Risk Management and Healthcare Policy

Dovepress
Taylor & Francis Group

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REVIEW

Beyond Side Effect: Immuno-Ethical Risk Analysis of Animal-Derived Ingredients in Pharmaceuticals

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Abstract: Animal-derived ingredients (ADIs) account for up to 75% of prescription drugs, triggering clinical risks such as alpha-gal syndrome (AGS), ethical-religious conflicts, and supply transparency issues. This calls for a systematic evaluation of ADIs and accelerated development of animal-free alternatives (AFAs). This critical review synthesizes evidence from the biomedical, regulatory, and ethical literature to analyze the persistence of ADIs, map their risk stratification (biological and religious), and evaluate progress in AFAs. ADIs persist due to their functional, regulatory, and biocompatibility advantages in various medical products. Methodologically, the proposed dual risk stratification framework integrates immunological risk profiles, specifically targeting the galactose-α-1,3-galactose epitope, with Halal jurisprudential criteria for categorizing pharmaceutical ingredients. Although various AFAs (plant-based, recombinant, and synthetic) have been developed and supported by global regulatory initiatives, significant challenges in scalability, cost, and bioequivalence remain. The transition to AFAs is crucial and increasingly technically feasible. A unified framework that integrates scientific, ethical, and religious analysis is needed to accelerate the adoption of safe and inclusive AFAs, while ensuring patient autonomy and safety.

Keywords: animal-derived ingredients, immunogenicity, pharmaceutical ethics, halal pharmaceuticals, risk assessment, excipient safety

Introduction

Animal-derived ingredients (ADIs) have long played a crucial role in the development of pharmaceuticals and medical technologies. ADIs include compounds derived from animal tissues, organs, or byproducts, used either as active ingredients or inactive excipients.[1] Surveys by regulatory agencies such as the FDA and EMA indicate widespread prevalence, with ADIs found in a significant percentage of prescription drug formulations, often hidden as common excipients such as gelatin in hard-shell capsules or magnesium stearate. The presence of ADIs in pharmaceuticals and medical devices is often invisible to patients or healthcare professionals, but their impact on clinical practice, ethics, and patient trust is significant. For nearly 25% of animal-free medicines available on the market, an independent certification mark would facilitate informed consumer decision-making.[2] Their production raises several ethical concerns regarding animal welfare. Furthermore, their biological origin is associated with a high risk of contamination, which often results in poor scientific data for clinical translation.[3]

The need for animal-free medicines impacts not only vegans and vegetarians, but also those with dietary restrictions due to other religious beliefs. In particular, the classification of "Haram" status in Islamic jurisprudence and the principle of "Ahimsa" in Hindu/Jain traditions create serious implications for patient autonomy. Globally, dietary and religious preferences play a significant role in shaping public attitudes toward healthcare products. Recent data estimates that 22% of the world's population identifies as vegetarian, with over 88 million people following a vegan diet.[4] Pork-derived

https://doi.org/10.2147/RMHP.S584055
Received: 24 November 2025
Accepted: 7 February 2026
Published: 26 February 2026

products, such as heparin (low-molecular-weight heparin/LMWH), are prohibited in Jewish and Muslim traditions, while gelatin is permitted in Islam only if it comes from halal animals slaughtered according to Islamic law. In the context of modern pharmaceuticals, the need to provide culturally and religiously inclusive drug formulations is becoming increasingly urgent.

Beyond social and religious preferences, the medical risks associated with ADIs are also receiving increasing attention. One emerging phenomenon that highlights this complexity is alpha-gal syndrome (AGS). AGS is an allergy triggered by tick bites (such as Amblyomma americanum), which causes sensitization through an Immunoglobulin E (IgE) antibody response to galactose-α-1,3-galactose (alpha-gal), a carbohydrate epitope found in the tissues of all non-primate mammals. AGS reactions to mammalian foods and medical products include delayed anaphylaxis, urticaria, gastrointestinal and cardiac symptoms.[5,6] In the United States, an estimated 450,000 people suffer from AGS, and a survey of 559 patients showed that more than 50% experienced anaphylaxis after using medical products containing alpha-gal.[7] Patients must modify their medication regimens to avoid ADIs, highlighting a real challenge in daily clinical practice. In addition to new immunological risks such as AGS, traditional risks remain, including anaphylactic reactions to gelatin in vaccines,[8] lactose intolerance to tablet excipients,[9] and concerns about zoonotic transmission such as Bovine Spongiform Encephalopathy (BSE).[10]

The issue of ADIs is not limited to prescription drugs but extends to a wide range of pharmaceutical products and everyday medical devices. Porcine-based heparin remains the gold standard in anticoagulant therapy worldwide.[1] Animal tissue-based thyroid hormone remains commercially available, although synthetic alternatives have been developed. Other commonly used products include porcine or bovine bioprosthetic heart valves, collagen-based surgical mesh, surgical sutures, and gelatin as a vaccine stabilizer. However, the transition to animal-free alternatives (AFAs) faces significant economic and technical hurdles. Production cost premiums often exceed 20–50%, and in specific cases of "humanising" primary cell cultures, the cost of animal-free media can increase by more than 600% due to the high price of human serum and recombinant stabilizers.[11,12]

Previous studies have explored partial aspects of ADIs, such as the risk of gelatin allergy, the halal and kosher dilemmas in vaccines, or the sustainability challenges in gelatin production, but the existing literature remains fragmented and lacks a unified framework. This review addresses this gap by presenting a multidisciplinary analysis of ADIs, using AGS as a clinical case study while examining its ethical, religious, regulatory, and environmental implications. This review offers a comprehensive dual-risk stratification framework to understand current risks and guide the development of safer, more inclusive, and sustainable animal-free alternatives.

Why are Some Animal-Derived Ingredients Still Necessary?

Despite ethical, religious, and clinical concerns, ADIs remain common in pharmaceuticals, anesthetics, and food products. Their persistence is explained by several key factors.

First, ADI offer unique functionality that is difficult to replicate with plant-based or synthetic alternatives. Difficulties in achieving key functional properties like emulsification and gelation further limit their ability to replicate animal-based products. Moreover, sustainable approaches for extracting high-quality proteins are still under development.[13] For example, gelatin provides irreplaceable gelling and stabilizing properties in capsules, vaccines, and confectionery. Similarly, heparin, derived from porcine intestines, remains indispensable as an anticoagulant, and collagen or lanolin continues to play roles in regenerative and dermatological applications due to their biocompatibility. However, animal-derived proteins like collagen type I, hyaluronic acid, and Matrigel™ present several drawbacks including biological risk contamination and batch-to-batch variability which leads to low data reproducibility.[3] Replicating the complex flavor profile of meat is difficult, as it involves intricate interactions between fat, protein, and cooking processes.[14]

Second, regulatory and clinical familiarity contribute to their persistence. Developing novel alternatives is a lengthy, expensive process involving extensive testing to prove safety and effectiveness before the FDA (US Food and Drug Administration) or EMA (European Medicines Agency) will grant approval, which can take over a decade. Regulators require substantial data, including results from adequately controlled clinical trials, to assess the risk-benefit profile of a new product before it can be used by the public. Established ADI, by contrast, have long safety records and wide clinical acceptance, making them the default choice in many therapeutic and manufacturing contexts.[15,16]

Third, economic and scalability factors favor ADI. As by-products of the meat and dairy industries, they are cheap and readily available at industrial scale.[17] In contrast, animal-free alternatives often require advanced biotechnological production, resulting in higher costs and limited accessibility, particularly in low- and middle-income countries.[18]

Finally, bioavailability and pharmacokinetics make some ADI clinically preferable. Certain animal-derived compounds are absorbed or metabolized more effectively than synthetic substitutes, ensuring therapeutic efficacy in critical care, perioperative, or pediatric settings.[19]

In short, ADI persist because they combine proven functionality, regulatory familiarity, affordability, and clinical reliability. While their use raises ethical and cultural concerns, detailed implications for patient autonomy, disclosure, and alternative development are best addressed within specific contexts such as pharmaceuticals and food applications.

Pharmaceutical Applications of Animal-Derived Ingridients

ADIs are deeply integrated into pharmaceuticals and medical products, functioning as both active pharmaceutical ingredients (APIs) and excipients.

Active Pharmaceutical Ingredients (APIs)

Heparin remains the most critical example of ADI dependence; as the gold standard anticoagulant for surgery and dialysis, no synthetic alternative currently matches its clinical scope. However, sourcing variability between Heparin Porcine Intestinal (HPI) and Heparin Bovine Intestinal (HBI) mucosa—which possess distinct anticoagulant activities of approximately 200 IU/mg and 100 IU/mg, respectively—presents significant safety risks. The 2009 bleeding incidents in Brazil highlighted the dangers of non-standardized interchangeability, leading to the landmark 2016/2017 Brazilian Pharmacopeia monographs. By standardizing HPI and HBI as distinct APIs, this regulatory milestone serves as a global model for ensuring patient safety through precise ADI differentiation.[19] Heparin products have evolved from animal-derived Unfractionated Heparin (UFH) to Low Molecular Weight Heparin (LMWH), synthetic Ultra-Low Molecular Weight Heparin (ULMWH), and most recently, bioengineered heparins. While UFH, LMWH, and fondaparinux remain FDA approved and in clinical use, fourth-generation bioengineered products represent the future, offering improved safety, consistency, and reduced reliance on animal sources.[20] Other APIs historically sourced from animals include insulin (porcine/bovine origin before recombinant forms) and desiccated thyroid hormones from porcine glands. Vaccines and biologics also rely on ADI: gelatin stabilizes viral vaccines such as MMR and varicella, egg proteins are used in influenza vaccines, and fetal bovine serum (FBS) supports cell culture for biologics and monoclonal antibodies.

In almost all human cultures, animals have been used as sources of medicinal products for treating numerous diseases and alleviating symptoms. More than 1500 animal raw materials are mentioned in Traditional Chinese Medicine. It is reported that 584 animal species are used in Latin America and 283 in Brazil for the treatment of various diseases. Two hundred fifty-two important medicinal compounds have been chosen by the World Health Organization, and 11.1% of these originate from plants, while 8.7% come from animals.[21]

Excipients

Common ADI-based excipients include gelatin for capsules, lactose from cow's milk as a filler, magnesium stearate (porcine/bovine fat) as a tablet lubricant, and glycerin which may be animal-derived. Other examples include chondroitin sulfate from bovine trachea or shark cartilage and vitamin D3 (colecalciferol) sourced from sheep's wool lanolin. These ingredients are widely used but often invisible to patients and clinicians.

Medical Devices

ADI also persist in biomaterials. Bioprosthetic heart valves are made from porcine or bovine tissue, and collagen-based wound dressings are widely used for tissue repair. Historically, surgical sutures (catgut) were derived from sheep or cow intestines, although synthetic sutures now dominate.

Approximately 75% of commonly prescribed medicines contain ADI, which can cause allergic reactions. In alpha-gal syndrome (AGS), patients develop IgE-mediated responses to mammalian-derived carbohydrates such as porcine or bovine gelatin and heparin. Importantly, non-mammalian sources such as fish or poultry do not contain alpha-gal, so fish

gelatin, marine omega-3 oils, and egg-based excipients are generally tolerated unless a patient has a conventional seafood or egg allergy. This distinction is critical in guiding safer therapeutic choices.

Beyond allergy, ADI raise ethical challenges. Their use is rarely disclosed in perioperative care, yet patients from religious or ethical backgrounds often expect to know. Applying Beauchamp and Childress' Four Principles, disclosure is ethically required, and legal precedents such as the Montgomery ruling in the UK emphasize the need to share risks significant to patients.[22] Surveys reinforce this: 63% of US patients, 44% of UK surgical patients, and 74% of dermatology patients desire disclosure, with many indicating it would affect their treatment decisions. Despite this, 40% of manufacturers cannot confirm ingredient sources, and 70% of physicians remain unaware of ADI content in the drugs they prescribe.[23]

ADI remain critical in APIs, excipients, and medical devices due to their functionality and lack of fully equivalent alternatives. However, they present both clinical risks (eg, AGS, allergies) and ethical challenges (informed consent, religious or dietary conflicts). Despite growing survey data highlighting patient concerns, peer-reviewed case reports of ADI-related refusal remain scarce, underscoring a gap between patient expectations and documented clinical outcomes. Greater transparency in labeling and proactive disclosure are essential while research continues to develop robust animal-free alternatives. The functional significance of the various ADI components in achieving the desired product characteristics can be seen in Table 1.

Table 1 ADI in Pharmaceutical and Its Functionality

Category/ Type	Specific Application/ Compound	Biological Origin	Functional/Pharmaceutical Utility	Critical Challenges/Limitations	Refs
Ingredient	Unfractionated Heparin	Porcine intestinal mucosa.	Binds to Antithrombin (AT) to inhibit Factor IIa (Thrombin) and Factor Xa. Indispensable for extracorporeal therapies (kidney dialysis, heart-lung machines) where synthetic alternatives cannot substitute.	Risk of contamination (eg, over-sulfated chondroitin sulfate); molecular weight heterogeneity requires strict biological assays. Global supply chain vulnerabilities.	[20]
	Insulin (Animal-derived)	Porcine and Bovine Pancreatic Tissue	Functions as a hormone replacement for diabetes therapy. Clinical studies have shown comparable efficacy to semi-synthetic insulin.	Animal sources are a limiting factor in meeting global demand. Lower purity than recombinant insulin. Immunogenicity: Causes higher antibody formation than recombinant insulin, although allergic reactions can be reduced with better purification.	[24]
	Desiccated Thyroid Extract (DTE)	Porcine thyroid glands	Hormone Replacement: Provides physiologic ratio of T4 and T3 for hypothyroidism.	Two RCTs showed no difference in QoL compared with levothyroxine. It can cause increased heart rate and decreased weight/HDL (indicating overdose). Long-term data and side effects are lacking due to poor design of most studies.	[25]
	Gelatin (Type A/B)	Porcine skin (Type A)/ Bovine bone (Type B)	Capable of forming a thermo-reversible gel. Used as an emulsifying and stabilizing agent. Used for the production of softgels and hard capsules.	Religious concerns (Halal/Kosher) due to the porcine/bovine source. BSE risk (bovine) requires strict BSE-free sourcing procedures. Functional properties, such as gel strength (bloom strength), vary significantly depending on the animal source and amino acid composition.	[26,27]

(*Continued*)

Table 1 (Continued).

Category/ Type	Specific Application/ Compound	Biological Origin	Functional/Pharmaceutical Utility	Critical Challenges/Limitations	Refs
	Lactose Monohydrate	Bovine milk whey	A basic excipient widely used in solid formulations (tablets/capsules).	Plays a significant role in the Maillard reaction (chemical degradation) when mixed with drugs containing primary amines (such as Metoclopramide HCl). The intensity of the reaction is influenced by pharmaceutical processing parameters (moisture/heat).	[28]
	Magnesium Stearate Pharmacopoeia and FDA.	Bovine/Porcine tallow (stearic/ palmitic acid)	Most commonly used to improve powder flowability and prevent adhesion to processing equipment. It is hydrophobic and capable of forming a film around other excipients.	Film formation due to prolonged mixing will significantly delay the drug's dissolution rate. Excessive use or mixing causes a decrease in tablet hardness and an increase in disintegration time.	[29,30]
	Glycerin (Glycerol)	Hydrolysis of animal fats (tallow)	Increases solubility of hydrophobic drugs; plasticizes coatings; humectant properties.	Highly susceptible to adulteration by Diethylene Glycol (DEG) and Ethylene Glycol (EG) due to chemical similarities and lower cost, triggering a WHO global warning. Sourcing Risk: Requires religious certification (Halal) if derived from pork/lard. DEG/EG limits are mandated by the Pharmacopoeia and FDA.	[31,32]
	Lanolin (Wool Wax)	Ovine wool (sebaceous secretions)	Emulsifier/Base: W/O emulsion stabilizer; high water absorption capacity for lipophilic drug delivery in topicals.	Poses a significant risk of contact allergy in dermatitis patients, with lanolin alcohol being the primary allergen tested. Obtained from raw wool, which requires a complex purification process to remove impurities and potential residues (such as pesticides) before it can be used in pharmaceuticals/ cosmetics.	[33,34]
	Fetal Bovine Serum (FBS)	Bovine fetal blood	Provides growth factors and attachment factors for hybridomas/CHO cells in mAb production.	Major source of batch variability; risk of adventitious agents (viruses, prions); ethical concerns regarding fetal harvest methods. Push for serum-free media (EMA).	[35,36]
	Ovalbumin/Egg Proteins	Avian (Chicken) Egg White (54% dari total protein).	Used as a culture medium for viral replication (eg, influenza, yellow fever, and triple viral vaccines).	It is the main natural allergen in eggs. Use in vaccines can induce allergic reactions (IgE-mediated) in individuals hypersensitive to egg components. Interactions with other drugs (eg, sulfonamides) can alter the protein's conformation and enhance its natural allergenicity.	[37,38]

(*Continued*)

Table 1 (Continued).

Category/ Type	Specific Application/ Compound	Biological Origin	Functional/Pharmaceutical Utility	Critical Challenges/Limitations	Refs
	Heparan Sulfate	Porcine intestinal mucosa	GAGs that regulate cellular function, differentiation, and wound repair. Function through interactions with receptors, cytokines, and growth factors (eg, enhancing their biological activity).	The chemical composition (especially the pattern and degree of sulfation) varies significantly between batches, directly affecting its biological and anticoagulant activity. Because it is manufactured alongside Heparin, it is susceptible to contamination issues (eg, viruses) and the same supply chain vulnerabilities as Heparin.	[39,40]
	Collagen Scaffolds	Bovine (Tendon, Dermis) or Porcine (Dermis, Skin)	Provides a natural extracellular matrix (ECM) structure to replicate tissue. Used for bone and soft tissue regeneration. Offers good biocompatibility and biodegradability.	Has poor mechanical properties and a rapid biodegradation rate. Requires chemical or physical cross-linking to improve stability. Chemical cross-linking (eg, glutaraldehyde) can pose a risk of cytotoxicity and calcification in vivo.	[41,42]
	Hyaluronic Acid (High MW).	Rooster combs (Avian)	Used to treat knee osteoarthritis due to its high viscoelasticity (non-Newtonian fluid properties). Used as a dermal filler in cosmetics.	Animal-derived HA can contain protein and nucleic acid residues that are difficult to remove, which can trigger allergic reactions (hypersensitivity). The industry has shifted to microbial fermentation to produce purer HA and eliminate the risk of animal protein-related allergies	[43,44]
	Chondroitin Sulfate	Bovine trachea/Shark cartilage	GAGs are used to treat osteoarthritis (OA). They inhibit the activity of proteolytic enzymes that cause cartilage degradation and promote chondrocyte anabolism.	High molecular weight (MW) results in low oral bioavailability (poor absorption). Susceptible to adulteration and significant variations in raw material composition, which requires strong efforts in standardization and purity testing.	[45,46]
	Keratin.	Ovine wool/ Human hair	Wound Healing: High cysteine content allows cross-linking; promotes cellular proliferation in wound matrices.	Harsh hydrolysis required for extraction often degrades protein integrity; varying extraction methods significantly affect biodegradability. Ethical human hair sourcing	[47,48]
	Surgical Gut (Catgut)	Ovine intestinal submucosa or bovine intestinal submucosa	Used as an absorbable surgical suture. Its mechanism of action is proteolytic degradation, where the body's enzymes gradually break down the suture over time, eliminating the need for removal.	Compared with synthetic polymers (eg, Polyglycolide (PGA)), catgut sutures can trigger more severe tissue reactions/ inflammation. Banned in some regions, particularly the European Union (EU), due to concerns regarding the risk of transmission of Bovine Spongiform Encephalopathy (BSE) from bovine sources.	[49,50]

(*Continued*)

Table 1 (Continued).

Category/ Type	Specific Application/ Compound	Biological Origin	Functional/Pharmaceutical Utility	Critical Challenges/Limitations	Refs
Device	Bioprosthetic Heart Valves (BHV)	Porcine Aortic Valve leaflets or Bovine Pericardium	Mimics native valve flow dynamics resulting in lower thrombogenicity compared to mechanical valves; reduces need for lifelong anticoagulation.	Glutaraldehyde fixation (used to reduce immunogenicity) can serve as a nucleation site for calcium deposits, limiting the lifespan of the device (Structural Valve Deterioration/SVD) to 10–15 years. Regulatory Safety: The risk of BSE/TSE transmission from bovine sources is strictly regulated (eg, ISO 22442).	[51,52]
	Surgical Sutures (Catgut/ Chromic).	Ovine (Sheep) or Bovine intestinal submucosa	The suture is broken down by proteolytic enzymes in the body, which allows for absorption in tissues where removal would be difficult.	High inflammatory response compared to modern synthetic, hydrolysis-based sutures (eg, Poliglecaprone). The material is banned in several jurisdictions due to BSE/TSE risk (Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy) and raises ethical concerns over animal sourcing.	[53,54]
	Deproteinized Bovine Bone Mineral (eg, Bio-Oss)	Bovine Bone Mineral.	Acts as a xenogenic scaffold with high porosity (75–80%) and hydroxyapatite crystals comparable to human cancellous bone. Provides surface area for osteogenic cell migration, adhesion, and integration).	Unlike autogenous bone graft (the gold standard), it lacks significant osteoinductive activity. Requires combination with osteogenic progenitor cells or growth factors to compensate for this limitation.	[55]
	Fibrin Sealants & Thrombin	Bovine/Porcine plasma proteins	Mimics the final stage of the coagulation cascade (conversion of fibrinogen to fibrin) to stop bleeding in complex surgeries.	Risk of developing antibodies against bovine thrombin which can cross-react with human Factor V, leading to coagulopathy. Regulatory scrutiny for viral inactivation (EMA/FDA)	[56,57]
	Acellular Dermal Matrix (ADM)	Porcine Dermis/Bovine Dermis	Provides mechanical and soft tissue support for implants, facilitating reconstructive techniques. Acts as a scaffold for host cell infiltration and neovascularization. Reduces radiation-induced fibrosis (including capsule thickness), regulates macrophage responses (immunomodulation), and promotes adipogenesis (adipocyte infiltration). Its flowability ensures optimal contact with ADM and host tissue.	Skin flap necrosis, edema, and prior radiation therapy can hinder integration. Clinical complications include seroma formation (due to delayed integration) and contour irregularities. Incompatibility: Incomplete decellularization can lead to chronic inflammation or encapsulation (rejection). High cost.	[58,59]

Scientific and Religious Basis for Risk Stratification

The classification of ADIs requires an integrated framework that combines scientific rationale and religious considerations. Alpha-gal syndrome (AGS) is an allergy triggered by tick bites that transmit the carbohydrate galactose-α-1,3-galactose, leading to IgE antibody formation and reactions to mammalian meat, dairy products, drugs, and vaccines containing this component. The condition can cause symptoms such as urticaria, anaphylaxis, and gastrointestinal distress that appear 2–6 hours after exposure, making diagnosis challenging. In the United States, the Centers for Disease Control and Prevention (CDC) has estimated around 450,000 cases by 2022, but the true number is likely higher since AGS is not nationally reportable and remains poorly recognized by healthcare providers. Surveys show that only a minority of physicians know AGS is caused by tick bites, and less than one-quarter feel confident in its diagnosis and management. As a result of delayed or missed diagnoses, patients may wait years for confirmation, which poses serious risks during medical procedures such as anesthesia or cardiac surgery involving mammalian-derived products.[7] Ingredients of ambiguous or mixed origin, such as stearates, glycerin, or polysorbates, fall into an intermediate category where supply-chain verification is essential. To understand the full spectrum of moral challenges in biopharmaceuticals, Table 2 below classifies and outlines the different ethical dilemmas arising from the integration of animal-derived materials into medical procedures and therapies.

The table below presents the data studied by Hassanein and Anderson. The degree of molecular complexity and processing also modulates risk. Complex proteins and polysaccharides, including gelatin and pancreatic enzymes, tend to preserve antigenic determinants and thus carry higher immunogenic potential, especially when sourced from mammals. Low-molecular-weight excipients such as glycerin or Polyethylene Glycol (PEG)-stearates may undergo chemical transformations that reduce antigenicity, but their risk classification depends heavily on documented origin. A general principle emerges: the closer an ingredient remains to its original biological structure, the higher the probability of α-gal retention. Risk is further influenced by the clinical route of exposure. Parenteral administration, including injections, infusions, and implants, poses the highest potential for systemic reactions, while mucosal, oral, and topical applications carry

Table 2 Ethical Dilemmas Regarding Animal-Derived Ingredients in Medical Treatment[60]

Case	Case Summary	Key Issue	Analysis & Ethical Considerations	Conclusion
Pulmonary valve stenosis in a 12-year-old child	Choice between a mechanical valve (animal-free, requires lifelong anticoagulants) vs a tissue valve (from an animal, no anticoagulant needed). Strict vegetarian parents choose the mechanical valve despite it being considered suboptimal by the medical team.	Conflict between quality of life, risk of re-operation, and the parents' moral/dietary commitments.	Anticoagulants carry risks (strict monitoring, drug/food interactions, activity restrictions) but are manageable. Ignoring the parents' moral/dietary preferences could violate autonomy.	The risk from anticoagulants is not significant enough to override the parents' choice. The parents' decision is respected.
Intubation of an 8-year-old child	After intubation, the father learns the hydrocolloid dressing contains porcine gelatin. He refuses its use due to religious reasons (Muslim) and believes this information should have been disclosed before consent.	Duty of disclosure in informed consent, especially regarding ADIs.	Incomplete disclosure as the material source was not revealed. Challenges: Healthcare Providers (HCPs) may not know the origin of materials; not all situations allow for detailed discussion; unclear who is responsible for initiating disclosure.	The case highlights the need for clear disclosure policies, but practical implementation is challenging.
Risperidone in a 14-year-old adolescent	Patient stops risperidone tablets after learning they contain bovine magnesium stearate (Buddhist). Symptoms worsen. Switched to an animal-free liquid formulation.	Sudden cessation of essential medication due to moral/dietary reasons; risk of disease relapse.	Prevention: HCPs asking about moral/dietary preferences or patients stating them. Challenges: HCPs may not know the origin of excipients; drug labeling is unclear.	Patient & HCP education is important; labeling of ingredients and their sources must be more transparent.

progressively lower risk. Dose, frequency, and formulation matrix (such as vaccines versus oral tablets) also shape the clinical relevance of risk categories.

In parallel, religious frameworks—particularly Islamic jurisprudence—classify ADI according to the source species and processing method. Substances derived from halal animals slaughtered in accordance with syariah are considered permissible, whereas those from pigs or improperly slaughtered animals are haram. This perspective intersects but does not fully overlap with α-gal risk stratification. For instance, bovine gelatin sourced from halal cattle may be permissible but still unsafe for AGS patients, whereas porcine gelatin is both haram and clinically high risk. Intermediate-risk ingredients such as stearates or glycerin can be halal when sourced from plants or halal animals, but haram if derived from pigs. Low-risk non-mammalian ingredients, such as those from fish or poultry, are generally deemed halal by most scholars, although some debate persists, for example regarding carmine from insects. The selection of the ADI has a direct impact on the safety of the drug formulation. Table 3 outlines the risk stratification of these ingredients, categorized based on key clinical parameters such as immunogenicity and pathogen transmission potential.

From a practical standpoint, these dual considerations emphasize that halal certification does not equate to safety for AGS patients, just as animal-free certification does not guarantee permissibility under Islamic law. Ideally, products intended for Muslim patients with AGS would be both halal and animal-free or based on non-mammalian sources. To ensure this, verification through Certificates of Analysis and halal certification remains critical.

Alternative Substitution for Animal-Derived Ingridients

The use of ADIs in pharmaceuticals, such as gelatin, heparin, collagen, and lactose, has long been an industry standard. These ingredients serve as critical excipients for drug stability, delivery, and formulation.[8] However, reliance on animal

Table 3 Risk Stratification of Animal-Derived Ingredients (ADIs) Based on Clinical

Risk Category	Criteria & Common Sources	Example ADI	Clinical Notes (AGS)	Ref
High	Mammalian origin; proteins/complex biopolymers; α-gal almost certain. Sources: cattle, pigs, sheep, goats	Gelatin, Heparin, Enoxaparin, Pancrelipase, Thyroid extract, Lactose, Magnesium/Stearic acid (animal), Sodium stearyl fumarate, Bovine serum albumin (BSA), Cholesterol/lanolin, Casein	Very high risk because complex mammalian proteins and glycoproteins preserve the α-gal epitope, which strongly cross-links IgE on mast cells/basophils → triggering systemic reactions. Parenteral exposure increases systemic bioavailability and severity. Lactose, while containing lower α-gal levels, has still been documented to cause anaphylaxis in sensitized patients.	[61,62]
Intermediate	Mixed/uncertain origin; small molecules with possible residues. Sources: animal or plant fats, synthetic	Polysorbate 80/20, Glycerin, Mono-/diglycerides, PEG-stearate, Sorbitan monostearate, Sodium lauryl sulfate, Stearate-coated talc, Crospovidone (animal process), Animal-derived insulin	Risk is variable because manufacturing sources differ; small molecules may retain trace mammalian lipids/proteins if animal-derived. Contaminating α-gal residues can persist after partial purification. Without supplier verification, batch-to-batch variation creates uncertainty.	[61,63]
Low	Non-mammalian origin; no α-gal. Sources: bees, insects, fish, poultry	Beeswax, Shellac, Carmine (cochineal), Chitosan, Shark squalene, Egg lecithin, Salmon calcitonin	Considered low risk because insects, fish, and poultry lack the α-gal epitope; thus IgE cross-reactivity is unlikely. However, egg lecithin may induce allergic reactions through protein allergens unrelated to α-gal. Concerns in this group are primarily ethical or religious rather than immunologic.	[63,64]

sources presents significant challenges that have driven the search for alternatives. Key challenges include: (1) Safety and Purity, including the risk of contamination with zoonotic pathogens (eg, Bovine Spongiform Encephalopathy (BSE)) and inter-batch variability; (2) Ethical and Religious Constraints, where animal-derived products (particularly pork or beef not slaughtered in a specific manner) are unacceptable to vegans, vegetarians, and those with certain religious beliefs (eg, Halal or Kosher); and (3) Supply Chain Limitations, which are dependent on animal availability and susceptible to disruption.[10,13]

Substitution in formulation—replacing one component with another while maintaining efficacy, safety, and stability—requires thorough evaluation. This chapter will explore various modern technological approaches that make ADI substitution highly feasible, with a focus on biosynthesis, chemical synthesis, and the utilization of non-animal natural resources.

Biosynthesis Approach

The biosynthesis, or bioproduction, approach utilizes biological systems as "cellular factories" to produce complex molecules. At the heart of this method is Genetic Engineering (GE), which modifies the DNA of a host organism (such as bacteria, yeast, or plant cells) to produce the desired target molecule. These engineered organisms are then cultured on a large scale using biotechnological processes such as Precision Fermentation (PF).[65,66] This approach offers unparalleled advantages in terms of purity, batch-to-batch consistency, and the elimination of the risk of animal pathogens.

A key success story in the production of recombinant proteins from genetic engineering is insulin. The pharmaceutical industry has completely shifted from extracting insulin from the pancreas of pigs and cows to recombinant human insulin produced by Escherichia coli.[21] This transition not only ensures a reliable supply but also produces products of superior purity and quality. The same principles are now being applied to collagen and gelatin. Using yeast expression systems such as Pichia pastoris, recombinant human gelatin (rHG) can be produced. This product is completely free from animal disease risks and has minimal batch variability, making it an ideal alternative for pharmaceutical applications.[67,68]

In addition to proteins, microorganisms can also be engineered to produce polymers directly. Certain prokaryotes naturally produce polyhydroxyalkanoates (PHAs) and poly-3-hydroxybutyrate (PHB) as energy reserves.[69] Through submerged fermentation from renewable resources (such as glucose), these biopolymers can be produced as environmentally friendly and biodegradable alternatives, replacing petrochemical-based excipients and some animal-derived polymers.[65]

Beyond end products, biosynthetic platforms—particularly mammalian cell culture (eg, CHO cells for monoclonal antibodies) and tissue engineering—have historically relied on ADIs as process aids. For decades, products such as fetal bovine serum (FBS) and Matrigel™ have been the gold standard in research and biomanufacturing.

However, their use raises serious scientific and ethical concerns. These products are susceptible to pathogen contamination, high inter-batch variability, and reproducibility issues. This is inconsistent with the 3R principles (Replacement, Reduction, Refinement) and Good Cell Culture Practice (GCCP). Although advances in serum-free media, synthetic hydrogels, and recombinant antibody technology offer promising alternatives, gold standards such as FBS and Matrigel™ are still widely used due to cost, technical complexity, and limited validation of these alternatives. Overcoming researcher resistance to change remains a major challenge, underscoring the need for robust scientific evidence and regulatory incentives to build trust in these alternatives.

New platforms such as microalgae and transgenic plants (eg, using CRISPR/Cas9) are also being explored as biofactories for complex pharmaceutical molecules, including antibodies and vaccines.[70] Despite the enormous potential of biosynthesis, key challenges remain, particularly in scaling up production to remain cost-effective. In addition, the use of Genetically Modified Organisms (GMOs) presents regulatory and public acceptance challenges that must be carefully managed.[71,72]

Chemical Synthesis

In contrast to biosynthetic approaches that utilize "cellular factories", chemical synthesis involves the ab initio (from scratch) construction of molecules or their controlled modification using chemical reactions. Its main advantages lie in precise control of the final molecular structure, molecular weight, and purity, as well as the complete elimination of the risk of biological contaminants from animal sources. This approach involves the total synthesis of complex drug molecules to replace biological products. The most successful heparin substitute, Fondaparinux, is a prime example. It is a complex saccharide molecule produced purely synthetically, replacing heparin traditionally extracted from porcine

intestine or bovine lung.[73] This total synthesis provides predictable anticoagulant efficacy without the immunogenicity or contamination risks associated with ADI. A chemoenzymatic hybrid approach has also been successfully used to produce non-animal heparin (BEH), which exhibits comparable biological characteristics to animal heparin, demonstrating the feasibility of a continuous, contamination-free production pathway.[74]

Chemical synthesis is prevalent in the excipients field, often used for the polymerization of monomers or the modification of natural, non-animal-derived polymers. Polylactic acid (PLA) is an example of a biodegradable polyester widely used in absorbable sutures and drug-delivery systems.[75] Although its monomer, lactic acid, is often produced through fermentation, the polymerization process to convert it into a long-chain polymer is purely a chemical reaction.

Chitosan, a natural polysaccharide extracted from crustacean shells (a non-mammalian source), is chemically modified to improve its solubility and mucoadhesive properties. This process transforms the natural raw material into an advanced biomaterial for nanoparticle delivery and wound healing.[76]

Despite its clear advantages in terms of control and purity, chemical synthesis presents significant practical challenges. This process often requires advanced polymer chemistry expertise and stringent control of reaction conditions (temperature, pressure).[77] Many monomers and catalysts can be expensive. Furthermore, the use of hazardous organic solvents and the potential for toxic byproducts raise environmental and safety concerns that require proper waste handling and disposal.[78] Consequently, at the laboratory scale, many researchers prefer to modify commercially available polymers (such as PEG, PLA) rather than synthesizing them from scratch.[75,79]

Substitution from Non-Animal Natural Sources

This approach focuses on utilizing naturally occurring biopolymers from plant (terrestrial) or marine (aquatic) sources as direct substitutes for ADI. Unlike biosynthesis or chemical synthesis, this method relies on the extraction and purification of raw materials. Plant-based sources offer an abundant, renewable, and widely accepted alternative (including for Halal/Kosher standards). Cellulose-derived polymers, such as Hydroxypropyl Methylcellulose (HPMC), have been successfully commercialized as vegetarian capsule shells, offering a stable, functional alternative to gelatin and a gelatin capsule replacement.[68]

Other plant-based polysaccharides such as starch, gum tragacanth, and mucilage (eg, from Hibiscus rosa-sinensis) are being extensively explored as functional ingredients.[80,81] They can serve as thickening agents, stabilizers, bioadhesives, and matrices in edible films, replacing the functional role of gelatin in formulations.[82] The main challenge with plant-based polymers often lies in their sensory and textural functionality. Although chemically functional, they may struggle to precisely mimic properties such as mouthfeel, creaminess, or chewy texture typical of gelatin or animal fat.[83,84]

Marine resources, particularly fishery by-products, provide valuable sources of biopolymers. Marine collagen, extracted from fish skin, scales, and bones, is a major alternative to bovine and porcine collagen.[85] This collagen is rich in Type I and has significant potential in biomedical applications, particularly for wound healing and tissue regeneration.[86]

The main drawback of fish collagen is its lower thermal stability (lower denaturation temperature) compared to mammalian collagen. This may limit its use in applications requiring heat resistance, although research on chemical cross-linking continues to address this drawback.[87]

In Silico Approaches as Supporting Tools

Unlike the previous three approaches, which focus on material production, in silico (computational) methods serve as crucial supporting tools and accelerators. This approach directly supports the 3R principle (Replacement, Reduction, Refinement) by reducing reliance on animal testing in the research and development process.[3]

Its primary role is to predict and screen alternative candidates before expensive and time-consuming laboratory testing. Methods such as QSAR (Quantitative Structure-Activity Relationship) and virtual screening can screen thousands of synthetic molecules (such as potential heparin substitutes) to predict their efficacy and toxicity.[3] For biosynthesis, bioinformatics tools can mine microbial genomes to discover new biosynthetic pathways for the molecule of interest.[88]

Docking and molecular dynamics (MD) simulations can model how alternative polymers (eg, HPMC) interact with drug molecules, or how recombinant proteins will behave in a biological environment.[3] By leveraging big data, predictive modeling, and Artificial intelligence (AI), in silico methods enable rapid, cost-effective, and ethical initial

screening. While limited in vitro and in vivo validation will ultimately be necessary, computational approaches drastically reduce the number of animals required and accelerate the pace of innovation in finding viable ADI replacements. With the growing need for more ethical and safe raw materials, various technology platforms have been developed to replace animal-derived materials. Table 4 presents a comparative analysis of these key technology platforms, highlighting their advantages, limitations, and feasibility.

Challenges of Implementation and Optimization of Replacement Formulation

From Material Substitution to Functional Formulation

Advances in biotechnology, chemical synthesis, and plant-based extraction have provided a range of viable technological platforms for producing substitutes for Animal-Derived Ingredients (ADI).[3] These alternatives—ranging from HPMC and plant-based polymers to recombinant gelatin and marine-derived collagen—fundamentally address the ethical, religious, and environmental concerns associated with traditional mammalian-derived ingredients.[62]

However, the availability of these alternative materials represents only the initial phase in pharmaceutical product development. The critical challenge shifts from ingredient substitution to the functional integration of these ingredients into complex dosage forms. Integrated approaches like Quality-by-Design (QbD) for these assessments, highlighting how ADI replacements, such as synthetic polymers for gelatin, must maintain performance without introducing risks.[100]

Table 4 Comparative Analysis of Technology Platforms for Replacing Animal-Derived Ingredients (ADIs) in Pharmaceuticals

Production Platform	Core Mechanism & Key Applications	Advantages/Innovations	Key Challenges (Technical & Regulatory)	Ref
Microbial Fermentation	Genetically engineered (GE) microbes (eg, yeast, bacteria) are used to produce recombinant proteins.Applications in human insulin, recombinant heparin, gelatin.	• Highly scalable • High product purity • Identical structure (bio-identical) to the human target.	High bioreactor capital cost; Downstream Processing (DSP) or purification is highly complex and expensive (can be 50–80% of total cost). Pathway is mature and clear.	[89,90]
Plant & Algal Platforms	Extraction of macromolecules, or Extraction: HPMC capsules (gelatin replacement), Plant-based Magnesium Stearate, Cellulose-based fillers (lactose replacement), Coconut-derived Glycerin.	• Low cost • Existing supply chains • High consumer acceptance	Limited functionality	[91,92]
	Molecular farming (using plants as bioreactors).Plant-derived antibodies, some vaccine proteins.	• Massive scalability • Low upstream production cost.	Recombinant protein yields can be variable, Strict GMO regulatory hurdles; risk of cross-contamination.	[93,94]
Cellular Agriculture	Culturing cell lines (mammalian or other) in vitro in bioreactors to secrete products or grow biologics. Cell-culture based vaccines (eg, Flucelvax®), Medical-grade Collagen, Monoclonal Antibodies.	• Produces 100% bio-identical molecules (eg, collagen's triple-helix structure). • Innovation in media reduces ADI dependency.	Extremely high cost of culture media (especially mitigating Fetal Bovine Serum/ FBS dependency); Scaling mammalian cell bioreactors is highly complex.Very complex (can be considered an ATMP - Advanced Therapy Medicinal Product).	[95,96]
Acellular Synthesis	In vitro production without living cells, Heparin Analogs (eg, Fondaparinux), Synthetic Glycerin, peptides.	Extremely high purity; can create non-natural molecules.	High cost of reagents/raw materials; Scaling (especially for CFPS) is still limited and expensive, Clear (standard NDA pathway);	[97,98]
	Enzymatic/CFPS (*Cell-Free Protein Synthesis*). Rapid vaccine prototyping, complex peptide production.	Speed (ideal for rapid research and prototyping).	Still new/developing for commercial products.	[98,99]

To achieve regulatory approval and clinical acceptance, revised formulations must demonstrate "functional equivalence". This requires comparable performance to the original ADI formulation. Successful implementation depends on a thorough understanding of how these new materials impact physicochemical compatibility, biopharmaceutical performance and bioequivalence, and long-term formulation stability.[100] The revised formulation should not present new or altered safety risks and must achieve the same desired clinical outcomes as the original product.

Challenges in Physicochemical Characterization and Compatibility

The success of ADI substitution depends on comprehensive physicochemical characterization. These challenges can be divided into three main domains: chemical-API compatibility, manufacturing process suitability, and patient acceptability.

First, chemical incompatibilities can directly compromise drug stability and efficacy. For example, replacing lactose (a cow's milk derivative)—which is known to be susceptible to the Maillard reaction with APIs containing primary amine groups—with an inert filler such as Microcrystalline Cellulose (MCC) can drastically alter the chemical stability profile of a formulation.[101] Similarly, functional groups in recombinant gelatin (rHG) may have a different interaction profile with the API compared to porcine-derived gelatin. To detect these interactions, bulk analysis techniques such as Differential Scanning Calorimetry (DSC) are essential to identify thermal transitions, while Fourier Transform Infrared Spectroscopy (FTIR) and X-Ray Diffraction (XRD) assess bonding and crystallinity changes. While these bulk methods are important for initial screening, high-resolution techniques such as Solid-State Nuclear Magnetic Resonance (ssNMR) can provide insights at the molecular level, while Raman Microscopy can visualize the sites of these interactions in situ at the API-excipient interface. The use of advanced sophisticated analytical equipment as well as orthogonal bioanalytical testing, the implementation of a dynamic regulatory cross-checking system, the development and use of machine learning and artificial intelligence tools, and the development of quality-by-design approaches and models have been recognized as the best methods for addressing these challenges.[102]

Second, mechanical compatibility is crucial for manufacturing scalability.[103] Small changes in excipients—such as replacing animal-derived Magnesium Stearate with a plant-based version, or replacing lactose with MCC—can significantly alter the flowability and compressibility of a powder blend, impacting tablet weight uniformity. This difference is also evident in capsule manufacturing: HPMC powder (a gelatin substitute) often has better flow properties but exhibits higher brittleness in low-humidity environments. This difference requires pilot-scale trials to optimize processing parameters to ensure product uniformity.[103,104]

Third, an often overlooked challenge is patient-centric formulation. In liquid formulations, plant-based thickeners replacing gelatin may require significant taste-masking efforts. This is also crucial for injectable preparations. Formulations of heparin substitutes (which are derived from porcine), such as Fondaparinux (synthetic), must be optimized not only for viscosity to avoid increased pain at the injection site, but also for osmolality and pH profiles to be comparable to the original biologic product, all of which impact patient compliance.[105]

Biopharmaceutical and Bioequivalence Performance Evaluation

The cornerstone of ADI substitution is the demonstration of bioequivalence (BE), which ensures that the reformulated product delivers equivalent therapeutic outcomes.[106]

The first-line assessment is in vitro dissolution, which compares drug release kinetics. Differences in excipients can have a significant impact here. A classic example is the replacement of gelatin capsules with HPMC; HPMC offers pH-independent release, while gelatin risks cross-linking over time, which can delay dissolution.[107] However, this challenge is not limited to capsules. In tablet formulations, replacing lubricants such as magnesium stearate (animal vs vegetable) can alter the hydrophobicity of the matrix, affecting disintegration time, while replacing fillers from lactose (soluble) to MCC (insoluble) can fundamentally alter the drug release mechanism itself.[108]

However, comparable in vitro dissolution does not guarantee in vivo BE. Standard in vitro dissolution and permeability tests are limited because no single test condition can fully mimic the complex environment of the human gut.[109] Therefore, human pharmacokinetic studies are essential to ensure the comparability of key parameters such as AUC (total exposure), Cmax (peak concentration), and Tmax (time to peak).[110] Seemingly small excipient changes, such as

switching from lactose to MCC, can significantly alter the bioavailability of APIs with low solubility (BCS Class III).[111] Similarly, for injectable products, differences in viscosity—whether in collagen substitutes in dermatological fillers or in synthetic heparin formulations (replacing porcine heparin)—can affect the rate of subcutaneous absorption, necessitating bridging studies to demonstrate non-inferiority.[112] Injections into the stomach with high viscosity (up to 15–20 cP) are well tolerated, regardless of the volume (up to 3 mL) or injection rate.[113]

Finally, the regulatory pathway for these changes presents a significant hurdle. Failure to achieve BE will delay market approval and undermine confidence in the replacement material.[114] Even if BE is achieved, substitutions of fundamentally functional excipients (such as capsule shells, primary fillers, or binders) are often classified as major variations (eg, EMA Type II variations or FDA SUPAC guidance). This requires a comprehensive data package well beyond a simple BE study, ultimately adding substantial cost and time-to-market barriers.

Long-Term Formulation Stability

Substituted ingredients must not only be stable, but also revalidate the entire formulation stability profile.[115] In many cases, these substitutions actively address the chemical and physical-biological stability issues inherent in ADIs, like gelatin, heparin, or magnesium stearate, must not only demonstrate individual stability but also trigger comprehensive revalidation of the entire formulation's stability profile to ensure no interactions compromise shelf-life, efficacy, or safety under International Council for Harmonisation (ICH) guidelines. Chemically, replacing lactose—which is notoriously susceptible to the Maillard reaction with APIs containing amine groups—with an inert filler such as MCC can dramatically improve the chemical stability of the API.[116] Physically-biologically, replacing gelatin capsules with HPMC eliminates the risk of age-related cross-linking, a phenomenon that can unexpectedly inhibit drug dissolution over time.[117]

However, these substitutes introduce new physical stability challenges, particularly related to environmental sensitivity. Plant-based polymers such as HPMC or mucilages (mucilages) are much more hygroscopic (readily absorb water) than gelatin.[117] This poses new risks for APIs that are highly sensitive to hydrolysis, where water absorption by the capsule shell can accelerate drug degradation. Conversely, under very low humidity conditions, HPMC shells can become more brittle than gelatin, which poses a risk of cracking during packaging or transportation (eg, during thermal cycling).[91]

Challenges also arise from new chemical impurity profiles.[115,118] Substituting excipients such as magnesium stearate or glycerin from animal sources for plant-based sources (eg, palm oil derivatives) introduces a different impurity profile. Trace metals or pro-oxidants different from these plant-based sources have the potential to catalyze previously unobserved API degradation pathways.[119,120] Therefore, accelerated stability testing (as per ICH Q1A guidelines, eg, 40°C/75% RH) and long-term, real-time stability programs are crucial, not only to predict shelf life, but also to ensure that new formulations do not fail during commercial distribution.

Balancing Innovation with Safety

In summary, substituting ADI with plant-based or recombinant alternatives is feasible and aligns with global demands for ethical pharmaceutical production, yet it requires substantial R&D investment to overcome physicochemical, biopharmaceutical, and stability challenges.[121] By prioritizing functional equivalence through advanced characterization, BE evaluations, and stability assessments, developers can ensure that these innovations enhance rather than compromise product quality, safety, and efficacy. Ultimately, this balanced approach not only mitigates risks associated with material transitions but also paves the way for next-generation formulations that are sustainable, vegan-compliant, and therapeutically superior. Ultimately, mastering these formulation challenges will create a more robust, predictable, and secure pharmaceutical supply chain, one that is resilient to the zoonotic risks and supply-demand volatility inherent in animal-derived materials.

Implications, Regulation, and Future Prospects

While meeting technical formulation criteria such as physicochemical compatibility, bioequivalence, and stability is a fundamental prerequisite for Animal-Derived Ingredient (ADI) substitution, achieving this does not automatically lead to market adoption or clinical integration. The transition from technical viability to real-world implementation relies heavily on navigating a complex non-technical landscape. Therefore, this analysis focuses on socio-economic, ethical,

and regulatory determinants. These factors act as both crucial drivers and barriers that ultimately determine the successful adoption of ADI alternatives.

Implications, Gaps, and Barriers to Adoption

Although technical and non-technical foundations provide a rationale for substitution, the real-world adoption of ADIs remains hampered.[122] The transition from theoretical feasibility to market implementation is critically dependent on overcoming regulatory barriers and closing persistent stakeholder knowledge gaps. Therefore, this analysis evaluates these implementation barriers, the resulting clinical and market implications, and proposes a framework for risk stratification.[123]

Significant knowledge gaps among key stakeholders remain a major barrier. Survey data demonstrate a mismatch: while the majority of patients (eg, 63%) desire ADI disclosure, very few (eg, 20% of vegetarians) proactively request it. This inertia burdens healthcare professionals, many of whom report facing ethical dilemmas due to awareness of ADIs but lack of drug-specific knowledge or adequate training to counsel patients.[1]

To address this gap, an operational decision-making framework is proposed. This heuristic is based on five key criteria: (1) identifying the biological source; (2) considering the molecular form and processing, as complex proteins increase risk; (3) assessing the route of exposure, with parenteral administration posing a higher risk; (4) verifying supplier documentation for intermediate-risk ingredients; and (5) accounting for inter-batch variability in a multi-supplier supply chain.

While this stratification framework offers a transparent and systematic basis for evaluation, its usefulness is limited by the lack of mandatory labeling and minimal manufacturer disclosure. This ambiguity often requires direct confirmation from the manufacturer, making risk classification dynamic and dependent on new supply chain information or clinical tolerability data.

This lack of labeling transparency has direct clinical implications, particularly for patients with Alpha-Gal Syndrome (AGS). High inter-manufacturer variability is common; A case study of Atorvastatin showed that many generic formulations contain ADIs (such as lactose), while others are available as "Certified Animal Chemical Free".[124] This variability highlights that without direct verification, healthcare providers cannot ensure safe prescribing.[62]

This regulatory and information gap simultaneously creates both market risks and opportunities. Recent projections published by Fairfield Market Research indicate an estimated growth of over 12% during 2019–2026, with revenues exceeding US$34.8 billion by the end of 2026.[125] Consequently, manufacturers that fail to innovate in excipient procurement face the risk of significant market share erosion. However, recent developments in 2024–2025 are beginning to bridge this gap through the convergence of ethical frameworks and industry innovation. From a clinical perspective, Lababidi et al (2024) highlighted critical gaps in halal drug delivery and proposed a 4-pronged approach—namely, manufacturer change, dosage form change, administration method modification, or drug substitution—as a pharmacotherapeutic strategy to uphold patients' religious autonomy.[126] This ethical imperative is increasingly being met by advances in biotechnology, such as the Health~Holland consortium's initiative to develop bioengineered heparin through fermentation technology to break the dependency on porcine tissue.[127] Furthermore, major industry players such as GlaxoSmithKline (GSK) have actively recognized the strategic transition of key excipients (magnesium stearate, gelatin, and lactose) to plant-based sources, driven by the need to mitigate disease risks and meet the demand for vegan-certified medicines.[128]

Perspective: The Future of Animal-Free Pharmaceuticals

The transition to animal-derived medicines has shifted from a niche issue to an ethical, medical, and environmental imperative, driven by technological innovation, regulatory evolution, and patient demand.[1]

The near-term outlook focuses on transparency and substitution. This includes the implementation of mandatory ADI labeling, "Certified Animal-Free" seals, and digital drug passports for real-time tracking of excipient sources. During this period, traditional ADIs such as gelatin, lactose, and stearate are expected to be widely replaced by plant-based, synthetic, or fermentation-based alternatives, driven by Environmental, Social, and Governance (ESG) pressures and the achievement of cost parity.[62]

The medium-term outlook is characterized by will be characterized by the integration of artificial intelligence (AI) and robotics within connected ecosystems, leading to highly automated and efficient smart factories. A comprehensive

review details AI's role in optimizing pharmaceutical life cycles, including real-time process monitoring and automation integration for connected factories, forecasting efficiency gains of up to 40% by mid-decade.[129] Precision fermentation is projected to dominate the production of biologics (eg, monoclonal antibodies, insulin) without the need for mammalian cell cultures. Technologies such as cell-free synthesis and pharmaceutical 3D printing are expected to enable rapid, safe, and sustainable drug production.[90,130,131] In parallel, the regulatory framework is expected to evolve to include a priority review pathway for animal products and global harmonization of standards (ICH), with ethical and religious certification (Halal, Kosher, Vegan) becoming industry standards.[132]

While this outlook is transformative, significant challenges remain, particularly inertia in existing supply chains, misinformation among stakeholders, and potential patent monopolies on new technologies. Overcoming these barriers requires coordinated action. This transition is seen as inevitable, promising to eliminate the clinical risks of hidden ADIs, ensure ethically inclusive patient access, and significantly reduce the pharmaceutical industry's carbon footprint.[133]

Conclusion

The pharmaceutical industry's historical reliance on Animal-Derived Ingredients (ADIs) now faces significant challenges related to allergic risks (such as AGS), ethical concerns, and religious restrictions (Halal/Kosher). This review paper has demonstrated that AFAs—whether through plant-based excipients, recombinant biologics, or purely synthetic compounds—are now technically feasible.

However, the transition to widespread adoption remains hampered by formulation challenges, cost, and a lack of regulatory harmonization. Currently, patients and healthcare professionals lack transparent data to make medical decisions that align with their clinical needs and personal values. As a concrete solution, the use of the dual-risk stratification framework proposed in this paper is crucial. It provides a practical tool for stakeholders to systematically balance clinical-biological risks and patients' ethical preferences.

To accelerate this transition, a coordinated effort is needed. Manufacturers should prioritize R&D on AFAs, while regulators are urged to establish clear global labeling standards (eg, "Animal-Free" certification). This investment in innovation and transparency is crucial for building a future pharmaceutical supply chain that is not only clinically effective, but also safe, ethical, and sustainable.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Authors gratefully acknowledge the Padjadjaran University, Indonesia for funding and support this research project. This research was funded by Equity Review Article Grant-WCU Padjadjaran University with contract No. 3999/UN6.3.1/PT.00/2025.

Disclosure

The authors report no conflicts of interest in this work.

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