GENERAL REVIEW AND ENFORCEMENT POLICIES

ESTABLISHING and PROCESSING INVESTIGATIONAL FOOD ADDITIVE FILES

I. Purpose

This guide specifies procedures for establishing and processing investigational food additive (IFA) files. The procedures require action by the Center for Veterinary Medicine (CVM), by companies or individuals (sponsors) investigating the safety and utility of unapproved food additives intended for use in feeds, or by both CVM and sponsors.

II. Establishment of IFA files

A. Action by sponsor: IFA files are intended to facilitate the food additive petition process by ensuring confidential exchange of ideas between CVM and a sponsor while the sponsor investigates the safety and utility of a food additive for its intended use. Sponsors are not required to use IFA files. Those that choose to use IFA files should write to request CVM to establish such files. Each request must be submitted in triplicate and contain the name of the food additive and its intended use or uses. Requests should be addressed to the Director, Division of Animal Feeds, Center for Veterinary Medicine, 7500 Standish Place, HFV-220, Rockville, Maryland 20855

B. Action by CVM:

1. *Director, Division of Animal Feeds*: The Division Director performs a cursory review of the submission to determine whether to grant the request to establish an IFA file, or to treat the request either as a general correspondence (GC) or as a request for informal opinion about the regulatory status of a feed or food additive (DAF).

   The request to establish an IFA file would be granted if the submission contained the following:

a. Protocols for experiments to evaluate the safety and utility of food additives intended for use in feeds.
b. Request for authorization to slaughter investigational animals for food, or to use edible products therefrom.
c. Data from experiments conducted to determine the safety and utility of food additives intended for use in feeds.

The request to establish an IFA file would be denied, and the submission treated as a GC, if the submission consisted of general information or inquiries about an IFA file or a Food Additive Petition (FAP).

The request to establish an IFA file would be denied, and the submission treated as a DAF, if the submission merely requested an opinion about regulatory status, sought advice as to the best approach to take to obtain approval, requested a "do not object" or "regulatory discretion" letter, and/or sought comments about safety.

The Division Director indicates the decision reached on the submission, and specifies the Team and scientist that will review the submission. If the submission qualifies for treatment either as an IFA file or GC, the Director forwards the submission and attachments, if any, to the Document Control Unit (DCU) for action. If the decision is to treat the submission as a DAF, the submission and attachments are forwarded to DAF log-in for action.

2. *Document Control Unit (DCU)*: The DCU date-stamps the submission, records its receipt, cross-checks records to verify that it is an original submission, assigns an IFA file number or a GC number to it and enters pertinent information into the STARS system. For submissions that are determined to qualify for treatment as GC, DCU forwards the submissions to the primary reviewers through Document Tracking (HFV-103). For a submission that is determined to qualify for inclusion in an IFA file, the DCU acts further on the submission as follows depending on the contents of the submission:

a. If the submission only contains a request for establishment of an IFA file, DCU drafts a letter (form letter # 1) that CVM would use to acknowledge CVM's receipt of the sponsor's request. The letter of acknowledgement should also inform the sponsor that an IFA file has been opened, provide sponsor with the appropriate IFA file number, include general information about food additives intended for investigational use by qualified experts, and specify the responsibilities of sponsors of such food additives. The draft letter is forwarded to the Division Director for comments and concurrence. If the Division Director concurs, DCU sends the letter to the sponsor and inserts a copy in the newly established IFA file. The DCU also sends copies of the letter to the Division Director, the Team Leader, and the scientist (primary reviewer) that is designated as being primarily responsible for reviewing submissions to the file.

b. If the submission contains a request to review data, in addition to sponsor's request for CVM to establish an IFA file, DCU writes a letter (form letter # 2) to the sponsor to acknowledge CVM's receipt of sponsor's requests. The letter of acknowledgement should inform the sponsor that an IFA file has been opened as requested. It should also provide the sponsor with the appropriate IFA file number, include general information about food additives intended for investigational use by qualified experts, and specify the responsibilities of sponsors of such food additives. In addition, the letter should indicate that the submission has been forwarded to an appropriate scientist for review. DCU inserts a copy of the letter of acknowledgement in the newly established IFA file and forwards the file to the primary reviewer through the Division Director, and Team Leader.

3. *DAF log-in*: For a submission that is determined to qualify for treatment as a DAF, the submission is handled like other DAFs and forwarded to a primary reviewer through the DAF-Tracking System, HFV-220.

III. Processing of IFA Files

The contents of an IFA file determine the manner in which the file is processed. The file could contain information about one or more of the sections specified for food additive petitions in 21 CFR 571.1, including the chemical composition of the food additive, its manufacture, utility, and safety to humans, target animals, and the environment. That information could be either protocols for experiments to be conducted (including requests to slaughter experimental animals for food), or data collected from experiments already conducted.

A. Action by CVM:

1. *Primary Reviewer*: The primary reviewer conducts a quick overview of the IFA file to determine if a consulting review is needed. If a primary reviewer decides to review all or portions of a submission, the reviewer evaluates experimental data contained in the submission as he/she would evaluate data submitted in support of an FAP. Similarly, the primary reviewer evaluates experimental protocols to determine whether or not experiments that are conducted using the protocols would yield data that can satisfactorily be used to support an FAP.

   If consulting reviews are needed, copies of the submission should be forwarded to appropriate CVM scientists through Document Tracking (HFV-103). This should be accomplished by the primary reviewer within two working days of receipt of the IFA file. Examples of information forwarded for consulting reviews include experimental protocols, or data about or involving:

   a. Statistics; review conducted by ONADE's Biometrics Team (HFV-124).

b. Human Food Safety; review conducted by ONADE's Toxicology (HFV-153) and/or Residue Chemistry (HFV-152) Teams. The information forwarded for review may include requests for authorization to slaughter investigational animals for food or to use edible products from the investigational animals.

c. Manufacturing Chemistry, and Target Animal Safety; reviews conducted by the Feed Safety Team (HFV-222), Division of Animal Feeds.

d. Environmental Impact; review conducted by Office of the Director, Office of Surveillance and Compliance (HFV-200).

After the return of consulting reviews, the primary reviewer identifies and collates information that the consulting reviewers want to transmit to the sponsor, and drafts a letter accordingly. The letter should be drafted for signature by the Division Director, if the letter is meant to point out deficiencies in the data or protocol, or to inform sponsor that the FDA finds the sponsor's protocol or data to be satisfactory. Letters that are meant to authorize (or refuse to authorize) the slaughter of investigational animals for food, or the use of edible products therefrom, should be drafted for signature by the Director, Office of Surveillance and Compliance.

Letters prepared for the Division Director's signature should be forwarded through the primary reviewer's Team Leader to the Division Director for comments and approval. Letters prepared for the Office Director's signature should be forwarded through the primary reviewer's Team Leader and Division Director to the Office Director for comments and approval. There are no legally specified time frames for the review of an IFA file. However, the Division strives to have the primary reviewer complete work on the draft of the pertinent letter(s) within 160 days.

2. *Consulting Reviewer*: The consulting reviewer evaluates experimental data contained in the submission as he/she would evaluate data submitted in support of an FAP. Experimental protocols are also evaluated to determine whether or not experiments that are conducted using the protocols would yield data that can satisfactorily be used to support an FAP.

The result of the review should include a section clearly stating the information that the consulting reviewer wants transmitted to the sponsor. The result should be passed through the consulting reviewer's Team Leader and Division Director for concurrence before it is forwarded to the primary reviewer. There are no legally specified time frames for the review of an IFA file. However, the consulting Division should strive to have the consulting reviewer complete work on the draft of the pertinent letter(s) within 120 days.

3. *Team Leader*:

   a. Reviews and evaluates the conclusions of all reviewers.

   b. Checks the materials submitted for completeness, accuracy, and conformance with regulations and policy.

   c. Concurs with the issuance of letter(s) as drafted or returns the entire package to the primary reviewer for discussion or revision.

   d. Forwards the entire package to the Division Director after all outstanding issues have been resolved and/or revisions have been made; initials the file copies of letters.

4. *Division Director*:

   a. Reviews and evaluates the conclusions of the reviewers and Team Leader.

   b. Concurs with the issuance of the letter(s) as drafted or returns the entire package to the Team Leader for discussion or revision.

   c. Signs and initials the original and file copies of the letters intended to be signed by the Division Director.

   d. Forwards letter authorizing, or refusing to authorize, slaughter for signature by the Director, Office of Surveillance and Compliance.

5. *Division Secretary*:

    a. Prepares the final versions of letters for signature and initialing.

    b. Circulates the final letter for signature and copies for initialing.

6. *HFV-226*:

    a. Distributes copies of letters.

    b. Returns IFA file to the DCU (HFV-199) for filing.

General

Even though data submitted to IFA files are evaluated as one would evaluate those submitted in support of an FAP, there are important differences in how the two are processed. Unlike an FAP whose filing must be publicly announced in the Federal Register, there are no requirements for FDA to acknowledge the existence of, or announce the establishment of an IFA file. An IFA file and its contents are confidential and not available through Freedom of Information.

Also unlike an FAP, an IFA file is not required to address all of the requirements specified in 21 CFR 571.1 for an FAP before the file can be considered for review by FDA. Thus, while an FAP is required to concurrently address issues such as chemical composition, manufacturing chemistry, human safety, target animal safety, utility, and impact on the environment, an IFA file can address one, all, or a combination of any of those issues. In addition, there are no legally specified time frames for the review of an IFA file as there are for the review of an FAP.

Finally, unlike an FAP whose approval is announced in the Federal Register and usually results in amendment(s) to existing regulations, information about favorable FDA action on an IFA file is shared only with the sponsor. Sponsors who want to parlay such favorable FDA actions into food additive regulations must file FAPs.