CHAPTER 71 – PRE-APPROVAL EVALUATION OF ANIMAL BIOTECHNOLOGY PRODUCTS REVIEWED BY THE CENTER FOR VETERINARY MEDICINE'S DIVISION OF BIOTECHNOLOGY

SUBJECT:	IMPLEMENTATION DATE:
Animal biotechnology products: Intentional genomic alterations in animals and animal cells, tissues, and cell- and tissue-based products pre-approval inspections for the Division of Biotechnology (DB)/Center for Veterinary Medicine (CVM) Approval Applications (NADA) Investigational files (INAD)	01/28/2026

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	68870 - Pre-Approval Animal Cells, Tissues, And Cell- And Tissue-Based Products (ACTPs) Inspections – CVM Related Biological Products 68870A - Pre-Approval Intentional Genomic Alterations (IGAs) Inspections - CVM Related Biological Products

Remarks:

1. Office of Inspections and Investigations (OII) programs/divisions should use this compliance program (CP) for pre-approval inspections (PAIs) of manufacturing or production facilities in support of pending DB applications.
2. Under this CP, OII is responsible for reporting inspectional results.
3. When PAI coverage is concurrent with or expanded to provide coverage of other inspection programs, follow the appropriate CPs for inspection and reporting.

FIELD REPORTING REQUIREMENTS:

1. CVM-OII PAI requests[1]

The CVM Pre-Approval Facilities Assessment Program (CPAFAP), in collaboration with CVM's DB, issues a PAI request to OII via creating an eNSpect activity and issuing a notification email (oiiobibiologicsinspectionpoc@fda.hhs.gov) (see Part II below). OII responds to the request via email[2] (cvmpai@fda.hhs.gov) within 10 business days.

[1] In this document, the synonymous terms *facility*, *firm*, *establishment, site,* and *person* cover entities subject to FDA manufacturing regulations and statutory authority. These terms may be used in place of *manufacturer* depending on context.

[2] In this document, CPAFAP's email refers to cvmpai@fda.hhs.gov unless stated otherwise.

2. Instructions for firm responses

The investigator instructs the firm's management to submit Form FDA 483 responses to CVM, with a copy to the lead investigator.

OII creates a CMS work activity that includes the firm responses and emails CPAFAP.[2]

3. Communication of Inspectional Results

The investigator communicates PAI concerns within two business days of closing the inspection and provides Form FDA 483 (if issued) with an initial field recommendation to the OII manager and CPAFAP.[2] The investigator completes the establishment inspection report (EIR), including coversheet, attachments, and exhibits, in eNSpect within established OII time frames.

OII emails CPAFAP[2] when the EIR is available in FDA's electronic repository systems or provides CPAFAP with available information about the inspection if the EIR is unlikely to be completed by the CVM application due date as outlined in the PAI request.

4. Facility recommendations

OII emails the appropriate initial field recommendation to CPAFAP[2] as soon as possible, but no later than two business days, after the close of the inspection. Then, the final field recommendation should be emailed to CPAFAP and entered in eNSpect before the CVM due date, if possible. OII summarizes the rationale for the recommendation as needed. OII recommends **approve** when none of the criteria for withholding approval apply (see Part V).

OII recommends **withhold** when there are significant findings (see Part V) or when there is information that, in OII's judgment, warrants further evaluation by CVM before recommending approval of the application. When OII finds that the "establishment is not ready for inspection" or "establishment is not doing the function that it is responsible for as stated in the application," then OII submits written documentation either obtained by the investigator or received from a responsible official at the establishment to support a **withhold** recommendation.

For a **withhold** recommendation, OII emails CPAFAP[2] as soon as possible:

- with their decision to make a **withhold** recommendation along with Form FDA 483; and
- if follow-up activities have changed the **withhold** recommendation (i.e., the Form FDA 483 response is found adequate or a follow-up PAI is performed).

5. Facility alerts

If marketed products are also covered during overall Current Good Manufacturing Practice (CGMP) surveillance coverage and the surveillance part of the inspection is likely to result in an Official Action Indicated (OAI) status, then email a potential OAI (pOAI) alert to CPAFAP[2] and CVM Compliance (CVMAnimalDrugGMP@fda.hhs.gov) as soon as practical.

Do not send a pOAI alert email solely because of violative PAI coverage under CP 7368.870 during which no marketed product was covered.

6. Firm profile class code updates

In general, OII manages the status (acceptable or unacceptable) of profile class codes covered during establishment inspections in accordance with Exhibit 5-14.6.3, Pre-Approval Inspections, in the Investigations Operations Manual (IOM).

- Profiles are **not updated** for product-specific PAIs (no CGMP surveillance inspection conducted) unless the PAI covers a new profile.

- For a PAI of an establishment with a new profile, the new profile can be added and made acceptable if the inspection is classified as No Action Indicated (NAI) or Voluntary Action Indicated (VAI) and an **approve** recommendation for the application is made.

- If the initial PAI of a new profile results in a **withhold** recommendation (the establishment inspection is classified as OAI), OII does not enter profile information. This ensures the product cannot be marketed in the United States until a follow-up inspection verifies implementation of appropriate corrective actions or until corrections are substantially verified through other appropriate means.

Final classification of withhold or surveillance OAI recommendations is determined by CPAFAP after review of the firm's 483 responses in the context of the EIR.

7. Sample-related reporting requirements

Office of the Chief Scientist (OCS)/Office of Analytical and Regulatory Laboratories (OARL) perform testing on samples collected. If an official sample is collected at an establishment, the investigator should use the appropriate product/assignment codes (PACs) for method verification or profile analyses.

OCS/OARL maintains completed analytical worksheets. The analyzing laboratory forwards a copy of the laboratory results to the OII office that requested or collected samples.

CONTENTS

PART I—BACKGROUND

Animal biotechnology is a rapidly growing area of product development. CVM is committed to using a science- and risk-based regulatory framework to further the advancement of emerging technologies for the development of safe and effective products, while ensuring consumer confidence. This compliance program (CP) is applicable to the following animal biotechnology product types:

- intentional genomic alterations (IGAs) in animals; and
- animal cells, tissues, and cell- and tissue-based products (ACTPs).

This CP only applies to manufacturing and production facilities of animal biotechnology products reviewed by CVM's DB. It does not apply to all biotechnology products (e.g., it does not apply to manufacturers of enzymes, growth factors, monoclonal antibodies) or to facilities that do not directly support animal biotechnology production and may be inspected under other programs (e.g., contract testing facilities). PAIs for IGAs in animals and ACTPs are conducted under the authority of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This CP is specific to inspections of establishments that produce IGAs in animals and ACTPs. It addresses the unique attributes associated with development and production of these products. Activities under this CP apply to investigational files (INADs) and approval applications (NADAs).

1. Background on IGAs in animals

IGAs in animals are changes to an animal's genomic DNA produced using modern molecular technologies, which may include random or targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions. The IGA can be introduced into the animal's genome using recombinant DNA, genome editing, or other technologies. IGAs in animals have many different intended uses, including applications in human health (e.g., reduced allergenicity; "biopharm" animals that produce substances [generally in their milk or eggs] for use in the production of human therapeutics; animals used as a source of organs for xenotransplantation; in improved animal health, well-being, and husbandry practices (e.g., disease resistance, heat tolerance), and in enhanced production and food quality (e.g., faster growth, feed efficiency, nutritional benefits). An example of production of an IGA in animals begins with introducing the alteration into a single animal (i.e., the founder animal), and then propagating this change through conventional breeding to create more animals with the IGA (i.e., animal lineage). The approval process for IGAs in animals includes characterization of both the alteration itself and the characterization of the animal lineage.

CVM's current thinking on the regulation of IGAs in animals is described in Guidance for Industry (GFI) #187A "Heritable Intentional Genomic Alterations in Animals: Risk Based Approach" and GFI #187B "Heritable Intentional Genomic Alterations in Animals: The Approval Process". GFI #187A describes FDA's risk-based regulatory approach to the oversight of heritable IGAs in animals and GFI #187B describes how the approval process applies to heritable IGAs in animals including how developers and producers of IGAs in animals can assemble data and information in support of their approval application submission(s) to CVM.

IGAs in animals have specific considerations. First, the regulated article (i.e., the IGA) is a change introduced into the animal's genome, involving different animal production techniques (e.g., mixture

of molecular techniques and traditional breeding or assisted reproduction) and different specifications (e.g., genotypic durability, phenotypic durability). Second, risk mitigation factors often include animal containment measures (e.g., procedural containment, physical containment), which may be a key focus of inspection for these products. Third, animal operations are typically a key aspect for these products. PAIs should focus on the key systems unique to the intended use of the IGA in the animal, including the quality; laboratory; facilities and equipment; and animal operation systems. Documentation, including standard operating procedures (SOPs), records, and staff training, is critical to, and forms the framework for, all activities related to each system; as such, these documents should adequately address risks at all stages of the product lifecycle. The intended use of the IGA in the animal will direct the inspectional focus and approach.

2. Background on ACTPs

ACTPs are articles containing, consisting of, or derived from cells or tissues that are intended for implantation, transplantation, infusion, transfer, or other means of administration to an animal recipient. Examples include animal stem cells, differentiated cells, and tissues (e.g., blood, platelet-rich plasma, and amnion).

CVM evaluates ACTPs using a risk-based approach that examines the risks and benefits of the product, as well as the likelihood of harm to other populations that may be affected by the treated animal (e.g., transmission of disease that may spread beyond the recipient animal). CVM's evaluation of the safety, effectiveness, and manufacturing quality of ACTPs is conducted on a case-by-case basis because the potential hazards and risks are likely to be unique to each ACTP. GFI #218 "Cell-Based Products for Animal Use" describes CVM's statutory and regulatory authority and risk-based approach to the regulation of ACTPs.

The manufacture of ACTPs presents unique considerations for complying with regulatory CGMP, especially as it relates to early handling of source materials (e.g., good tissue practice) not covered under 21 CFR 210 and 211. GFI #253 "Current Good Manufacturing Practice for Animal Cells, Tissues, and Cell- and Tissue-Based Products" provides guidance for how establishments that manufacture ACTPs can meet statutory and applicable regulatory CGMP.[3] Some examples of these unique considerations relate to early processing and recovery of source materials, donor eligibility, and other product-specific considerations for handling, yield, and product variability. GFI # 254 "Donor Eligibility for Animal Cells, Tissues, and Cell- and Tissue-Based Products" provides guidance on appropriate methods and considerations for determining donor eligibility for ACTPs to comply with CGMP. Persons performing operations required to produce an ACTP, such as recovery, processing, testing, storage, labeling, or distribution are considered manufacturers. Guidelines and guidances for the production of human cell, tissue, and cell- and tissue-based products (HCT/Ps) may be applicable for the production of ACTPs, but there may be species-specific considerations that impact risk (e.g., location of recovery establishment in a field/barn, donor eligibility considerations).

[3] There are both statutory and regulatory requirements for CGMP. The CGMP statutory requirements are found in section 501(a)(2)(B) of the FD&C Act. The CGMP regulatory requirements are found in Title 21 of the Code of Federal Regulations, parts 210 and 211 (21 CFR parts 210 and 211).

PART II—IMPLEMENTATION

1. Scope

PAIs support the assessment of marketing applications by ensuring that any establishment named, or referenced, in support of an application can perform the proposed operations in conformance with CGMP requirements and that data submitted in the application are accurate and complete. The scope of activities covered in animal biotechnology PAIs may include unique processes and systems. These specific considerations for both IGAs in animals and ACTPs are outlined below.

A. Pre-approval facility evaluations for animal biotechnology products

For animal biotechnology products undergoing pre-approval review, CVM initiates the pre-approval inspection (PAI) by assembling a facilities evaluation team (FET) to perform the facilities quality assessment. CVM considers information about each facility named in an approval application, the proposed product, and other information in the application to determine whether a PAI is needed before the application can be approved from a quality perspective. The FET is comprised of the Office of New Animal Product Evaluation (ONAPE) review team,[4] CPAFAP members, and the associated branch chief(s), as appropriate. In performing the facilities quality assessment, the FET determines the need for PAIs of facilities listed in the application by assessing:

- product risk and manufacturing and/or production (process and facility) risks; and
- the accuracy and reliability of the information provided in the application.

The assessment of the accuracy and integrity of the information from a site, in support of the application, is an important factor in determining the need for a PAI. A PAI can be triggered when there is a need to confirm the accuracy and reliability of the quality data, which is critical in determining the safety, effectiveness, and quality of the product. Additionally, a PAI can be triggered to confirm that the facility's operations match those proposed in the application. In conclusion, the FET determines the need for PAIs based on the cumulative risk assessment of the application. Alternative tools may be used in lieu of or in advance of a PAI (see Attachment A).

For animal biotechnology products, the facilities that generate the product, as well as additional facilities that support the production, may be subject to evaluation.

- IGAs: The laboratory that introduces the alteration may be considered for inspection as well as any facilities that play a role in durability testing, morbidity/mortality monitoring or other activities described in the durability plan. In general, once the lineage has been established and is propagated via natural breeding, any facility that is solely used to naturally breed animals with IGAs (e.g., commercial farms), and that is not included in the durability plan activities, is not typically subject to inspection.

[4] The ONAPE review team consists of subject matter experts across ONAPE who are responsible for different aspects of the approval review.

- ACTPs: Establishments that perform steps in the manufacture of an ACTP are classified as Category A or Category B establishments. Category A establishments are establishments that manufacture finished ACTPs, other than Type II[5] finished ACTPs. Category B establishments are establishments that either 1) perform steps in the manufacture of an ACTP that do not process cells or tissue for the manufacture of the finished ACTP products, other than Type II finished products, or 2) only manufacture Type II finished products. See GFI #253 for examples of Category A and Category B establishments. Both Category A and Category B establishments may be subject to inspection.

B. Pre-approval inspections for animal biotechnology products

OII, with CVM participation, evaluates the adequacy of the production processes and control strategy to ensure commercial product quality and conformance to application, facility, and applicable CGMP requirements. CVM uses information from the inspection in conjunction with other information to determine whether to approve the product application. The regulated article and the related production processes that are subject to inspection vary by product type.

- IGAs: The regulated article for these products is the genetic alteration in the animal. As such, the PAI focuses on the materials and processes used to generate the founder animal(s) (e.g., clustered regularly interspaced short palindromic repeats [CRISPR]- Cas 9, zinc finger nucleases) and the processes used to establish effectiveness and demonstrate genotypic and phenotypic durability. The aim of the PAI is to evaluate the adequacy of the production processes starting from generation of the IGA in the founder animal to the establishment of a lineage of animals with the IGA, ensuring that all animals contain the appropriate IGA and verifying the procedures used to evaluate health of the animals with the IGA.

  Typically, the key aspects include molecular laboratory functions, such as those used to test effectiveness parameters and the durability specifications (e.g., PCR methods, ELISA assays), animal operations (e.g., animal health evaluation SOPs, lineage establishment and maintenance procedures), and, if applicable, containment measures (e.g., perimeter fencing, security badges).

- ACTPs: ACTPs are complex biological products with complex mechanism(s) of action, and the whole ACTP is considered the regulated article. Key aspects of ACTP manufacturing that are evaluated during the PAI to determine approvability with respect to risk mitigation include (but are not limited to): donor eligibility; tissue recovery; tissue processing and controls; prevention of contamination and cross-contamination; a quality system with SOPs to evaluate and document CGMP deviations and report possible contamination to all facilities involved in manufacturing; processing of ACTPs; receipt, pre-distribution shipment, and distribution shipment; and tracking for traceability from donor to finished product.

  The production facilities for both IGAs and ACTPs should meet the CGMP requirements as applicable. In some cases, regulatory CGMP does not fully or specifically address those aspects

[5] Type II ACTPs are described in GFI #218. On a case-by-case basis, after completion of a risk review, CVM may consider other ACTPs appropriate for regulation as Type II ACTPs. Investigators can contact CVM for questions on determining the establishment category using the contact information on the inspection request.

of animal biotechnology product production that are necessary to ensure the safety, identity, strength, quality, and purity of the product. For example, regulatory CGMP does not directly address critical items that we consider necessary to meet statutory CGMP such as donor eligibility or recovery of ACTPs. These regulations also do not cover specific conditions of the approval that are needed to conform to the application, such as animal containment. GFIs #187A, #187B, #253, and #254 explain our current thinking on how the CGMP requirements can be met as well as covering unique aspects of these animal biotechnology products.

This CP also provides risk-based strategies for the scope of inspectional coverage and clarifies roles to establish efficient communication.

2. Strategy: inspection by objective

There are four primary inspectional objectives for PAIs. During the application review, the ONAPE review team identifies risks and concerns that impact the facility risk assessment. This information informs the strategies used to address each inspectional objective.

- **Objective 1: Readiness for Commercial Manufacturing/Production**
- **Objective 2: Conformance to Application**
- **Objective 3: Data Integrity Audit**
- **Objective 4: Commitment to Quality in Product Development**

FDA uses a holistic approach to identify risks that should be evaluated during an inspection (e.g., the facility's role in the application, previous inspection history of the facility, process complexity, or information obtained through the use of alternative tools). ACTPs and IGAs are different product types and the inspectional coverage for each product type is slightly different (see product-specific information and examples in Part III- Inspectional).

The investigator should meet with the FET prior to the inspection to discuss the risks for each facility and product. Additional input from the FET is provided in the PAI request, which is sent to the investigator prior to inspection. Some objectives may need to be covered on every inspection. The investigator determines the areas of coverage during the PAI with input from the FET, as applicable. The depth of coverage of each objective may vary depending on the risks identified. If significant issues are observed during the PAI, this CP allows for adjustments to the inspectional strategy (e.g., expanding the PAI coverage to add overall CGMP surveillance coverage).[6]

[6] During the PAI, if necessary (e.g., systemic CGMP deficiencies are discovered), the scope of the inspection can be expanded to add CGMP coverage of marketed product(s).

A. Objectives table

The following table illustrates coverage considerations for each objective of this CP.

Objective*	Coverage
Objective 1: Readiness for commercial manufacturing/production Determine whether the establishment has a quality system (QS) that is designed to achieve sufficient control over the facility and commercial operations.	
Objective 1a: Laboratory, production, and manufacturing capabilities, changes, deviations, and trends relating to product development have been adequately evaluated to ensure readiness for product production. Animal operations, changes, deviations, and trends relating to the development of the IGA and the lineage of animals with the IGA or ACTP donors have been adequately evaluated to ensure readiness for production. SOPs exist to ensure animal health.	Cover on every PAI.
Objective 1b: Adequate procedures exist for production and release. Records exist to demonstrate product quality and animal health to ensure specifications are met. For ACTPs, a sound and appropriate program to sample, test, and evaluate components (including biologic articles), in-process materials, finished products, containers, and closures for purposes of releasing materials or products has been established, including a robust supplier qualification program.	Cover: • on the initial PAI; • periodically on subsequent PAIs, with frequency based on risk; or • when there have been major changes to the QS, management team, or corporate structure. Depth of coverage will vary based on the risk and application-specific issues.
Objective 1c: Sufficient controls are in place to ensure containment of the product and/or to prevent contamination.	Cover: For IGAs: • on every PAI, if applicable to the conditions of approval; For ACTPs: • on the initial PAI; • periodically on subsequent PAIs, with frequency based on risk. Depth of coverage will vary based on the risk and/or the inspectional findings.

Objective*	Coverage
Objective 1d: Adequate procedures exist for change management and investigating failures, deviations, complaints, and adverse events, and for reporting this information to FDA (e.g., through FARs).	When determining whether to cover, consider risk factors such as: • there is no history of prior coverage of these elements; • the QS has changed since the last inspection; or • previous facility information (e.g., previous inspections, RRAs) has identified deficiencies in these areas. Depth of coverage will vary based on the risk and application-specific issues.
Objective 1e: For ACTPs, the proposed commercial process and manufacturing/production record, including instructions, processing parameters, and process control measures, appear feasible and scientifically and objectively justified, as applicable.[7]	Cover on every PAI. The depth of coverage will vary based on the extent of process validation activities and any application assessment issues identified at the time of the inspection.
Objective 2: Conformance to application Verify that the production methods, analytical (or examination) methods, and animal health (including containment) and/or batch records are consistent with descriptions contained in the application.	Cover on every PAI.
Objective 3: Data integrity audit Audit and verify raw data and controls at the facility that are associated with the product.	Cover on every PAI. The depth of coverage will vary based on the inspectional findings.
Objective 4: Commitment to quality in product development Assess the level of maturity of the product development program by evaluating the extent to which it is supported, defined, managed, and continuously assessed for its effectiveness as well as its use in supporting continual improvement of the firm's QS.	Cover: • on the initial PAI; • periodically on subsequent PAIs, with frequency based on risk; or • when there have been major changes to the QS, management team, or corporate structure. Depth of coverage will vary based on the risk and application-specific issues.

[7] For IGAs, there is typically no batch record; instead, the production controls are managed under the SOPs and the animal health records and are evaluated as described in Objectives 1a and 1b.

3. Program management instructions

A. Inspection request

When CVM requests a PAI for an animal biotechnology facility, the following actions occur.

- CPAFAP requests the PAI by email and eNSpect with clear justification and provides specific information on the inspectional strategy regarding the risk and concerns identified.
- If the FET determines that the participation of CVM subject matter experts (SMEs) may be beneficial, the request for their participation in the inspection is noted in the PAI request.
- OII evaluates the request, schedules the inspection, and notifies CPAFAP and DB (via the contact information included in the inspection memo).
- To the extent possible, OII and CVM collaborate on planning and timing of inspectional activities.
- OII leads the inspection and CVM SMEs participate with appropriate (CVM and OII management) concurrence.
- The lead investigator reports the findings and provides an initial recommendation to CVM.
- All members of the inspection team, including CVM SMEs, are responsible for preparing and collaborating on the portion of the EIR pertaining to their inspectional activities and supporting exhibits and providing it to the lead investigator according to OII's timeline.
- CVM evaluates the inspection team's results within the context of the application.
- For PAI **withhold** recommendations from OII or significant deficiencies noted by the inspectional team, CVM evaluates the inspectional findings and the firm's response and makes the final recommendation on the adequacy of the firm for the covered PAI and application. CPAFAP updates the profile class codes as necessary.

B. Scheduling and preparation

A PAI should be requested and performed at the earliest opportunity, well before the user fee goal date. When scheduling the PAI, OII should (1) consider the benefit to the application assessment process of resolving concerns observed during the PAI, and (2) allow sufficient time for the firm and applicant to address such concerns after the PAI. A PAI may be scheduled with other inspection programs for efficient inspectional coverage. OII management may add a systems-based CGMP inspection under specific circumstances, such as when:

- the establishment is on the Center for Biological Evaluation and Research's or CVM's current fiscal year site surveillance inspection list;
- a for-cause inspection has been issued; or
- findings from the PAI indicate the need for coverage of marketed products.

OII may choose to contact the facility before a PAI is conducted to coordinate with production or operation schedules, if necessary. FDA reserves the right to conduct facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect. If inspectional planning has started and the facility is not ready for inspection, the establishment should provide a written explanation and the date when it will be available for inspection.[8]

Any postponement of a scheduled inspection by the establishment or applicant should be reported to CVM promptly by OII, as should any delays in gaining access to records or information that could affect FDA's time frames for assessing an application.[9]

CVM (i.e., the FET) prepare for a PAI by conducting the following activities.

- Identify any inspectional concerns. The FET communicates concerns to the OII manager and investigator in the PAI request and provides insights and advice about covering these concerns during inspection planning or onsite, so the investigator can develop an inspection plan.

- Participate in the meeting(s) scheduled by the investigators to discuss the inspectional strategy.

- Either participate in the inspection as SMEs or support the inspection with background information or product specialist support needed by the investigator.

Investigators prepare for a PAI by conducting the following activities.

- Discuss the inspection request with CVM prior to inspection to obtain copies of the relevant information. Become familiar with relevant section(s) of the application and related master files. Applications often contain trade secrets or confidential commercial information, and it is essential that the information be carefully protected to prevent its release outside FDA.

- Schedule a meeting with all inspection participants to discuss the inspection. Typically, this meeting is held approximately two weeks before the inspection start date.

- Develop an inspection plan with the inspection team that is specific to the establishment and product being inspected and is consistent with this CP's objectives as well as inspectional and data auditing techniques. Review the firm history and Form FDA 483 observations from previous inspections.

C. Inspection team

OII leads PAIs and CVM participates, as necessary, with appropriate concurrence (CVM and OII management). OII assigns experienced investigators and analysts, if needed, to conduct PAIs, and may also request support directly from other offices, or national expert investigators. Team members conducting PAIs should have appropriate training and experience. Typically, one or more CVM SME(s) participate in the inspection for animal biotechnology products.

[8] The written response should be from a responsible official at the facility or a designee.

[9] Follow existing procedures for documentation and referral of refusals of access to information during inspection.

PART III—INSPECTIONAL

1. Inspectional/audit coverage, objectives, and techniques

This section describes the type and depth of inspectional/audit coverage needed to address each PAI objective, along with appropriate regulatory citations. There are key differences between ACTPs and IGAs; product-specific examples are provided in the descriptions for each objective.

Related guidances for IGAs and ACTPs: The applicable CVM guidances include the following: GFI #145, GFI #187A, GFI #187B, GFI #218, GFI #253, GFI #254.

A. Objectives

(1) Objective 1: Readiness for commercial manufacturing/production

Determine whether the establishment has a QS that is designed to achieve sufficient control over the facility and commercial operations.

Related statutory provisions and regulations: 501(a)(2)(B) of the FD&C Act [21 U.S.C. § 351(a)(2)(B)], 21 CFR parts 210 and 211

Objective 1a: Laboratory, production, and manufacturing capabilities, changes, deviations, and trends relating to product development have been adequately evaluated to ensure readiness for product production.

Animal operations, changes, deviations, and trends relating to the development of the IGA, the lineage of animals with the IGA, or ACTP donors have been adequately evaluated to ensure readiness for product production. SOPs exist to ensure animal health.

Evaluate whether the laboratory facility is fit for purpose to perform indicated operations. It should be of suitable size, construction, location, infrastructure, and adequately equipped.

Evaluate whether the laboratory, production, and manufacturing operations include:

- appropriate equipment maintenance, performance, and calibration;
- proper and complete investigations of relevant laboratory, equipment, and production/manufacturing issues, including:
  - calibration failures associated with commercial equipment planned for use in the proposed commercial or production batch record,
  - investigations and trending associated with the performance and capability of the commercial equipment listed in the proposed commercial batch/production record,
  - manufacturing or production investigations (e.g., significant deviations, rejects, complaints/returns) and trending associated, and
  - significant facility or equipment failures (e.g., failure to include appropriate labeling on freezers containing carcasses of animals with IGAs, inadequate maintenance of equipment used to assess ACTP potency);

- appropriate personnel training (e.g., maintenance, cleaning, recordkeeping);
- laboratory grade and/or USP grade or higher reagents, if available; and
- appropriate handling of any unexpected laboratory events (including results that fall outside of the specifications or acceptance criteria) that occur during stability, in-process, and release, if applicable.

Evaluate whether the animal operations include:

- appropriate maintenance for the animal facility(ies) (e.g., disposal, lighting, room cleaning, ventilation, rodent, insect, and wild animal control);
- adequate husbandry and daily care (e.g., feeding frequency, water access, health monitoring as described in the application); and
- adequate veterinary care (e.g., personnel training, licensed veterinarians) and oversight.

SOPs exist to ensure animal health, product quality, and appropriate reporting of deviations and adverse events. Animal health SOPs should ensure:

- animals are managed, screened, and/or tested per the application and in a manner to characterize animal health and reduce the risk of adventitious agents and relevant disease agents (e.g., SOPs to describe quarantine procedures for new animals entering a donor animal group); and
- appropriate identification of the source animals and/or tissue. This could include animal identification (e.g., ear tags, ear notches, microchips) and/or pen labeling.
    - For ACTPs, a system should be in place to track all ACTPs from the donor through final distribution. The system should be able to track a specific product back to the donor.

Determine whether the establishment has a QS that is designed to achieve sufficient control over the facility and commercial manufacturing/production operations.

- Evaluate the QS, including the firm's change management practices.
    - Review product-specific or manufacturing or production-related changes implemented by the firm to confirm that there are data supporting effectiveness of the changes.
    - Evaluate and confirm that changes are documented (with justification) and that quality risk management is used to evaluate proposed changes for potential risks and their impact on product quality.
    - Evaluate the appropriate implementation of product- or production-related changes to confirm a high degree of assurance that there are no unintended consequences.
    - Review any discrepancies found during method validation (particularly issues that may have occurred in its final stages) or technical transfer. For IGAs, this includes method validation associated with the durability assessment and plan. For ACTPs, this includes method validation associated with the release and stability methods.
    - Evaluate changes in an analytical method after completing the method validation or technical transfer because of an inability to use the method as written.

- Verify that records/forms match what is required by SOPs (see Objective 1b for examples of applicable SOPs for each product type).
    - E.g., for IGAs, durability SOPs should result in the collection of durability data, which should be captured in the corresponding records/forms.
    - E.g., for ACTPs, donor eligibility SOPs should result in the collection of health data, (e.g., results of disease agent testing), on the corresponding records/forms.

Objective 1b: Adequate procedures exist for production and release. Records exist to demonstrate product quality and animal health to ensure specifications are met.

For ACTPs, a sound and appropriate program to sample, test, and evaluate components (including biologic articles), in-process materials, finished products, containers, and closures for purposes of releasing materials or products has been established, including a robust supplier qualification program.

Product quality SOPs coverage varies by product type. The SOPs should describe the proposed commercial process and manufacturing/production record, including process control measures, instructions, and processing parameters, and should match what has been submitted to CVM.

- For IGAs: this covers both SOPs related to the animal containing the IGA and SOPs related to the IGA itself. These SOPs may cover some of the following topics:
    - animal containment (e.g., physical, biological, procedural);
    - animal waste and carcass disposal procedures (e.g., incineration, composting);
    - animal transport procedures (e.g., containment, identification, carrier);
    - durability testing performed according to the submitted durability plan (e.g., product-specific disease screening and/or testing); and
    - durability methods (e.g., match what has been validated and submitted).
- For ACTPs: SOPs should ensure the following are described:
    - appropriate identification of the source animals and/or tissue;
    - donor selection criteria (screening and testing criteria) and donor management procedures for allogeneic and xenogeneic products;
    - donation procedures;
    - final donor eligibility determinations;
    - processing and manufacturing procedures; and
    - a sound and appropriate program for sampling, testing, and evaluating components,[10] in-process materials, finished products, containers, and closures for purposes of releasing materials or products, including a robust supplier qualification program.

[10] The term *component* includes APIs, excipients, and processing aids [21 CFR 210(b)(3)].

Verify that complete health records exist for each animal.

- For IGAs, the generation of animal health records should begin at birth and should comprise veterinary care and routine observations (e.g., frequency, personnel). Animal health records should be retained according to the submitted schedule. Record disposition should match what has been described in the SOPs (as applicable).

- For ACTPs, health records are considered complete if they document information as described in the application. This may include information regarding selection criteria for medical history, travel and ownership history, signalment, physical exams, observations, other screening procedures, and relevant disease agent test results.

For IGAs, records should be evaluated to ensure acceptable results of all genotypic and phenotypic durability testing; appropriate handling of any out-of-specification (OOS) results, OOS investigations, and resultant corrective/preventative actions; and properly recorded morbidity/mortality results. Additional records may include shipping records, disposal records, and any records related to maintaining or ensuring containment is in place, which should be evaluated to ensure that the product conforms to the approval conditions.

Objective 1c: Sufficient controls are in place to ensure containment of the product and/or to prevent contamination.

Observe the firm's operations and review blueprints, floor plans, or as-built diagrams of utility systems (such as the purified water system piping and air handling systems). Verify that procedures for appropriate physical and procedural containment of new animals or components introduced into the facility, including quarantine procedures, are being followed as outlined in the SOP(s), if applicable. Verify that the establishment has facility, equipment cleaning, maintenance, and utility system controls in place (or planned) that are designed to prevent contamination that could be deleterious to the product and ensure that controls are in place to prevent cross-contamination of and by the product.

Inspect new construction intended for the product, as well as the installation of new equipment, and other significant changes to the existing facility or practices relating to material/personnel flow. Ensure that the practices related to material and personnel flow ameliorate risk for cross-contamination such as cross-species and cross-product contamination. Evaluate the establishment's proposed compliance with related CGMP requirements.

For IGAs, ensure that the physical, procedural, and biological containment outlined in the SOP(s) matches what is present in the facility and is adequate to contain the animals with the IGA. Procedural and biological containment vary between products and should be discussed with the ONAPE review team prior to inspection. Containment measures should be thoroughly examined to ensure they match the conditions of approval, where applicable. Examples include:

- for aquatic species, if the SOPs and/or conditions of approval include multiple levels of physical containment, including drainpipe covers, floor drain covers, tank nets.
- for terrestrial species, if the SOPs and/or conditions of approval include physical containment appropriate to the species and use, including pens, fencing, barn buildings.

Objective 1d: Adequate procedures exist for change management and investigating failures, deviations, complaints, and adverse events, and for reporting this information to FDA (e.g., through FARs).

SOPs and procedures should exist to govern the firm's change management practices.

- Evaluate whether changes are implemented promptly to mitigate the risk of product quality issues to future production [e.g., changes based on investigations, corrective actions and preventive actions (CAPAs), ongoing process performance, and product quality monitoring signals].

- Review the establishment's quality and change management procedures and audit the establishment's compliance to its procedures for already marketed product, as appropriate [e.g., selecting actual failures, deviations, and complaint investigations; related adverse drug experience (ADE) reports, including submissions to FDA, if required].

- Review sampling plans and procedures, including those described in production records, to evaluate the establishment's intended approach to sampling components, in-process materials, and finished product, as appropriate. Check the sampling plans to confirm that representative samples are collected and tested/examined to verify product quality. The method of selecting samples, number of samples taken, statistical criteria for the number of samples taken, and acceptable and unacceptable quality limits should be scientifically based and appropriate. Consider the extent of experiences with the proposed commercial process when determining adequacy of sampling plans. Also, areas of criticality or process vulnerability should receive special attention because these points in a process generally require more extensive sampling.

SOPs should ensure appropriate reporting of ADEs and any other adverse events to CVM are described. Examples of ADEs and other adverse events may include the following:

- lack of effectiveness (as described in the indication);
- morbidity/mortality to the recipient of the ACTP or animal with the IGA;
- for IGAs, animal escape from a setting that is required to be contained under the SOPs and/or the conditions of approval; and
- for ACTPs, infectious disease in a donor population.

SOPs should ensure appropriate investigating and reporting of any failures or deviations to CVM. Examples of deviations may include:

- for IGAs, deviations are failures to meet the genotypic or phenotypic durability specifications as described in the application; or
- for ACTPs, CGMP deviations that may result in adverse events or product defects/ manufacturing defects should be reported to other establishments that may be impacted by the deviation. If the ACTP is in distribution and the CGMP deviation may result in an adverse event, it should be reported to FDA within 3 working days.

Objective 1e: For ACTPs, the proposed commercial process and manufacturing/production records, including instructions, processing parameters, and process control measures, appear feasible and scientifically and objectively justified, as applicable.

ACTP manufacture should occur at the scale described in the application. Batch records, in-process data, or process monitoring records should be evaluated to ensure:

- there are no processes outside of the range of expected variability;
- consistent execution of the batch record and manufacturing instructions or operator workarounds (possible indication of poor process design or training);
- control measures appear to align with raw development data [e.g., important parameters or material attributes that impact critical quality attributes (CQAs) are being monitored or measured at the appropriate frequency]; and
- the data collection processes for justifying critical process parameters are adequate.

Review completed studies in the process validation lifecycle for related products to evaluate the firm's capabilities and procedures. If unable to provide sufficient process validation lifecycle coverage, state as such in the inspection report. OII should cover these processes during future surveillance inspections.

For finished product facilities purchasing multiple lots of components from an external supplier, evaluate the suppliers' variability and the specification criteria. The firm should establish statistical criteria for component, in-process, and finished product variability in comparison with the specification criteria.

(2) Objective 2: Conformance to application

Verify that the production methods, analytical (or examination) methods, and animal health and/or batch records are consistent with descriptions contained in the application.

For both IGAs and ACTPs, verify that SOPs, forms, and other procedures are the same as those in the application. Conformance to the application under this objective may be relevant to Objective 3, Data Integrity Audit. This typically involves verification of the factual integrity of the information filed in the application and the contextual integrity of information supporting that filed information.[11]

[11] Information that has factual integrity is original and corresponds directly to that submitted to FDA (e.g., for ACTPs, the raw data for an ELISA output measuring protein levels in the ACTP or produced by the ACTP supports in process control or release criteria values reported in the application). Information that has contextual integrity supports submitted information about the testing or manufacturing area and related products/processes (e.g., for IGAs, copy number method results that show all the samples and that do not reveal failing values). Missing records (batch, animal health, or testing) and unexplained losses of inventory of components used in production may call into question the contextual integrity of the information filed in an application.

For IGAs, verify that durability testing, containment, and conditions of use are consistent with the application. This includes ensuring that the durability plan is executed using the validated methods, the durability testing results are reported under the schedule that were submitted to the file, and the conditions described in the environmental assessment (EA) are consistent with those at the facility. To address this objective for IGAs, conduct the following activities.

- Inspect the actual performance of the durability methods during the PAI, including laboratory deviations, trends, and other indications of a lack of method reliability. Not all methods need to be covered during the PAI. Coverage should be given particularly to methods/testing that are unique to the product application under inspection or technically complicated to perform. Consultation with the ONAPE review team may be useful in identifying such methods.

- Walk through the facility, take pictures of the conditions described in the application (e.g., containment, animal identification), and compare conditions on the ground with those in the EA and durability plan [physical and procedural containment, animal identification, waste and carcass storage (if applicable), transportation method (if applicable)].

- If there is a perimeter fence and it acts as a layer of physical containment that is a condition of the approval, walk the entire perimeter to ensure it is in good condition with no breaks.

- Observe the affected environment and ensure that it matches the description in the EA (e.g., rural, semi-rural, proximity to water, residents/farms nearby).

For ACTPs, verify that the formulation, manufacturing, or processing methods; analytical (or examination) methods; batch records; and donor eligibility selection criteria and donor data are consistent with descriptions contained in the application. To address this objective for ACTPs, conduct the following activities.

- Verify that proper vendor qualification has been carried out as described by the establishment's SOPs.

- Observe the processing lines, unit operations [both scale and type (including aseptic or sterilization processes)], and laboratory methods and compare with the description and/or batch records submitted to CVM.

- Audit the detailed manufacturing records and ensure their consistency with the general description of the processing methods described in the application. Compare actual manufacturing records to the production method described in the application and contact CVM if significant differences are observed. It is also important to ensure that batches placed on stability for expiration date (or retest date) determination are representative of the proposed marketed product.

- Verify that the registration and stability batch sizes are as submitted to CVM. Inspectional coverage of analytical methods validation for tests described in the application should include methods for testing the components, in-process materials, and finished product. Compare the methods in the application with the methods in use in the facility. Review the

validation data and reports for each test method to ensure that there are no significant variations from the method and specifications in the application.

- Inspect the performance of the methods during the PAI, including laboratory deviations, trends, and other indications of a lack of method reliability. Not all methods need to be covered during the PAI. Coverage should be given particularly to methods/testing that are unique to the product application under inspection, technically complicated to perform, or measure a high-risk CQA. Consultation with the ONAPE review team may be useful in identifying such methods.

- Audit records and data that support information submitted in the application. Records that are considered good candidates for audit include donor eligibility, shipping records, equipment use logs, inventory records, analytical testing results, and related batch records.

- Inspect laboratory methods and audit research and development notebooks. Review of inventory or receiving records of components is a way of verifying and evaluating the context and integrity of batch information submitted in applications.

- Verify that the source tissue was collected according to the application and that the donors are correctly identified throughout manufacturing.

- Verify that donor eligibility selection and related procedures were conducted according to the application (e.g., ensuring that all donor eligibility forms have been completed, management procedures are being conducted according to the application, final donor eligibility determinations are being conducted according to the application).

- Verify that, if pooling of donor material is allowed for the product, it is limited to what is stated in the application. Inspect records related to pooling to ensure that only the correct number of donors/samples are being pooled and that no other pooling at other stages of manufacture is occurring. Verify that donor tissue is correctly identified throughout manufacturing and pooling.

- Verify that there have been no changes in elements that may impact the biologic activity of these products, including storage conditions, reagents, culture media, and transport media.

- Verify that the establishment has implemented a risk management system to ensure hazards [e.g., cross-contamination, adulteration, relevant disease agent(s), endotoxin, antibiotics/ antimycotics] are identified, evaluated, addressed, communicated to firm management and to FDA, and continuously reviewed as needed throughout a product's lifecycle. It may be helpful to consult with the ONAPE review team regarding potential hazards or hazardous risk before the inspection. If risks are identified, consult the ONAPE review team as appropriate, and include coverage of one or more of the following, as needed.

    - Verify that the establishment has conducted a risk assessment for hazards and has implemented strategies and a corresponding risk management system (e.g., actions to address sources of variability, release testing, reduction or elimination of hazards,

cleaning validation) to control and mitigate the risk. Ensure that this includes hazard risks identified in the application.

- Verify that unacceptable levels of hazards are documented, and risks are mitigated.
- Verify that the establishment has a control strategy for operations identified as at risk of forming hazards.
- Confirm that acceptable specification limits have been established for hazards if identified in components, the finished product, or as a degradant throughout the product's lifecycle.
- Determine whether changes that may impact the type or level of hazards are appropriately evaluated within the establishment's change management system throughout the product's lifecycle.

Related statutory provisions and regulations: 501(a)(2)(B) of the FD&C Act [21 U.S.C. §351(a)(2)(B)], 21 CFR parts 210 and 211

(3) Objective 3: Data integrity audit

Audit and verify raw data at the facility that are associated with the product. This information can, among other things, help to authenticate the data submitted in the application as relevant, accurate, complete, and reliable for CVM assessment.

Audit the accuracy and completeness of data reported by the facility for the product. Not every data summary must be audited to accomplish this objective. The inspectional strategy may select key data sets from product development (e.g., claim validation, animal health, formulation development, process validation) or other data filed in the application selected by CVM. For IGAs, animal morbidity/mortality data are good candidates for audit. For ACTPs, individual donor data and data on finished product release or stability that support product CQAs are good candidates for audit.

In addition to summary tables, applicants typically submit additional testing for the finished product's quality. During inspection, compare the laboratory's raw data (hardcopy or electronic), such as lab analyst notebooks, and information with the summary data in the application. Raw data files should support a conclusion that the data reported by the site is complete and accurate. Data integrity concerns may include failure to scientifically justify not reporting relevant data (e.g., disease agent test results), aberrant test results, or absences in a submitted sample sequence.

When data discrepancies are observed, identify the firm personnel involved. Determine which actions or inactions contributed to the data integrity problem and whether corrective actions were or are to be taken. Also determine whether data that should have been reported in the application were not reported. For example, did the firm substitute passing data (i.e., within specification or otherwise favorable) for failing data (i.e., OOS or unfavorable) without a sufficient investigation and resolution of the discrepancy? Did the firm improperly invalidate OOS results?

The following are possible indications of data integrity problems:

- alteration of raw, original data and records (e.g., the use of correction fluid);

- records, reports, or information referring to failed studies;
- backdating durability/stability test results to meet required commitments;
- fabrication of acceptable test results without performing the test;
- use of test results from previous animals or batches to substitute testing for another animal or batch;
- inconsistencies in production documentation (e.g., identification of actual equipment used) and other information in the submission;
- multiple analyses of a test supporting a specification using the same sample without adequate justification;
- exclusion of specific animals or batches from the stability/durability program or donor data to avoid submitting failed results;
- reworking or process modifications not adequately justified or appropriately reported;
- manipulation of a poorly defined analytical procedure and associated data analysis to obtain passing results;
- the site does not actually manufacture the product as described in the application or the master file(s) referenced therein;[12] and
- discrepancies within and completeness of animal health/donor eligibility records.

The investigators should clearly indicate in the EIR whether their findings call into question the reliability of the submitted data. Specific data/information filed in the application should be referenced, when possible. It is essential that OII notify CVM of data reliability concerns promptly to trigger an immediate evaluation of the impact on the application. If such situations are observed, thoroughly document the unreliable data (see Section III.2.B).

For ACTPs, data integrity concerns impacting donors or cells/tissues that are used to make multiple products or that present a risk of contamination (e.g., a donor for product A had a relevant disease agent that was not identified prior to bringing that donor's tissue into the facility that also manufactures products B and C, potentially resulting in an increased risk for contamination of products B and C) are critical areas of focus.

If a pattern of data reliability issues is identified during a PAI, then the investigator should consider expanding the coverage to surveillance of marketed products manufactured in the facility, if applicable. If data reliability issues are documented for other products during an expanded inspection, this suggests a broader pattern that implicates all products manufactured at the facility. If so, OII should consider submitting a recommendation that CVM consider invoking

[12] The inspection team determines if the operations appear beyond the firm's capability and reviews various production records to determine if the product was truly produced at the site or is being produced at a subcontracted shadow factory without FDA knowledge.

the Application Integrity Policy [13] or that a for-cause inspection be planned to further define the scope of the data reliability issues.

Related statutory provisions and regulations: 21 CFR parts 210 and 211

(4) Objective 4: Commitment to quality in product development

Assess the maturity of the product development program by evaluating the extent to which it is supported, defined, managed, and continuously assessed for its effectiveness as well as its use in supporting continual improvement of the firm's QS.

Assess the establishment's ability to develop and manufacture products of consistent quality. Determine whether an establishment has implemented and follows a development program that applies sound science and principles of material science, biological science, engineering, knowledge management, and quality risk management in a holistic manner.

Evaluate the maturity of the product development program by determining whether:

- resources are provided to perform activities related to development of the product or process;
- procedures, written reports, and actions of employees and management ensure comprehensive process and product understanding to the extent possible; and
- management is aware of residual risks, and an appropriate quality management system has been implemented to ensure robust product development, prevent errors, and enable continual improvement through the change management system.

Evaluating the product's development and proposed implementation at commercial scale can assist in understanding the overall product development program. There are four elements supportive of the firm's commitment to quality during development:

1. Product development program

   Review the tools, procedures, or strategies put in place by the facility as part of its overarching product development program and determine whether the product development report for the application product aligns with the development program.

2. Senior management commitment to quality

   Determine whether there are adequate documents describing the roles and responsibilities of the relevant disciplines in the development process. Determine whether there is quality assurance oversight in product development and technology transfer, thus ensuring development processes and procedures are implementable at the commercial scale.

[13] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/application-integrity-policy.

Determine whether upper management takes an active role to ensure that product quality is achieved, such as ensuring a multidisciplinary integrated development team.

3. Multidisciplinary integrated development team

   Verify that the product development team is represented by integrated, cross-functional departments of the firm's relevant disciplines (e.g., animal health, process development, quality assurance), and verify that the cross-functional departments are actively involved during development, technology transfer, and commercial production.

4. Quality risk management in development

   Determine whether adequate risk assessment activities are included as part of the product development program and whether risk assessments identify potentially high-risk formulation and production variables (e.g., plasma, combination products, risk of disease transmission) that could impact product quality. Confirm procedures are put in place to reduce or mitigate the risk. Assess the firm's use of quality risk management principles during development and verify that adequate steps are included as part of the development program that will minimize product and manufacturing/production defects.

   Cite significant discrepancies or deficiencies that are identified with Objective 4 coverage on Form FDA 483 under Objectives 1, 2, or 3, as applicable. Failure to conform with an element described above should not be cited on Form FDA 483 unless the discrepancy or the deficiency can be linked to a CGMP violation. The information gathered from Objective 4 coverage during a PAI is generally used for data analysis or internal trending by FDA and may assist in identification of risk factors (e.g., risks related to process, firm history, and product) for future PAI decisions. Coverage of Objective 4 helps FDA's decision-making related to the effectiveness of developing new products and integrating changes within an establishment and provides insight into the level of effectiveness of this aspect of the firm's QS in ensuring CGMP compliance.

Related statutory provisions and regulations: Regulations described in Objectives 1, 2, and 3 support commitment to quality. FD&C Act sections 506A and 512(d)(1)C).

B. Investigator questions and concerns during an inspection

CVM and OII collaborate to provide an efficient and effective use of inspectional resources. Any deficiency identified by a CVM inspection participant should be discussed with the lead investigator to clarify follow-up activities and responsibilities. Questions that arise during an inspection should normally be directed to the FET and OII management. Questions and concerns may, for example, relate to facility control, process control, batch release, donor eligibility, quality assurance, production/manufacturing procedures, product development summaries, product attributes, or test methods. The assigned CPAFAP and DB contacts for a given application are listed in the initial PAI request.

The investigator may find that the inspected establishment was not responsible for performing some of the process development activities and studies, and that reports for development studies are not available for inspection. The investigator should collect information about each

establishment involved in process development (e.g., name, address, responsible person, work performed). This information should be included in the EIR. The ONAPE review team then determines if additional facilities need to be evaluated or inspected.

2. Inspection reporting

A. Issuance of Form FDA 483

Reportable inspectional observations, such as significant CGMP deficiencies pertaining to the products and significant instances of application nonconformances, are issued to the firm on Form FDA 483, as described in the IOM.[14] Examples of PAI findings that can potentially impact product quality and should appear on Form FDA 483 include:

- findings that differ from the information or process in the application; e.g., formulation(s), equipment used, or donor eligibility data that does not match the reviewed criteria;
- inadequate or insufficiently specific proposed animal health or batch records to provide for reproducible operations;
- inadequate procedures or instructions for controlling the process or equipment intended to support commercial operation;
- missing data or unreliable data;
- a pattern of inappropriately disregarding test results or inadequate or lack of justification for not reporting data/information;
- insufficiency, discrepancy, or failure of the method validation program;
- lack of suitability of the facility, equipment, or operations intended for making the finished product to the CGMP regulations; and
- as applicable, other specific nonconformance (e.g., conditions, practices, and procedures, including inadequate knowledge sharing and ineffective or nonexistent CAPAs) to statutory CGMPs and the applicable CGMP regulations appropriate for the product.[15]

If it is a concurrent CGMP inspection and PAI, organize Form FDA 483 according to the IOM.

B. Completion of the EIR

The inspection team prepares a narrative EIR per instructions in the IOM (Chapter 5). The EIR should be completed as follows, using the objectives and coverage described in Part III.

1. Organize the EIR's "Manufacturing/Design Operations" section by the PAI objectives.[16]

[14] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual.

[15] FDA recognizes that the production of animal biotechnology products presents unique considerations for complying with CGMPs, and product-specific approaches are needed to comply with statutory CGMP. GFI #253 provides guidance to help manufacturers of ACTPs meet statutory and applicable regulatory CGMP.

2. Summarize the responsibilities of the inspected firm in relation to the assigned application.

3. Describe the manufacturing/production operations and summarize inspectional coverage.

4. Address application-related inspectional concerns communicated by the FET with specific data, areas covered, citations, and discussion with management.

If the inspection is a concurrent CGMP inspection and PAI, then the EIR should be organized into surveillance and PAI sections.

3. Sample collection or sample submission requests

Investigators should not collect samples during the PAI unless requested as a part of CVM's inspection assignment or on a for-cause basis. Investigators may collect samples only after getting approval from their supervisor and notifying the relevant CPAFAP contact.

[16] The investigator indicates in the EIR which of the four objectives in Part III.1.A pertain to each observation.

PART IV—ANALYTICAL

For products pending a regulatory decision, product samples and test methods can be collected to:

- verify whether the firm's test methods are suitable for regulatory use and whether the product meets the firm's specifications;
- authenticate the proposed product; and
- provide a reference standard for post-marketing surveillance.

OCS/OARL perform testing on samples collected. The analyzing laboratory maintains completed analytical worksheets. The analyzing laboratory forwards a copy of the laboratory results to the OII office that requested or collected samples.

If warranted, OII may recommend an appropriate regulatory action to CVM.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

1. OII recommendations

Based on the PAI outcome, OII makes an **approve** or a **withhold** recommendation and emails CVM.

A. Approve recommendation

OII makes an **approve** recommendation if there are no significant issues that would adversely impact the establishment's ability to perform its designated functions described in the application.

B. Withhold recommendation

OII makes a **withhold** recommendation if there are significant issues that would adversely impact the establishment's ability to perform its designated functions, as described in the application; e.g.,:

1. significant data integrity problems, including misrepresented data;
2. for ACTPs, lack of complete manufacturing and control instructions in the master production record, lack of donor eligibility information, or lack of data to support those instructions;
3. for IGAs, lack of animal health records or containment that does not match what was described in the application;
4. lack of capacity to generate the product (if the firm is not ready for an inspection, OII should request a letter from the establishment);
5. failure to meet application commitments (e.g., the firm is not performing functions as listed or described in the application);
6. incomplete or unsuccessful method validation or verification;

7. significant failures related to the stability or durability study;
8. failure to report adverse findings or failing test data without appropriate justification; and
9. delaying, denying, limiting, or refusing an inspection.[17]

2. Additional considerations

If OII recommends **withhold** for an application because of deficiencies and findings for overall CGMP surveillance inspectional coverage, OII provides CVM a pOAI alert via email (cvmpai@fda.hhs.gov) and considers recommending an advisory or enforcement action. CVM's Division of Drug Compliance reviews OII's recommendation for appropriate action if necessary, including when significant CGMP findings are identified that may affect marketed product.

CVM reviews the PAI results (EIRs, Form FDA 483s, firm responses, OII division evaluation of the firm responses) when OII divisions recommend **withhold** and provides a final recommendation. CPAFAP updates the final decision and profiles (as appropriate) in eNSpect and shares the review of the EIR, final facility recommendation, and impact on the regulatory action with the CVM review team. In addition, CVM updates the Compliance Management System (CMS) with information pertinent to the review.

Should additional information (e.g., firm response or its evaluation by OII) become available within a reasonable time frame before the application due date, the FET may update its assessment and facility recommendation. Alternatively, the FET may defer further assessment to the next assessment cycle for the subject application. A FET decision to recommend facility approval depends on satisfactory correction of the findings that led to the initial **withhold** recommendation. CVM and OII may confirm satisfactory corrective action using a follow-up inspection.

When OII recommends **withhold** for a PAI of an establishment that does not market FDA-regulated products, a warning letter is not usually the appropriate regulatory action. However, if objectionable findings are observed and the findings affect marketed products, refer to the appropriate CP.

[17] See GFI "Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection".

PART VI—REFERENCES, ATTACHMENTS, PROGRAM CONTACTS, AND ACRONYMS

1. References

A. Code of Federal Regulations, Title 21

https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

Parts 210 and 211: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs and Current Good Manufacturing Practice for Finished Pharmaceuticals

Part 510: New Animal Drugs

Part 514: New Animal Drug Applications

Part 25: Environmental Impact Considerations

B. Compliance programs

https://www.fda.gov/animal-veterinary/compliance-enforcement/cvm-compliance-programs

7368.001—*Pre-Approval Inspections: New Animal Drug Applications (NADA); Abbreviated New Animal Drug Applications (ANADA); Investigational New Animal Drug Applications (INAD); Generic Investigational New Animal Drug (JINAD) Applications; and Conditional New Animal Drug Applications (CNADA)*

7371.001—*Animal Drug Manufacturing Inspections*

7356.002—*Drug Manufacturing Inspections*

7356.002A—*Sterile Drug Process Inspections*

7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*

C. Compliance policy guides

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/manual-compliance-policy-guides

CPG Sec. 490.100 *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*

D. Guidances

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

(1) Guidances for industry

GFI #145 Bioanalytical Method Validation (May 2018)

GFI #187A Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach (May 2024)

GFI #187B Heritable Intentional Genomic Alterations in Animals: The Approval Process (Jan 2025)

GFI #218 Cell-Based Products for Animal Use (June 2015)

GFI #253 Current Good Manufacturing Practice for Animal Cells, Tissues, and Cell- and Tissue-Based Products (October 2022)

GFI #254 Donor Eligibility for Animal Cells, Tissues, and Cell- and Tissue-Based Products (October 2022)

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)

Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection (October 2014)

PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (September 2004)

Process Validation: General Principles and Practices (January 2011)

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994)

*Also see FDA's Scale-Up and Postapproval Changes (SUPAC) guidances for industry.

(2) Draft guidances for industry[18]

Conducting Remote Regulatory Assessments: Questions and Answers (February 2024)

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities (October 2023)

[18] When final, these guidances will represent FDA's current thinking on these topics.

(3) VICH guidance for industry

Draft GFI #286 (VICH GL60) Good Manufacturing Practice for Active Pharmaceutical Ingredients used in Veterinary Medicinal Products." (January 2024)

E. FDA procedures and references

Guides to Inspection, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides

- *Biotechnology Inspection Guide*
- *Pharmaceutical Quality Control Laboratories*
- *Microbiological Pharmaceutical Quality Control Laboratories*
- *Validation of Cleaning Processes*
- *Foreign Pharmaceutical Manufacturers*

Investigations Operations Manual, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual

Pharmaceutical Quality for the 21st Century—A Risk-Based Approach: Progress Report (May 2007), https://www.fda.gov/about-fda/center-drug-evaluation-and-research/pharmaceutical-quality-21st-century-risk-based-approach-progress-report

Staff Manual Guide 6001.1, *FDA Remote Regulatory Assessment Standard Practices* (January 2025), https://www.fda.gov/about-fda/reports-manuals-forms/staff-manual-guides

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

Field Management Directive No. 135, "Pre-operational Reviews of Manufacturing Facilities": https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/field-management-directives/pre-operational-reviews-manufacturing-facilities

FDA Regulatory Procedures Manual, Chapters 7 and 8, 2008

Field Management Directive No. 145 "Procedure for Release of Establishment Report to the Inspected Establishment": https://www.fda.gov/media/83055/download

PPPM 1240.3622 Good Manufacturing Practice Compliance Status: https://www.fda.gov/media/69997/download

F. FDA user fee programs

https://www.fda.gov/industry/fda-user-fee-programs

Animal Drug User Fee Act (ADUFA)

2. Attachments

A. Remote regulatory assessments

3. Program contacts

A. Center for Veterinary Medicine

PAI-related questions: email - CVMPAI@fda.hhs.gov

Compliance-related questions: email – CVMAnimalDrugGMP@fda.hhs.gov

B. Office of Inspections and Investigations

Office of Biological Inspections: email - oiiobibiologicsinspectionpoc@fda.hhs.gov

4. Acronyms

ACTP:	animal cell, tissue, and cell- and tissue-based product	**INAD:**	investigational file
ADE:	adverse drug experience	**IOM:**	Investigations Operations Manual
ADUFA:	Animal Drug User Fee Act	**NADA:**	approval application
API:	active pharmaceutical ingredient	**OAI:**	Official Action Indicated
CAPA:	corrective action and preventive action	**OARL:**	Office of Analytical and Regulatory Laboratories
CPAFAP:	CVM Pre-Approval Facilities Assessment Program	**OC:**	Office of Compliance
CGMP:	current good manufacturing practice	**OCS:**	Office of the Chief Scientist
CMC:	chemistry, manufacturing, and controls	**OII:**	Office of Inspections and Investigations
CMS:	Compliance Management System	**ONAPE:**	Office of New Animal Product Evaluation
CQA:	critical quality attribute	**ORS:**	Office of Regulatory Science
CVM:	Center for Veterinary Medicine	**PAC:**	product/assignment code
DB:	Division of Biotechnology	**PAI:**	pre-approval inspection
DMT:	Division of Manufacturing Technologies	**PAM:**	pre-approval program manager
EIR:	establishment inspection report	**pOAI:**	potential Official Action Indicated
FD&C Act:	Federal Food, Drug, and Cosmetic Act	**QS:**	quality system
FET:	facilities evaluation team	**VMF:**	veterinary master file
IGA:	intentional genomic alteration		

ATTACHMENT A: REMOTE REGULATORY ASSESSMENTS (RRAS)

In addition to its inspectional authority, FDA may conduct RRAs, under certain circumstances, to support oversight of FDA-regulated products and establishments.[19] An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human and animal health, informing regulatory decisions, and verifying certain information submitted to the Agency. RRAs used in lieu of or in advance of inspections have allowed FDA to remotely evaluate manufacturing and production establishments to mitigate risks. However, RRAs are not the same as an inspection as described in section 704(a)(1) of the FD&C Act.

The following RRAs, along with applicable FDA policies, can be used to support the objectives of this CP when, in the opinion of FDA experts, they would enable FDA to determine whether the establishment meets applicable requirements for the product's identity, strength, quality, and purity for an application subject to section 512 of the FD&C Act.

1. FDA records and other information requests under Section 704(a)(4) of the FD&C Act (statutorily authorized RRA)

In 2012, with the passage of the FDA Safety and Innovation Act to amend the FD&C Act, Congress gave FDA the authority to request "any records or other information" in advance of or in lieu of an inspection related to human or animal drugs. Section 704(a)(4) of the FD&C Act requires "a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug" to provide FDA, upon request, records or other information that FDA may inspect under section 704(a)(1). With regards to this CP, a 704(a)(4) request may be used in lieu of or in advance of a preapproval inspection (PAI) to support assessment of a pending application or supplement.[20] The use of 704(a)(4) authority does not prevent an FDA investigator from requesting records or other information on inspection.

2. Remote Interactive Evaluation (voluntary RRA)

A remote interactive evaluation (RIE) is an evaluation of a firm's compliance with regulations and/or conformance with an application submission that a firm participates in voluntarily.[21] RIEs are defined as FDA's use of any combination of remote interactive tools (e.g., remote livestreaming video of operations, teleconferences, screen sharing) to evaluate facilities where products are manufactured, processed, packaged, or held. FDA may request to conduct an RIE whenever a program office determines it is appropriate based on mission needs. With regards to this CP, an RIE may be used in lieu of or in advance of a PAI to support assessment of a pending application or supplement. During an inspection, FDA may collect copies of previously received documents and other documents not previously requested.

---

[19] See FDA's "An Update to the Resiliency Roadmap for FDA Inspectional Oversight", section 704 of the FD&C Act, and draft GFI "Conducting Remote Regulatory Assessments: Questions and Answers" (February 2024). When final, this guidance will represent FDA's current thinking on this topic.

[20] SMG 9004.1, "Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection".

[21] See draft GFI "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities" (October 2023). When final, this guidance will represent FDA's current thinking on this topic.