#260

Type VII Veterinary Master File for Research and Development and Risk Reviews

Guidance for Industry

Draft Guidance

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Table of Contents

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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance for industry (GFI) provides information regarding the use of Type VII Veterinary Master Files (Type VII VMFs) for research and development and risk review.[1] This guidance also describes the circumstances under which developers ("you") should open a Type VII VMF.[2] The scope of this guidance is limited to the use of Type VII VMFs for research and development and risk review requests. There are other potential uses of Type VII VMFs not addressed in this document.

The use of a Type VII VMF as described in this draft guidance is appropriate for information related to research and development of animal cells, tissues, and cell- and tissue-based products (ACTPs), gene therapies[3], and heritable intentional genomic alterations (IGAs in animals), and for risk review of ACTPs and IGAs in animals. For these types of novel products and rapidly evolving technologies, there may be unique regulatory considerations, concerning different types of issues, that call for interactions with CVM at an earlier stage than would take place with traditional products that CVM regulates. CVM believes it is important to incentivize these interactions. As described in this guidance, developers may open a Type VII VMF to cover these interactions with CVM.

This GFI concerns two circumstances where you should open a Type VII VMF instead of an investigational file:

- First, you should open and maintain a suitable Type VII VMF if your product falls within the categories described above and is used for research and development as defined in this guidance. Although the requirements for investigational products apply (21 CFR 511.1), a VMF provides an alternative process for sharing information with FDA. We

[1] VMFs are described at https://www.fda.gov/animal-veterinary/development-approval-process/veterinary-master-files. GFIs concerning other VMFs, i.e., Types I-VI, are not relevant to Type VII.

[2] For this GFI, the term developer includes sponsors, researchers, or any other individuals interacting with CVM through the Type VII VMF.

[3] For the purposes of this document, gene therapy products modify or manipulate the expression of a gene or alter the biological properties of living cells by introducing a new or modified gene to treat a disease.

will determine if you meet the circumstances for opening a VMF on a case-by-case basis with consideration of factors such as: (1) whether your research involves novel or rapidly evolving science or technologies; (2) whether you have submitted the appropriate study information; and (3) whether your studies have progressed to a point where you are prepared for binding product development discussions with CVM, such as a presubmission conference, to pursue approval of a defined product. We recommend that you contact CVM to determine if a Type VII VMF is appropriate for interactions with CVM concerning the research and development of your product.

- Second, we would not expect you to establish an investigational file but instead open a Type VII VMF where you are requesting a risk review and determination of whether FDA would find it appropriate to exercise enforcement discretion over approval requirements for your product.[4] FDA will make such determinations on a case-by-case basis after considering data and information and determining whether we understand the product's risks and we have no safety concerns at that time.

The benefits of the Type VII VMF include: (1) confidential exchange of information with FDA that is not subject to user fees; (2) an opportunity for increased communication with FDA during early stages of product development; and (3) a process for reporting research studies outside of an investigational file.

This guidance also describes when a Type VII VMF is not appropriate and when developers should open an investigational file.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Terminology

A. Type VII Veterinary Master File

A Type VII VMF is a file that can receive submissions to CVM that may contain confidential data and information related to unique regulatory considerations such as research and development of an ACTP, IGA in an animal, or gene therapy, or a risk review for an ACTP or IGA in an animal, where the information submitted is generally not intended to support product approval.

[4] GFI #187A, "Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach," (May 2024); GFI #218, "Cell-Based Products for Animal Use," (June 2015). In the case of IGAs, risk review is described as a Category 2 determination in GFI #187A.

B. Research and Development (R&D)

R&D as used in this guidance refers to the early stages of product development that typically take place prior to determining the precise product and indication. R&D includes the investigational use of a product under 21 CFR part 511. FDA jurisdiction over investigational products does not depend on whether the R&D activities ultimately result in development of a product intended for marketing.

R&D may be conducted by developers, including academic institutions and government agencies. R&D interactions with CVM may relate to scientific information regarding a novel product, challenges associated with product development, investigational use of a novel product including discovery and clinical proof-of-concept studies, reporting of adverse events, or exchange of other information intended to facilitate research and development. R&D interactions may include interactions with FDA relating to issues that impact human or animal health, as well as interactions that help define the pathway to approval.

Once you have addressed early product development considerations, if you are prepared to pursue approval of a defined product (as opposed to risk review), you are no longer in the R&D phase and should establish an investigational file. See section IV. *Investigational Files* of this guidance for information on when to establish an investigational file.

C. Risk Review

Following a review of data, CVM may exercise discretion and not expect submission of an application for approval for certain products. In these cases, we understand the product's risks for the specified intended use, the risks would be appropriately mitigated, and there are no additional safety concerns at that time. In such situations, CVM may, on a case-by-case basis, decide to exercise enforcement discretion for the product. If you believe your product is appropriate for this determination (see GFI #218[5] and GFI #187A), you may initiate a request for a risk review and submit data and information supporting that request to a Type VII VMF.

III. Type VII Veterinary Master File

A. When a Type VII VMF is Appropriate

1. R&D

FDA recommends the use of a Type VII VMF for R&D information when there are unique regulatory considerations for novel or rapidly evolving science or technologies

[5] The risk factors CVM considers for a particular ACTP include the criteria in GFI #218 for Type II products. On a case-by-case basis, CVM may consider risk review appropriate for other ACTPs if the developer can address the risk factors specific to that product to support the determination.

that call for interactions with CVM at an earlier stage than would take place with traditional products. For example:

- The research involves use of novel technologies that have the potential to raise food, environmental, user, or target animal safety concerns.
- The product involves rapidly evolving science and technology:
    - for which it may not be clear how current regulations apply;
    - where early regulatory input is critical to determine the initial product development plan; or
    - where early interaction with CVM is necessary to support the research at a university or other institution.
- The type of technology utilized requires early clinical research in the target animal or in an animal with the naturally occurring disease to assess proof of concept rather than research *in vitro* or in laboratory animal models.

A Type VII VMF is appropriate only where the product is used for *bona fide* scientific investigations conducted as part of discovery or proof-of-concept studies. The investigations should, and may be required to, have the following elements:

- Be conducted under a protocol;
- Be conducted in accordance with appropriate oversight procedures (Institutional Animal Care and Use Committee, Institutional Review Board, etc.);
- Be conducted by qualified investigators;
- Maintain complete records of the investigation;
- Where applicable, for studies in client-owned animals:
    - the studies should be small and support proof-of-concept or discovery only;
    - have owner consent; and
    - if appropriate, include methods to mitigate risk to the owners or the animals; and
- Product development has not progressed to a point where you are prepared to reach an agreement with CVM regarding investigational requirements or are ready to submit data in support of an approval.

For products in R&D, if you are opening a Type VII VMF, you should do so prior to the initiation of R&D as described in this guidance document (e.g., you should open a Type VII VMF prior to production of IGAs in an animal, or initiation of studies in client-owned animals for gene therapy products or ACTPs). If there are multiple entities involved in the development of the product, one entity should assume responsibility for opening the Type VII VMF and any associated interaction with CVM.

2. Risk Review

The use of a Type VII VMF is appropriate for requesting that CVM review data on product risk to make a determination of whether it may exercise discretion and not expect submission of an approval application for a product. Prior to establishing a Type VII VMF for this purpose, you should contact CVM to determine if initiating a request for a risk review is appropriate for your product. If appropriate, you should open the Type VII VMF prior to submitting information to support your request.

If there are multiple entities involved in the development of the product, one of them should assume responsibility for opening the Type VII VMF and any associated interaction with CVM.

B. Confidentiality

CVM has an obligation to protect confidential commercial information (CCI). CCI is valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs (see 21 CFR 20.61(b)). Data and information submitted or divulged to CVM that fall within the CCI definition are not available for public disclosure (21 CFR 20.61(c)), unless otherwise permitted by law (see, e.g., 21 CFR 20.91). This includes any CCI that a developer submits to a Type VII VMF. The existence of a Type VII VMF may be considered CCI if you have not disclosed to the public that the information has been submitted to CVM.

C. User Fees

VMFs do not, by themselves, make the applicant a sponsor that would be subject to user fees. Therefore, our current interpretation is that opening a Type VII VMF alone would not create user fee obligations (see 21 U.S.C. §§ 379j-11, 379j-12).

D. Considerations for Grouping Products Within a Type VII VMF

If you have multiple products using a similar technology platform, then you may group similar products under a single Type VII VMF. A single Type VII VMF may also include products being developed for multiple potential intended uses or for multiple species. If you are developing or researching multiple products, then you should contact CVM to determine which products may be submitted under a single Type VII VMF.

E. Contents of a Type VII VMF

Below is a summary of the type of information that you should provide in your Type VII VMF.[6]

[6] There are templates in eSubmitter to provide you with the appropriate information for each submission type. https://www.fda.gov/industry/fda-esubmitter/cvm-esubmitter-program-animal-drugs-office-new-animal-drug-evaluation.

1. Opening a Type VII VMF

Your request to establish a Type VII VMF should include contact information for the file holder (and any representatives), as well as a project summary and description of the product. You should also provide any information on completed, new, or ongoing studies (see section III. E.2. below), as well as animal husbandry/veterinary practices and any available information on the shipment of the product or animal.

2. Initiating a study in client-owned animals or IGAs in animals

a. Initiating a study in client-owned animals

Information including, but not limited to, the following items should be submitted to CVM prior to initiating each study:

(1) Identity of the investigational product. Examples of the applicable information for this section include:

For ACTPs, the following information: a description of the donor animals and donor eligibility procedures, relationship of the donor and recipient, a description of the cell or tissue source, a description of the storage and shipping conditions for the product, a description of the processing, manipulations, and manufacturing performed on the cells or tissues, a description of the formulation to include concentration of the cell and tissue-based ingredient(s), and the excipients (carrier, diluents, salts, media, etc.) in a single dose.

For gene therapies, the following information: a description of the technology (viral or non-viral based platform), a description of the recombinant DNA construct or applicable construct, identification of any antimicrobial markers contained in the vector, method of administration, intended target cells, potential off-target effects, an assessment of potential shedding for viral vectors, and human user safety mitigation strategies;

(2) Summary of the study to be conducted (purpose, type of study, indication, dose and dosing regimen, route of administration, study design, etc.) or protocol;

(3) Study title and number;

(4) Species;

(5) Owner consent form;

(6) Proposed number of animals to enroll in the study;

(7) Dose to be administered to each animal;

(8) Proposed amount of product delivered to each study site and the proposed date of shipment[7];

(9) Name and address of each investigator(s);

(10) Proposed beginning and ending dates of study conduct for each site;

(11) Record keeping procedures;

(12) All labeling and other pertinent information supplied to the investigators;

(13) Name, address, and transferred obligations to any contract research organization;

(14) Name of research organization(s) participating in the study; and

(15) If recipient animals are a food-producing species, a statement that the edible products from such animals shall not be used for food without prior authorization from FDA.

You should submit an update to the Type VII VMF prior to adding a new site or increasing the proposed number of animals enrolled in the study.

Regardless of the use of a Type VII VMF, FDA generally expects compliance with the requirement that investigational products be clearly labeled as investigational (21 CFR 511.1). If animals with IGAs are being shipped, the shipment should identify the investigational animals and include a statement that edible products of investigational animals must not be used for food without prior authorization from FDA. Appropriate investigational labeling statements include the applicable statements in 21 CFR 511.1 and may include any statements identified in the letter from CVM acknowledging establishment of your Type VII VMF.

Labeling may be attached to, or accompany, the investigational product or animal as appropriate. If the container is too small to accommodate the labeling statements, then the statements should be printed on the carton or other labeling that accompanies the investigational product. Investigational products may only be used for research (21 U.S.C. § 360b(j)). Animals treated with such articles, and any products of such animals, may only be marketed for food use with prior authorization from FDA (21 CFR 511.1(b)(5)).

b. Initiating a study of IGAs in animals

Information including, but not limited to, the following items should be submitted to CVM prior to initiating a study involving the development of animals with IGAs:

(1) Description of the project;

[7] Delivery of an investigational product includes transferring investigational product from a laboratory or manufacturing site to a clinical operation within the same campus.

(2) Description of IGAs in the animal and description of the technology used to introduce these IGAs into the animal's genome;

(3) Description of physical containment and surveillance procedures at the facility used for development of these animals;

(4) Description of animal and waste disposal procedures at the facility;

(5) Description of the animal identification procedures;

(6) Description of shipping procedures if you intend to ship animals, including the proposed number of animals and recipient locations (if known);

(7) Record keeping procedures;

(8) Description of any significant safety hazards and procedures for unintended event reporting (e.g., adverse health events in the target animal, animals inadvertently sold at auction, animals unintentionally entering the food supply, escape from animal facilities, or other scenarios of public health concern); and

(9) If recipient animals are a food-producing species, a statement that the edible products from such animals shall not be used for food without prior authorization from FDA.

All investigational animals and their products that are being shipped must bear labeling that clearly identifies the products as investigational. Appropriate investigational labeling statements include the applicable statements in 21 CFR part 511 and may include any statements identified in the letter from CVM acknowledging establishment of your Type VII VMF.

3. Adverse Event Reporting

If a serious adverse event occurs during the handling or use of your product, you should inform CVM and all investigators immediately and submit to the Type VII VMF information including, but not limited to, the following items:

- Summary of the serious adverse event;
- Medical records or case report forms describing the event;
- Outcome of the event; and
- Mitigation strategies, where applicable.

4. Risk Review

If you are seeking risk review and CVM agrees that a risk review request is appropriate for your product, we will discuss the data and information that should be submitted for us to determine whether CVM understands the product's risks for the specified intended use, the risks are appropriately mitigated, and we have no additional safety concerns at that time.

5. Periodic Reports

The Type VII VMF should be updated periodically. For most products, periodic reports should be submitted on an annual basis. For products with higher potential risk to public or animal health, CVM may recommend that reports be submitted more frequently.

a. Periodic reports for all Type VII VMFs should contain information including, but not limited to, the following items:

(1) Updates to the product description;

(2) Updates on other aspects of product development or changes to previously provided information;

(3) Updates on studies conducted or planned to be conducted;

(4) A list of authorized users (e.g., any investigator who has been granted right of reference to the file);

(5) A summary of all adverse events and other information relevant to the safety of the product; and

(6) A statement that edible products from food-producing species treated with or containing the product, have not entered the food or feed supply OR reference to the submission authorizing such food use.

b. Periodic reports for Type VII VMFs supporting studies should contain information including, but not limited to, the following items:

(1) Updated information regarding completed, ongoing and upcoming studies including:

- A list of ongoing and completed studies including the study title and number
- Number of animals enrolled to date in each study and the number of animals enrolled since the last periodic report
- Proposed number of animals to be enrolled in the next year in each study
- A summary of all adverse events for each study
- If the study is completed, a summary of the study findings
- A list of upcoming studies that may be initiated in the next year;

(2) Updated shipment/delivery information;

(3) For IGAs in an animal, this information should include, but is not limited to, updates regarding:

- Shipping procedures
- Animal carcass and waste disposal procedures
- Intentional genomic alterations under development
- Lines of animals under development
- Animal identification procedures
- Physical and procedural containment
- Number of animals or tissues sent
- Name of the receiving party
- Receiving party contact information and address; and

(4) For all other studies, this information should include, but is not limited to, updates regarding:

- The actual date of product shipment/delivery
- The actual dose administered to each animal
- A current list of investigators and their contact information, including name and address for each shipment/delivery.

Note that delivery of an investigational product includes transferring an investigational product from a laboratory or manufacturing site to a clinical operation within the same campus.

c. Periodic reports for Type VII VMFs supporting risk review:

(1) If CVM has conducted a risk review and decided it intends to exercise enforcement discretion over approval requirements for the product, you should submit product-specific information to CVM as specified in the letter documenting CVM's risk review determination.

(2) For all other Type VII VMFs supporting a risk review, you should submit periodic reports annually and include the information described in this section.

F. Examples of when to Establish a Type VII VMF for R&D and Risk Reviews

Example 1: A company is in the early stages of developing a cell-based product for use in dogs. The company is investigating multiple tissue sources to determine which cell is most appropriate for use in its product. To make this determination, the company plans to conduct a small study in 12 client-owned animals to compare products derived from three different tissue sources. The company intends to seek approval for a product, but the product is not yet defined, and therefore the company is not ready to reach an agreement with CVM regarding investigational requirements related to their product development.

The company should open a Type VII VMF and submit updates to CVM about the project throughout development.

Example 2: A research scientist in a university laboratory has developed a gene therapy to correct a disease condition in companion animals. They intend to conduct a small proof-of-concept study in approximately 10 client-owned dogs. If the study shows promising results, then they intend to pursue approval for use in companion animals. The university should open a Type VII VMF and submit updates to CVM about the project throughout development.

Example 3: A research scientist/veterinarian in a university laboratory develops an IGA in a companion animal. The study is an early proof-of-concept study to evaluate safety and potential effectiveness in two litters of cats. The university should open a Type VII VMF and submit updates to CVM about the project throughout development.

Example 4: A company is in the early stages of developing an IGA in an animal for commercial purposes. The company plans to produce an IGA animal but has not yet decided on the future direction of the project. The company should open a Type VII VMF and submit updates to CVM about the project throughout development.

Example 5: A company is developing an IGA in an animal that is equivalent to naturally occurring mutations and results in the same phenotype as found in conventional animal agriculture and with a history of safe use. The developer has had initial conversations with CVM about their product and, based on CVM's input, intends to request a risk review. The developer should open a Type VII VMF and submit a request for risk review.

Example 6: A company is developing an ACTP that is minimally manipulated, intended for homologous use and not combined with other articles, drugs, or devices. The developer has had initial conversations with CVM about their product and, based on CVM's input, intends to request a risk review. The developer should open a Type VII VMF and submit a request for risk review.

IV. Investigational Files

A. What is an Investigational File?

An investigational file is the file type to which a developer submits investigational data and information intended to support an application for approval (see 21 CFR 511.1).

B. When to Open an Investigational File

If you intend to seek FDA approval of a product, you should open an investigational file when you have completed your proof-of-concept studies and are ready to conduct studies in support of an approval of a specific product. An investigational file should be opened in the following circumstances, among others:

1. You intend to seek approval of the investigational product and are ready for formal interaction with CVM regarding product development (e.g., a presubmission

conference to discuss your product characterization or molecular characterization or your general development plan for safety, effectiveness, and manufacturing). These interactions may include binding agreements on product development, protocol review, and review of data intended to support an application for approval or conditional approval.

2. You intend to pursue an investigational food use authorization for entering investigational animals into the food supply.
3. You intend to pursue approval of the product and are ready to conduct studies in client-owned/producer-owned animals and:
    a. There is a possibility that the study results may serve to support development of an approved product (or may be provided to another entity to support approval of a product); or
    b. The intent of the study(ies) is beyond the scope of discovery or initial proof of concept.

    You should contact CVM if you have questions regarding the correct file type for your investigational activities.

C. User Fees

As noted in GFI #173,[8] you are considered an "animal drug sponsor" if you submit an investigational submission that has not been terminated or otherwise rendered inactive by FDA; therefore, by opening an investigational file you may be subject to user fee obligations (see 21 U.S.C. §§ 379j-11, 379j-12). You may be eligible for a user fee waiver, such as when the fee "would present a significant barrier to innovation" or the product is for a minor use or minor species indication (see 21 U.S.C. 379j-12(d); GFI #170, "Animal Drug User Fees and Fee Waivers and Reductions"[9]).

D. Examples of When to Establish an Investigational File

Example 1: A company is developing a bone-marrow-derived mesenchymal stem cell product for the control of inflammatory bowel disease in dogs. The company intends to get the product approved, has determined the indication, and is currently conducting characterization studies that will describe the marketed product. The company is ready to request a meeting with CVM for a detailed discussion of their product characterization and specific questions impacting the overall development plan. The company should open an investigational file and request a presubmission conference.

Example 2: A researcher in a university laboratory has developed a gene therapy to correct a disease condition in companion animals that mirrors a human disease. The researcher has conducted a proof-of-concept study in a small number of client-owned animals to help

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-173-animal-drug-sponsor-fees-under-animal-drug-user-fee-act-adufa (Feb. 2005).

[9] https://www.fda.gov/media/69918/download (April 2023).

support human approval. The proof-of-concept study showed promising results and the researcher is interested in conducting a study in 50 client-owned animals. The results of the study may be used to support a product approval. Prior to conducting this study, the university should open an investigational file.

Example 3: A company is developing IGAs in an animal to be used as a source of tissues and organs for xenotransplantation. The company has produced animals, generated data and information in support of product characterization and is close to being ready to submit their product characterization technical section to CVM. The company should open an investigational file and request a presubmission conference with CVM prior to submission of their first technical section.

Example 4: A researcher in a university laboratory is developing an IGA in an animal and would like to pursue an investigational food use authorization for entering investigational animals into the food supply. The university should open an investigational file and submit a request for an investigational food use authorization along with supporting data.