Manager.

Supplements: Supplements to approved NADA, ANADA, and CNADA applications providing for CMC changes will also undergo a review to determine the cGMP compliance and conformance with filing requirements made in the respective supplement(s).

The pre and post-inspection administrative responsibilities for CVM and ORA are outlined in the CVM/ORA MOU provided in the Attachment.

Districts are required to promptly update the firm profile in accordance with the Investigations Operations Manual. As soon as the District becomes aware of any significant adverse information which could affect the Agency's product approval decisions with respect

to a firm, the District should immediately notify the CVM cGMP Pre-Approval Program Manager.

C. REGULATORY ACTIONS

When the firm markets FDA regulated veterinary products, ORA should forward recommendations for regulatory actions to both CVM's Division of Compliance, HFV-230, and the CVM cGMP Pre-Approval Program Manager. CVM Compliance is designated as lead for all regulatory action in the Compliance Management Services (CMS).

PART III - INSPECTIONS

A. PRE-APPROVAL INSPECTION

1. Domestic Establishments

The district office will conduct inspections on assignment from the CVM cGMP Pre-Approval Program Manager. The district office pre-approval manager will notify CVM of the scheduled inspection date or of any justification for not performing the requested inspection.

2. Foreign Establishments

ORA's Office of Medical Products and Tobacco Operations (OMPTO) will conduct inspections on assignment from the CVM cGMP Pre-Approval Program Manager. ORA will select an investigator and make travel arrangements for the foreign inspection. If ORA determines there is justification for not performing the requested inspection, CVM will be informed of the rationale. Once the investigator is identified, ORA will notify CVM and include an estimated date of inspection. CVM will provide a bi-weekly CVM Pre-Approval Inspection priority list to ORA as described by the CVM/ORA MOU in the Attachment.

3. Application Reference Materials

The investigator is encouraged to contact the CVM cGMP Pre-Approval Program Manager or reviewer to discuss the inspection request prior to inspection or to obtain copies of manufacturing information in applications. CVM may also send relevant reviews to assist in the inspection, but the reviews should remain confidential. Additionally, appropriate DMT staff are generally available at times during the inspection to provide background information or product specialist support needed by the investigator. Contact information for the DMT reviewer associated with a particular submission is included on the CVM's cGMP inspection request or can be obtained from the CVM cGMP Pre-Approval Program Manager.

B. INSPECTION APPROACH

The inspectional information presented in the Investigations Operations Manual (IOM) Chapter 5 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. Active pharmaceutical ingredients should be evaluated under the inspectional guide in CP 7356.002F with additional information found in GFI, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Type A Medicated Articles should be evaluated under CP 7371.005.

1. Inspection Team

Whenever appropriate, ORA should compile an inspection team composed of experts from within the District, other Districts, or Headquarters to provide needed expertise and experience including the use of national experts or members of the Pharmaceutical Inspectorate. Contact OMPTO if technical assistance is needed. CVM reviewers are available to participate in inspections to serve as subject matter experts, particularly for novel or critical products and processes. Requests for CVM participation should be sent to the CVM cGMP Pre-Approval Program Manager.

2. Inspection Strategy

There are three primary inspectional objectives of this PAI program. These objectives are:

Objective 1: Readiness for Commercial Manufacturing
Objective 2: Conformance to Application
Objective 3: Data Integrity Audit

If one or more criteria is met and the district recommends that a PAI should be performed, at least one objective must be addressed during the PAI. Based on the specific responsibilities of the establishment to be inspected and whether new profile classes are related to inspected profile classes, the district determines the degree of coverage.

Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

a. Manufacturing and laboratory changes, deviations, and trends relating to the development of new drug substance and product manufacturing have been adequately evaluated.
b. A sound and appropriate program for sampling, testing, and evaluation of components, in-process materials, finished products, containers and closures for the purpose of releasing materials or products has been established, including a robust supplier qualification program.
c. The establishment has sufficient facility and equipment controls in place to prevent contamination of and by the application product (or API).
d. Adequate procedures exist for batch release, change control, investigating failures, deviations, complaints, and adverse events; and for reporting this information to FDA, such as field alert reporting.
e. The feasibility of the proposed commercial process and manufacturing batch record, including instructions, processing parameters and process control measures, are scientifically and objectively justified. This objective is linked to the firm's process validation program.

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 inspection of facilities manufacturing minor use or minor species products, contact the CVM cGMP Pre-Approval Program Manager or the DMT reviewer as specified in the inspection request.

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the pivotal batches, when applicable, the proposed commercial scale batch, and the API(s).

Objective 3: Data Integrity Audit
Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, processes and controls) were submitted in the CMC section such that DMT reviewers can rely on the submitted data as complete and accurate.

C. NEW FACILITY REVIEWS

For the inspection of 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.

D. SURVEILLANCE

Investigators should be alert to the use of unapproved facilities, unapproved API suppliers, or other significant cGMP violations during these inspections. Use of unapproved facilities should be reported immediately to the CVM cGMP Pre-Approval Program Manager. The investigator should report other cGMP violations to appropriate District Investigations and Compliance Branches.

E. 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/INAD/JINAD/CNADA review process. This is especially important in those cases when significant cGMP deficiencies or deviations from filing information occur.

Reasons for recommending a delay in the acceptance of the proposed facility and not recommending the approval of the application include:

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. The facility is found to be in a state of non-compliance with the cGMP regulations.

NOTE: Whenever the District recommends that approval be withheld, the District must send a letter to the applicant informing them of the 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.

PART IV - ANALYTICAL

Any planned sample collection will be performed only on assignment from CVM. Decisions concerning the types of analysis required should be made in consultation with CVM and the Office of Regulatory Science.

Any discretionary sampling will be on a "for cause" basis at the option of the investigator at the time of inspection. Any "for cause" samples collected by the investigator at his/her discretion during a pre-approval inspection are the responsibility of the District.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Domestic

For domestic facilities, the responsible District should recommend withholding approval when there are significant deviations from cGMP regulations, or other application requirements, even if it is not prepared to seek regulatory action at the moment. The investigator should discuss cGMPs, and other problems having an impact on a NADA/ANADA/INAD/JINAD/CNADA 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.

Foreign

For foreign facilities, the investigator submits their initial recommendation directly to the CVM cGMP Pre-Approval Program Manager via email. The final recommendation for the facility will be determined by CVM for foreign facility inspections. The investigator should also discuss cGMPs, and other problems affecting a NADA/ANADA/INAD/JINAD/CNADA application with the appropriate facility management. The firm's response following issuance of the FDA-483 should be submitted to the CVM cGMP Pre-Approval Program Manager with a copy to the investigator. Direct the facility to submit responses to the following address.

Document Control Unit (HFV-199)
Attn: Robin Stone
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

If the response is received by the investigator prior to their completion of their final report, the investigator should provide any comments concerning the firm's response in the EIR. EIRs must report adverse findings in full regarding both cGMP and application deficiencies. Every effort should be made to have the inspection report submitted to CVM within 30 days upon return to the United States. If that is not possible, the District PAI Manager and/or Investigator's supervisor should notify the ONADE Pre-Approval Manager or follow appropriate District procedures regarding communicating with CVM. OMPTO should also be notified about the status of the EIR. EIRs and FDA 483s will be reviewed by ONADE/DMT staff. If there is a potential regulatory concern, then the inspectional package is also reviewed by CVM's Division of Compliance, HFV-230. In many cases a team approach (including CVM's Compliance Consumer Safety Officer, the ORA Investigator, and the DMT Reviewer and Team Leader), is utilized to resolve potential regulatory concerns.

Administrative

When significant cGMP deviations are encountered, the firm profile should be updated

promptly once 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 approved products must be corrected. The sponsor should be advised that in some instances a supplement to the NADA/ANADA/INAD/JINAD/CNADA 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 Animal Drug Manufacturing Inspections Compliance Program (7371.001) as appropriate where violative cGMP practices are encountered or manufacturing practices do not comply with NADA/ANADA/INAD/JINAD/CNADA requirements.

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 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 the CVM cGMP Pre-Approval Program Manager and CVM's Division of Compliance (HFV-230).

When significant deviations are encountered and the firm fails to make prompt corrections, the District should consider regulatory and/or administrative action against any other approved product affected by 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. 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

2. Pharmaceutical cGMPs for the 21st Century-A Risk-Based Approach, Final Report – Fall 2004

3. Food and Drug Administration Safety and Innovation Act, 21 USC 301.

4. Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001.

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

6. ORA Investigations Operations Manual, Chapter 5-Establishment Inspection.

7. CPG 490.100 - Process Validation Requirements for Drug Products Subject to Pre-Market Approval

8. CPGM 7371.001 - Animal Drug Manufacturing Inspections

9. CPGM 7371.005 - Type A Medicated Articles

10. CPGM 7356.002 - Drug Process Inspections

11. CPGM 7356.002A - Sterile Drug Process Inspections

12. CPGM 7356.002F - Active Pharmaceutical Ingredients

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

14. CDER GFI: Guideline on Preparation of Investigational New Drug Products, March 1991

15. FDA Regulatory Procedures Manual, Chapters 7 and 8, 2008

16. ORA Biotechnology Inspection Guide, November 1991

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

18. PPPM 1240.3622 Good Manufacturing Practice Compliance Status

B. PROGRAM CONTACTS

1. ORA Contact:

For technical questions concerning inspections contact:

Office of Regulatory Affairs (ORA)
Office of Medical Products and Tobacco Operations (OMPTO)
Division of Medical Products and Tobacco Program Operations (DMPTPO)
Telephone number: 301-796-0358
FAX number: 301-827-9791
ORAHQOMPTODMPTOManagers-VMAIL@fda.hhs.gov

b. Analytical

i. Microbiology: Angele Smith, OO/Office of Regulatory Science (HFC-141), Phone: 301-796-4200, FAX: 301-827-9806

ii. Chemistry: Shari Kahn, OO/Office of Regulatory Science (HFC-141), Phone: 301-796-8154, FAX: 301-827-9806

2. Center Contacts

a. Robin Stone, CVM cGMP Pre-Approval Program Manager

Division of Manufacturing Technologies (HFV-140)

Contact: cvmgmpstatus@fda.hhs.gov
Phone: 240-402-0678

b. Regulatory Actions

Division of Compliance (HFV-230)
Phone: 240-276-9201
Fax: 240-276-9241

C. ATTACHMENT: ADUFA AND AGDUFA Pre-Market Applications Assignment Tracking Procedures Between CVM and ORA

ADUFA and AGDUFA Pre-Market Applications
Assignment Tracking Procedures Between CVM and ORA

INTRODUCTION AND SCOPE

The Animal Drug User Fee Act of 2003 (ADUFA), Amendments of 2008 (ADUFA II), and the Generic Animal Drug User Fee Act of 2008 (AGDUFA) authorize FDA to collect the following fees from veterinary drug sponsors:

- application fees
- establishment fees (only ADUFA)
- product fees
- sponsor fees

Under the user fee legislation, FDA agreed to pursue a comprehensive set of review performance goals to improve the timeliness and predictability of the review of veterinary drug submissions.

The following types of pre-market applications and submissions are encompassed by the ADUFA legislation:

- new animal drug applications (NADA) (ADUFA timeframes at 180 days),
- supplemental NADAs (ADUFA timeframes at 120 days),
- investigational animal drug application (INAD) (ADUFA timeframes at 180 days),
- master files (ADUFA timeframes equivalent to referencing application).

The following types of pre-market applications and submissions are encompassed by the AGDUFA legislation:

- original abbreviated animal drug applications (ANADA) (AGDUFA timeframes at 270 days),
- supplemental ANADAs (AGDUFA timeframes at 270 days),
- generic investigational new animal drug application (JINAD) (AGDUFA timeframes at 270 days),
- master files (AGDUFA timeframes equivalent to referencing application).

The Secretary's determination of the approvability/adequacy of these pre-market applications may include inspectional requirements in addition to filing requirements as set forth in pertinent sections of the Code of Federal Regulations.

PROCEDURES

The following are procedures that were agreed upon between the Center for Veterinary Medicine (CVM) and the Office of Regulatory Affairs (ORA), and have been cleared through the Veterinary Field Committee. The purpose of these procedures is to ensure that the timeliness of Domestic and

Foreign Inspections are equitable with the review performance goals set forth in the user fee legislation.

DOMESTIC INSPECTIONS

Responsibilities:

CVM responsibilities are as follows:

Pre-Inspection:

- Upon receipt of a submission, the CVM Document Control Unit will log the document into the CVM Corporate Database prior to forwarding it to the review division. This process usually takes 2 working days.
- Within 10 calendar days of receipt of a chemistry, manufacturing, and controls (CMC) submission that may require an inspection, the Division of Manufacturing Technologies (DMT) will initiate the following activities:

    - The CMC Reviewer will submit a cGMP status check request to the CVM Pre-Approval Manager;
    - The CVM Pre-Approval Manager will collect information (for past five years) regarding the status of the facility from a variety of sources (FACTS, COMSTAT, etc.) and forward the information to the CMC Reviewer;
    - The CMC Reviewer will perform a risk assessment by entering applicable information regarding the facility inspection history and the complexity of the manufacturing process steps into the Pre-Approval Inspection Decision Support System (PAIDSS). **Note:** CMC information pertinent to the risk assessment will not be available until review of the CMC submission has been accomplished. When the review of the CMC submission has been completed, additional information from the review may be included in the risk assessment and may change the priority of the inspection recommendation. An inspection recommendation will be forwarded to the CVM Pre-Approval Manager along with the results of the PAIDSS risk assessment;
    - The CVM Pre-Approval Manager will confer with the appropriate Team Leader and CMC Reviewer to confirm the accuracy of the recommendation. If a pre-approval inspection (PAI) request is indicated, it will be forwarded to the appropriate District Office within 10 days. The inspection request will be identified in FACTS as ADUFA with PAC code 68001 or AGDUFA related with PAC code 68001G and include the due date of the inspection. FACTS will be updated as follows:

        - The DUE DATE will be listed in FACTS under the "REQUESTER CMPLTN DATE" box in FACTS
        - The SUBJECT line in FACTS will state "ADUFA PAI INSPECTION" or "AGDUFA PAI INSPECTION" as a visual reminder that the assignment falls under the timelines of the user fee program.

- The FACTS assignment will include the CVM Point of Contact (POC) name and the PAC code (68001 for ADUFA or 68001G for AGDUFA)
- The written assignment will state in the subject line that this is either an ADUFA PAI INSPECTION or an AGDUFA PAI INSPECTION.
- The supporting application information and the written assignment will be forwarded to the appropriate District Contact.
- The assignment memo will also indicate whether or not a pre-inspection briefing is warranted prior to the start of the inspection.

- If CVM has specific knowledge that a facility is not ready for inspection, CVM will not submit an inspection request to the appropriate District Office until CVM is notified by the applicant that the facility is ready for inspection. If the domestic inspection request has already been issued and CVM is notified by the applicant or the appropriate District Office that the firm is not ready for inspection, CVM will cancel the request and will re-issue the request when CVM has been notified by the applicant that the facility is ready for inspection.

District Office responsibilities are as follows:

Pre-Inspection:

- Upon receipt of an inspection request for the evaluation of a domestic establishment submitted by the CVM Pre-Approval Manager, the District will respond to the inspection request within 10 calendar days and will respond to the CVM Pre-Approval Manager indicating the appropriate District Office recommendation. In some cases, CVM may be unaware of a recent domestic inspection that is currently being initiated or evaluated in another Center. If this is the case, the District Office should inform CVM within the same 10 calendar days so that CVM can evaluate the additional information prior to the District Office initiating the inspection. If the facility indicates they are not ready for inspection, the District should immediately notify the CVM Pre-Approval Manager. The District Office should collect the necessary documentation from the firm or manufacturer if they are not ready for the pre-approval inspection and send it to the CVM Pre-Approval Manager.
- When a 10 day assessment results in an inspection, every effort should be made to have the inspection initiated or completed within 30 calendar days following the initial 10 day assessment response. If the 30 days cannot be met, the District Office will contact the CVM Pre-Approval Manager. The District Office will notify the CVM Pre-Approval Manager when the inspection is scheduled and include the name, location and telephone number of the Investigator assigned to the inspection.

Post-Inspection:

- District PAI Manager will email District's initial recommendation based on the inspection and FDA-483 to the CVM Pre-Approval Manager.
- Within 30 calendar days of the completion of the inspection, the District will complete the EIR, review the firm's responses to FDA 483 items, issue the FMD-145 letter if necessary, and forward the entire EIR package, including the District's final inspection

recommendation to the CVM Pre-Approval Manager, per ORA's established procedures. Every effort should be made to meet the 30 day timeframe to forward the recommendation to CVM. If that is not possible, the District PAI Manager should notify the CVM Pre-Approval Manager or follow appropriate District procedures regarding communicating with CVM.

FOREIGN INSPECTIONS

Mutual Exchange of Information

CVM will provide:

A bi-weekly Foreign Inspection priority list containing; GMP assignment #, Reviewer name, FEI #, firm name, firm location, application #, submission #, U.S. Agent, sponsor, PAI request date, due dates, status, priority, and related applications. This list will be sent directly to Rebecca Hackett, Branch Chief of DFI's International Operations. CVM will update the list bi-weekly.

Pertinent information such as reviews or other related information is to be shared with the Investigator by the CVM Pre-Approval Manager or CMC Reviewer upon notification by DFI that the inspection is scheduled.

ORA/DFI:

ORA will provide a bi-weekly update to CVM's foreign inspection priority list that will include the inspection date and the name of the Investigator who will be conducting the inspection, if available at the time of the update.

Responsibilities
CVM responsibilities are as follows:

Pre-Inspection:

- Upon receipt of a submission, the CVM Document Control Unit will log the document into the CVM Corporate Database prior to forwarding it to the review division. This process usually takes 2 working days.
- Within 10 calendar days of receipt of a chemistry, manufacturing, and controls (CMC) submission that may require an inspection, DMT will initiate the following activities:

    - The CMC Reviewer will submit a cGMP status check request to the CVM Pre-Approval Manager;
    - The CVM Pre-Approval Manager will collect information (for past five years) regarding the status of the facility from a variety of sources (FACTS, COMSTAT, etc.) and forward the information to the CMC Reviewer;
    - The CMC Reviewer will perform a risk assessment by entering applicable information regarding the facility inspection history and the complexity of the manufacturing process steps into the Pre-Approval Inspection Decision

Support System (PAIDSS). **Note:** CMC information pertinent to the risk assessment will not be available until review of the CMC submission has been accomplished. When the review of the CMC submission has been completed, additional information from the review may be included in the risk assessment and may change the priority of the inspection recommendation. An inspection recommendation will be forwarded to the CVM Pre-Approval Manager along with the results of the PAIDSS risk assessment;

- The CVM Pre-Approval Manager will confer with the appropriate Team Leader and CMC Reviewer to confirm the accuracy of the recommendation. If a pre-approval inspection (PAI) request is indicated, it will be forwarded to the appropriate District Office within 10 days. The inspection request will be identified in FACTS as ADUFA with PAC code 68001 or AGDUFA related with PAC code 68001G and include the due date of the inspection. FACTS will be updated as follows:

    - The DUE DATE will be listed in FACTS under the "REQUESTER CMPLTN DATE" box in FACTS
    - The SUBJECT line in FACTS will state "ADUFA PAI INSPECTION" or "AGDUFA PAI INSPECTION" as a visual reminder that the assignment falls under the timelines of a user fee program.
    - The FACTS assignment will include the CVM Point of Contact (POC) name and the PAC code (68001 for ADUFA or 68001G for AGDUFA)
    - The written assignment will state in the subject line that this is either a ADUFA PAI INSPECTION or AGDUFA PAI INSPECTION. The supporting application information and the written assignment will be forwarded to Division of Field Investigations, International Operations Branch for issuance to the appropriate Field Investigator.
    - The assignment memo will also indicate whether or not a pre-inspection briefing is warranted prior to the start of the inspection.

- **Note:** If changes in the inspection recommendation occur as a result of the review of the CMC submission and prior to the completed inspection, CVM and ORA will together make a determination how to proceed.
- If CVM has specific knowledge that a facility is not ready for inspection, CVM will not submit an inspection request to ORA/DFI until CVM is notified by the applicant that the facility is ready for inspection. If the foreign inspection request has already been issued and CVM is notified by the applicant or ORA/DFI that the firm is not ready for inspection, CVM will cancel the request and will re-issue the request when CVM has been notified by the applicant that the facility is ready for inspection.

Post-Inspection:

- Whenever possible, CVM will attempt to base its decision on the investigator's recommendation (i.e., as stated on the 483 or fax received at the Center).

- If CVM does not receive the investigator's fax recommendation soon after the inspection is completed, CVM will notify Rebecca Hackett for follow-up actions.
- For Foreign facilities, upon receipt of the Establishment Inspection Report (EIR) and the firm's responses to FDA 483 observations, the CMC Reviewer will review the firm's responses and make a recommendation on the adequacy of the firm's responses.
- The CMC Reviewer and Team Leader will reach agreement on the adequacy of the firm's responses.
- If the firm has satisfactorily addressed all FDA 483 observations, CVM will release an FMD-145 letter and the EIR to the firm.
- If the firm has not satisfactorily addressed all FDA 483 observations, an incomplete letter will be sent to the firm and additional information will be requested to address outstanding deficiencies. CVM will include a carbon copy (cc) to the appropriate District Office.

ORA/DFI responsibilities are as follows:

Pre-Inspection:

- Upon receipt of an inspection request for the evaluation of a foreign establishment submitted by the CVM/ONADE/Division of Manufacturing Technologies, every effort should be made to have the inspection completed
  - within 100 calendar days of the receipt of CVM's request for ADUFA submissions or,
  - within 190 calendar days of the receipt of CVM's request for AGDUFA submissions.
- 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/DFI should inform CVM within 10 calendar days so that CVM can evaluate the additional information prior to ORA/DFI initiating the inspection. If the facility indicates they are not ready for inspection, ORA/DFI should immediately notify CVM. ORA/DFI should collect the necessary documentation from the firm if they are not ready for the Pre-Approval Inspection and send it to the CVM Pre-Approval Manager.
- If the inspection can not be completed according to the timeline described above, ORA/DFI will contact CVM. ORA/DFI will notify CVM when the inspection is scheduled and include the name, location and telephone number of the Investigator assigned to the inspection. Notification will be via the bi-weekly report listed above under "Mutual Exchange of Information". ORA/DFI will also inform CVM if an assignment has been scheduled as part of a CDER request.

Post-Inspection:

- If CVM has any question(s) or issue(s) with the investigator's recommendation, ORA will respond immediately to facilitate meeting the review timeline of the submission.
- DFI will monitor the completion of the Investigator's inspection reports to assure the EIR is complete within the 30 calendar days of the completion of the inspection trip. The EIR and applicable exhibits will be sent to the CVM Pre-Approval Manager.

Investigator/District Office:

Pre-Inspection:

- The Investigator will prepare as per established procedures for the CVM pre-approval inspection and contact the CVM Pre-Approval Manager or CVM CMC Reviewer before the inspection, if s/he has questions.
- The Investigator will conduct the inspection in accordance with the established CPGM for CVM Preapproval Inspections.

Post Inspection:

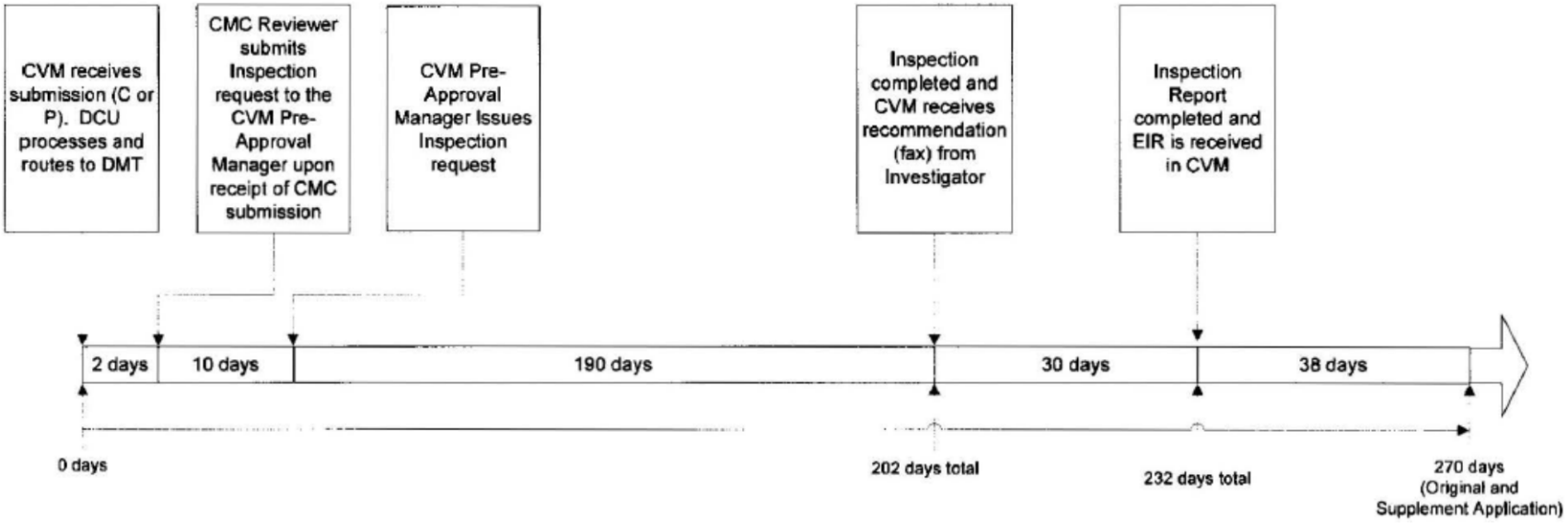
- The Investigator will send a fax summary and FDA-483 if issued, after the inspection has been completed. The fax summary will be sent during the Investigator's planned trip and will be sent to the CVM Pre-Approval Manager within 24 hours of the close out of the inspection regardless of the inspection classification (OAI, VAI, NAI). A second copy will be sent to ORA/ORO/DFI.
- If CVM has any question(s) or issue(s) with the investigator's recommendation, ORA will respond immediately to facilitate meeting the review timeline of the submission.
- All attempts will be made to have the inspection report submitted to CVM within 30 days upon return to the United States. Every effort should be made to meet the 30 day timeframe for EIR completion. If that is not possible, the District PAI Manager and/or Investigator's supervisor should notify the CVM Pre-Approval Manager or follow appropriate District procedures regarding communicating with CVM. DFI should also be notified about the status of the EIR.

This agreement is hereby approved, to be implemented beginning October 1, 2007, as amended March 26, 2010, between the Center for Veterinary Medicine and the Office of Regulatory Affairs.

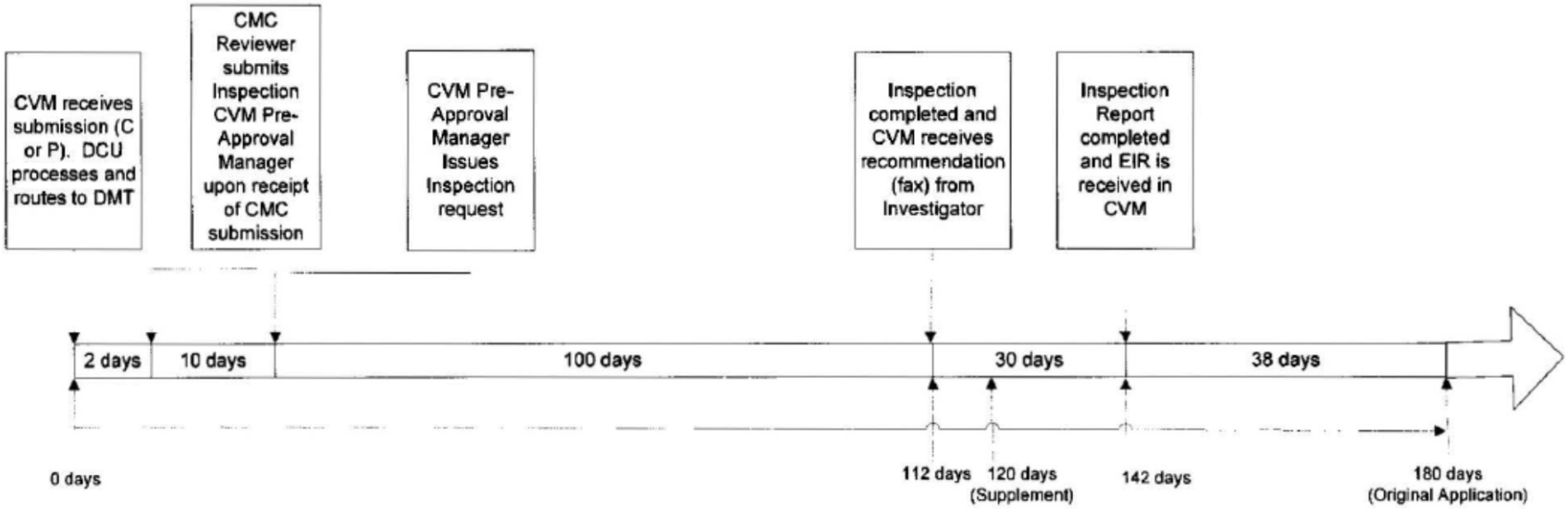
David F. Wardrop, Jr.
Associate Director for Management
Center for Veterinary Medicine
Food and Drug Administration

David K. Elder
Director, Office of Regional Operations
Office of Regulatory Affairs
Food and Drug Administration

Business Process for Foreign AGDUFA Inspections



Business Process for Foreign ADUFA Inspections



Business Process for Domestic ADUFA and AGDUFA Inspections