

ANIMAL-DERIVED INGREDIENTS, THE FDA AND REGULATIONS

WHAT ARE ANIMAL-DERIVED INGREDIENTS (ADI'S)?

FDA defines “animal-derived ingredient” as a substance of animal origin used to manufacture a drug product. They are primarily derived from byproducts of food production and include extractions from certain animal material and milked animal fluids (like venoms) and may even be human-derived. Products of animal cell cultures, including monoclonal antibodies and therapeutic proteins, are not considered animal-derived.

ADI's are obtained after material processing and purification of animal parts in facilities known as a “Livestock Processing Establishment” (LPE). FDA advises that both ingredient and drug product manufacturers fully understand the potential for pathogenic agent contamination beginning with the livestock processing establishment (LPE) and continuing through subsequent handling and processing. It is FDA's expectation that stringent controls to prevent contamination be established. All manufacturers shall understand that pathogens vary among different animal species. Further, pathogenic risk associated with different animal species will vary even between different organs and tissues with a species. Healthy animals can be a source of pathogens, too, and improper handling of materials can spread contamination.

Animals from which ingredients are rendered must be healthy and free of disease. Ensuring the health of livestock for food supply is the purview of the U.S. Department of Agriculture (USDA), and FDA references the relevant food safety regulations in titles 9 and 21 of the Code of Federal Regulations (CFR). Additionally, each state will have its own board or department of health that works in cooperation with the USDA by inspecting LPE's for compliance with USDA regulations and any other state requirements. These agencies monitor and control disease in livestock and poultry populations through activities such as inspections, testing, vaccinations and treatments, quarantining, etc.

Ingredient manufacturers are encouraged to select LPE's that comply with all state and federal regulations, and to obtain assurance of compliance through supplier auditing activities. FDA advises that LPE's are to have SOPs for sanitation at key points in the animal processing sequence. Specifically called out is sanitation of the raw materials directly after butchering, inclusive of refrigerated temperature conditions, use of preservative methods, storage and sanitation of containers, and transportation conditions.

WHAT ARE THE CONCERNS ABOUT ADI'S?

Pathogenic contamination in animal-derived ingredients can surface at any point along the processing continuum and FDA advises that ingredient manufacturers are to assume all ADI's harbor and support the growth of pathogenic agents such as bacteria, molds, viruses, protozoa, parasites, and prions. Contaminated ingredients present potential health risks that may affect various patient populations, including immune-compromised patients, as well as

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otherwise healthy people of all ages. Pathogenic agents can enter the manufacturing facility on the animal material and contaminate excipients, water, processing equipment, personnel, environment, or packaging.

An agent may be considered pathogenic if its presence represents a significant risk to patient safety. Factors affecting the pathogenic agent's ability to cause harm include the pathogenicity and virulence of the agent, amount of agent present, the growth and survivability of the agent along the processing sequence and in the end-use ingredient. Also, to be considered is the type of drug product for which the ADI is intended to be incorporated, and the drug's patient community and length of therapeutic treatment. From these known aspects, an assessment of risk is made.

The March 2018 Guidance Document entitled, **"Questions and Answers on Current Good Manufacturing Practices for Drugs – Control of Components and Drug Product Containers and Closures"** provides a detailed account from FDA on the kinds of pathogenic contamination commonly seen in ADI processing. From vegetative bacteria, toxin-producing microorganisms, spore-forming bacteria, fungi, molds, viruses, and parasites to prions, we know where and when these agents are likely to present in the ADI derivation process. As an example, FDA advises that spore-forming bacteria can be difficult to eliminate from the manufacturing environment because the spores may be extremely resistant to common processing or sanitation variables, like heat, freezing, extreme pH, and chemical agents. Spores can remain dormant for long periods of time but if re-established in a growth facilitating environment, they can become active again and begin to produce harmful endotoxins. Similarly, we know that viruses can remain viable and transmissible on hard, non-porous surfaces with no apparent food source. The inadvertent use of materials from virus-infected animals can transmit viral bodies and particles to patients and thus presents serious risk.

WHAT DO THE REGULATIONS TELL US ABOUT ADI'S?

Since ADIs are ingredients that will be used in finished pharmaceuticals or drug products, ingredient and drug product manufacturers are responsible for the quality and safety of the material they produce for use in those finished pharmaceuticals. We know, at the most basic level of compliance, drugs made with contaminated ADI's will fall within the meaning of the FD&C Act under sections 501(a)(2)(A) and 501(a)(2)(B). Therein we know that a drug is considered adulterated if it has (A) been made and held under conditions of filth or rendered injurious to health, and/or (B) if it has been made under conditions that do not meet current good manufacturing practices (cGMPs), as defined in 21 CFR 210 & 211, and whereby the quality attributes of safety, identity, purity, etc. cannot be confirmed.

The text of 21 CFR 211 and the relevant guidance documents on handling ingredients (referred to as "components", which may be either and "excipient" or "active pharmaceutical ingredient") speak to the avoidance of contamination along the entire processing and handling of a manufacturing process versus a final testing of the end product to confirm absence of contamination. Indeed, final testing is necessary, but does not fulfill obligations under the requirements of the cGMPs. Ingredient and drug product manufacturers must employ key control strategies along the entire manufacturing schematic to avoid contamination.

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FDA advises that facility, equipment, and process controls be in place and fully implemented at the ingredient and finished drug product manufacturing establishments in order to reduce risk of pathogenic contamination from and in ADI's. Facility and equipment controls such as a comprehensive program for environmental monitoring that includes the identification of microbial isolates and how to eliminate such microbes, and the development of effective cleaning protocols and procedures to remove all traces of ingredients and materials from surfaces between batches are two illustrations of such control strategies. Adherence to all other cGMP regulations is necessary.

Process controls that FDA calls out for handling ADI's include minimization of the holding and storage time to reduce likelihood of pathogenic agent propagation, determined by appropriate qualification studies that include sampling at varying points of temperature, time, and processing conditions. Analytical results of such sampling will yield characteristic and activity information on any pathogenic agent contamination or potential agents of contamination. Routine manufacturing processes such as filtration, purification and concentration may also reduce the risk of pathogenic agent contamination, should they be designed appropriately for the process. These kinds of controls, taken with initial supply considerations like the use of only healthy animals as source material and selection of LPE's that are in compliance with all federal and state laws, are essential for ADI and subsequent drug product manufacturers.

Instruction and FDA's current thinking on ADI's are found in drug guidance documents such as **"Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients"**, and also in guidance documents for biotechnology products and medical devices. **"Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin"** and **"Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)"** are two such references. Therein we can find discussion on potential sources of viruses, testing for viruses, evaluation of virus clearance procedures, and special considerations and controls for use of animal tissues.

REFERENCES:

1. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-current-good-manufacturing-practices-drugs>
2. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-containing-materials-derived-animal-sources-except-vitro-diagnostic-devices>
3. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q5a-viral-safety-evaluation-biotechnology-products-derived-cell-lines-human-or-animal-origin>
4. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q7-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients-guidance-industry>