SMG 4102

FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM DIRECTIVES

COMBINATION PRODUCTS

INTERCENTER COORDINATION OF REGULATORY ACTIVITIES FOR GENETICALLY ENGINEERED ANIMALS AND THEIR EXPRESSION PRODUCTS

Effective Date: July 21, 2015

1. PURPOSE AND SCOPE

This staff manual guide (SMG) provides procedures for FDA staff engaged in intercenter collaboration involving the review of genetically engineered (GE) animals and their expression products. In particular, FDA staff should use this SMG when animals containing articles produced by modern biotechnology that CVM regulates under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (e.g., GE animals) produce substances that, in turn, other agency Centers regulate under provisions of the FD&C Act, and the Public Health Service Act (PHS Act). The overarching purpose of this SMG is to ensure efficient and non-redundant review of the article in the GE animal and its expression product(s) by the Centers having regulatory authority. Each Center will make regulatory decisions, including issuing approvals, separately based on data and information submitted to each application or license.

Background

On January 15, 2009, FDA issued "Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs[1]" (GFI 187). In this Guidance, FDA defines GE animals as those animals modified by rDNA techniques, including the entire lineage of animals that contain the modification. The term GE animal can refer to both animals with heritable rDNA constructs and animals with non-heritable rDNA constructs.

[1] Although the article regulated by CVM is actually the rDNA construct in the GE animal, for ease of reference, we will refer to this as the regulation of the GE animal.

The rDNA construct in a GE animal intended to affect the structure or function of the body of the GE animal meets the definition of a drug in the FD&C Act. Generally, section 512(a)(1) of the Act (21 U.S.C. 360b(a)(1)) requires that a new animal drug be the subject of an approved new animal drug application (NADA) based on a demonstration that it is safe and effective for its intended use unless it is for investigational use and conforms to investigational requirements.[2] CVM is responsible for reviewing all NADAs, including those for rDNA constructs in GE animals.[3]

While GE animals are subject to regulation under the new animal drug provisions of the FD&C Act, these animals can be used to produce products that are also subject to separate FDA regulation under the FD&C Act or the PHS Act.

Because of the interrelationship between FDA regulation of the new animal drug, for which CVM has responsibility ("the first regulated article"), and the related expression products that the GE animals may produce, for which CBER, CDER, CDRH, or CFSAN may have responsibility ("the second regulated article"), it is critical that there is an effective pathway for communication and coordination between or among the responsible Centers.

This SMG will help ensure that all Centers engage their counterparts in the review process for products manufactured using GE animals using established intercenter collaboration procedures rather than ad hoc processes that are unique to the individual Centers. This will allow for an efficient and non-redundant review of the regulated articles. For the purposes of this SMG, the default intercenter review model will be the collaborative review (see Definitions). There will be at least two separate approvals[4] for the two regulated articles, issued individually by the relevant Center.

Intercenter reviews for GE animals and related products may, on occasion, require a mechanism to address differences in scientific opinion or regulatory interpretation that involve input from more than one Center. Dispute resolution should proceed in accordance with SMG 9010.2 *Cross-Center Dispute Resolution at the FDA*. Differences of scientific opinion are expected to be resolved in a manner that limits delays on regulatory action.

[2] NADAs intended for use in minor species or for a minor use in a major species may be conditionally approved or indexed, however, GE animals are not eligible for these provisions. 21 U.S.C. §§ 360ccc, 360ccc-1.
[3] Although all GE animals that contain a new animal drug are subject to premarket approval requirements, in certain circumstances, based on the risk(s) the animals pose, CVM intends to exercise enforcement.
[4] We are using the term "approval" here although if the second product is a device it might be subject to a 510(k) clearance or if it is a CFSAN-regulated product there may be regulatory decisions separate from an approval.

2. POLICY

The FDA will follow the intercenter coordination processes prescribed in this Guide for regulatory activities of genetically engineered animals and their expression products.

3. DEFINITIONS

Collaborative Review

A review activity in which reviewers in two or more Centers each have primary review responsibility and decision-making authority for a specified component of the two applications to the two Centers (e.g., rDNA construct and related biologic application). Each Center will make regulatory and scientific decisions for the portion of the review assigned to them according to their existing policies and authorities. This is the default review type for the purposes of this SMG and will allow for iterative review and discussions across the two Centers.

Consultative Review

In some cases (e.g., when the GE animal only exists overseas outside CVM jurisdiction), only the human product center will make an approval decision, and may contact CVM for a consultative review. In this instance, the reviewer(s) in the human product Center should request consultative advice from reviewer(s) in CVM on specific questions or issues raised in the review of a submission. The requesting center will use the consultative review in making appropriate regulatory/scientific decisions.

Point of Contact for Each Center's Review Team

This individual will generally be the regulatory project manager (e.g., in CDER or CBER) or the lead reviewer (e.g., in CVM and CDRH), or Consumer Safety Officer (e.g., CFSAN) but may be any Agency individual who conducts or is otherwise responsible for the review of the submission or request, e.g., branch/lab chief, division director, etc.

4. RESPONSIBILITIES

All Center review teams will work together at the outset of the review process to determine if a process other than collaborative review is required at the outset of the review process.

Each Center will adhere to the established plan for ongoing communication.

Each Center will make its own decision regarding the article over which it has regulatory authority, and communicate those decisions to the other Center.

5. PROCEDURES

A. General overview

Goal: To ensure Centers with regulatory authority engage in efficient and non-redundant review of the article in the GE animal and its expression product(s), this document establishes a pathway for coordination and communication between or among responsible Centers.

CVM Contacted First: When CVM learns that a sponsor intends to introduce an rDNA construct into an animal in order to produce drugs, food, devices, or cosmetics, either as the result of a sponsor opening an INAD file, or via other means, CVM will notify the Point of Contact for all the human product Centers as soon as possible so that they can determine which Center/Office has the jurisdictional authority to regulate the relevant product.

Human Product Center Contacted First: When CBER, CDER, CDRH, or CFSAN learns that a product they regulate has been produced in whole or in part by a GE animal, that Center will notify CVM as soon as possible.

Points of Contact: Each Center will identify a primary and alternate point of contact, per their existing internal processes, and post these staff members' contact information on the Center's internal website. The Centers should update this information as needed. This primary contact may or may not be the same person who is identified as the review point of contact once the coordination of review activities commences.

Communications Among Centers: The Centers will work out on an ad hoc basis document control processes for submission sharing to meet the statutory requirements that govern submissions to some Centers. The Centers will establish a plan for ongoing communication, with milestones and statutory timelines for the respective submissions clearly identified.

Approval/Regulatory Decisions: Each Center will make its own decision regarding the article over which it has regulatory authority, and communicate those decisions to the other Center.

B. Procedures

The collaborative review process is expected to be the default process for coordination of review activities, except in the instance when a GE animal only exists overseas i.e. outside U.S. jurisdiction. These procedures will be the same for CVM and the second product Center.

1. The Center that originates the request for collaborative review, will:

a. Assign a point of contact for all communications.

b. Notify the appropriate review or project management personnel in the collaborating Center when a sponsor requests a pre-submission conference, or when the Center receives a submission, whichever comes first.

c. Send review requests and goal timelines for the coordinated review to appropriate personnel in collaborating Center(s).

d. Provide all necessary and requested data and information to review.

e. Establish a plan for ongoing communication between the Centers, including appropriate review timelines, milestones, and deadlines. Notify the collaborating Center personnel of key internal and sponsor meeting dates (if applicable) for which the Center's presence is required. Provide a meeting agenda with topics for discussion clearly identified.

f. Coordinate the intercenter exchange of reviews and any other pertinent regulatory information and decisional documents.

g. Notify collaborating Center of the final recommendations/comments to be conveyed to the sponsor.

h. Document reviews and relevant materials in the Center's document archiving system.

2. The Center receiving the collaborating request will:

a. Assign a point of contact for all communications regarding the coordinated review.

b. Contact the request originator by telephone or e-mail immediately if a request or any aspect of the request (e.g., due date) is believed to be incomplete, inappropriate, or in error.

c. Attend and participate in key internal and sponsor meetings (if applicable) as requested by the originating Center.

d. Notify the request originator promptly if the review will be delayed, and either negotiate a new due date through the supervisory chains of both Centers, or reassign the request so that the previously established due date can be met.

e. Perform a complete review of those areas specified by the request originator in a timely manner or within specifically mandated review timelines.

f. Assure that all reviews are in electronic format and include a brief summary of the portion of the submission that was reviewed, recommendations for action (as necessary), and letter-ready comments and/or any requests for information to be conveyed to the sponsor.

g. Obtain the appropriate clearances/sign-off per Center/submission requirements and forward the review documentation to the request originator.

h. Document reviews and relevant materials in the Center's document archiving system, including a cross-reference to any other Centers that may have been involved in decision-making.

In the case of a consultative review, the Center requesting a consultative review will contact the Center with the relevant expertise and request a consultative review from the Center on specific questions or issues raised in the review of a submission. The Center providing the consultative review will perform a complete review of those areas specified by the Center requesting a consultative review and do so within specifically mandated review timelines. The Centers will work together to establish and adhere to a plan for information sharing and on-going communication.

C. Examples

1. Sponsor approaches CVM and human product Center at the same time:

Sponsor files an INAD with CVM for a GE animal, and an IND with CDER for a monoclonal antibody produced by that GE animal. Sponsor has indicated they will provide detailed information on the rDNA construct and the generation of the GE animal lineage and associated GE animal health data to CVM, and CDER may cross-reference these data as appropriate to their review of the monoclonal antibody. CVM and CDER will identify the individual points of contact in each Center for coordination of submission-sharing, and review activities. This may include coordination for joint sponsor meetings where possible, access to each other's electronic databases where present, and internal meetings to discuss review of submitted data, as required.

2. Sponsor approaches the human product Center only:

Sponsor approaches CBER for a pre-IND meeting, for a xenotransplantation product derived from GE minipigs. Once CBER receives this meeting request, they will remind the Sponsor of their regulatory responsibilities regarding the

GE animal and advise them to open an INAD file with CVM. CBER will also contact CVM and invite them to participate in the pre-IND meeting. Once the sponsor has established an IND/INAD, CVM and CBER will collaborate and coordinate their review activities.

3. Sponsor maintains GE animals outside the US and approaches the human product Center:

   Sponsor produces and maintains a GE pig colony outside the U.S. and files an IDE with CDRH for a device derived from these GE pigs, for marketing in the US. CVM will consult for CDRH, and provide expertise, as required, in the review of GE animal data submissions such as evaluation of GE animal health, clinical observations, etc.

6. REFERENCES

- Guidance for Industry 187: *Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs*. http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm113903.pdf

- SMG 9010.2 *Cross-Center Dispute Resolution at the FDA*

7. EFFECTIVE DATE

The effective date of this guide is July 21, 2015.

8. Document History – SMG 4102, Intercenter Coordination of Regulatory Activities for Genetically Engineered Animals and Their Expression Products

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	06/24/2015	N/a	CVM/OD/ ABIG	Bernadette M. Dunham, D.V.M., Ph.D., Director, CVM