agriculture

MDPI

Review

The Mechanism of Drug Carryover in Feed Manufacturing as a Function of Drug Properties and Equipment Design—A Brief Review

Esther Y. Akoto * and Dirk E. Maier

Department of Agricultural and Biosystems Engineering, Iowa State University, Ames, IA 50011, USA; dmaier@iastate.edu

* Correspondence: eyakoto@iastate.edu

Abstract: This paper thoroughly reviews the mechanism of veterinary drug carryover in feed manufacturing facilities, factors resulting in varying concentrations of drug carryover in processing equipment, the impact of chemical and physical properties of drugs, and the effect of equipment type and design. The Google Scholar database (from 1998 to 2023) was searched with words and phrases such as drug carryover, feed manufacturing, equipment cleaning and validation, food allergen control, sources of drug carryover, and process parameters in drug carryover. Some papers were from the Iowa State University Library database and PubMed. Drug carryover is a function of ingredients, nature of drugs, equipment type, process parameters, and cleaning procedures. The gaps are the lack of commercial feed mills data on the role and interaction of nanomaterials, molasses, equipment type, and process parameters in drug carryover in animal feed. Modification of process parameters, e.g., airflow in bucket elevators and the interaction of feed ingredients, composition, equipment type, and design, need to be investigated in the commercial setting to address drug carryover. Rhetorically, can big data facilitate the standardization of cleaning procedures at feed mills? The findings can result in drug carryover prevention/control in animal feed and animal-based human food.

Keywords: drug carryover; drug properties; equipment design; feed equipment cleaning; feed manufacturing; mechanisms of drug carryover; nanomaterials in feed processing; process parameters

Citation: Akoto, E.Y.; Maier, D.E. The Mechanism of Drug Carryover in Feed Manufacturing as a Function of Drug Properties and Equipment Design—A Brief Review. *Agriculture* **2023**, *13*, 1834. https://doi.org/10.3390/agriculture13091834

Academic Editor: Zoltán Györi

Received: 19 August 2023
Revised: 12 September 2023
Accepted: 18 September 2023
Published: 19 September 2023

1. Introduction

Veterinary drugs administered to food-producing animals have shown tremendous and good impacts by increasing the quality of life of the animals [1–3]. Veterinary drugs are any substances applied or administered to food-producing animals, including meat or milk-producing animals, poultry, fish, or bees, for therapeutic, prophylactic, or diagnostic purposes or modification of physiological functions or behavior [4]. According to the Codex Alimentarius Commission (CAC), there are eleven (11) functional classes of veterinary drugs, including Adrenoceptor agonists, anthelmintic agents, antibacterial, antifungal, and anthelmintic, antimicrobial agents, antiparasitic agents, antiprotozoal agent, Beta-adrenoreceptor blocking agent, Glucocortisteriod, Growth promoters, insecticides, production aid, Tranquilizing agent and Trypanocides [5]. There are approximately eighty-six (86) veterinary drugs recognized by the Codex Alimentarius [5]. In simple terms, veterinary drugs are classified as antimicrobial, coccidiostats, and growth promoters [6]. Veterinary drugs are administered to the animals through the oral route and parenteral route (including intravenous, intramuscular, subcutaneous, and intra-articular), but oral administration is mostly preferred due to the difficulty in working with large groups of animals [6,7].

Veterinary drugs have been added to feed for animals at manufacturing facilities to accommodate large-scale animal feed production to meet demand. Most of the drugs used for animals are significant in human health and can pose regulatory and global trade

issues in countries with "zero" tolerance for residues [6]. In some cases, veterinary drugs, e.g., Antibiotic residues, are linked to antimicrobial resistance [8,9]. Several systems, such as Good Manufacturing Practices (GMPs), Hazard Analysis and Critical Control Points (HACCP), and Hazard Analysis and Risk-Based Preventive Controls, are enforced by countries to control veterinary drug residuals in commercial feed manufacturing [6]. The US FDA 21 CFR part 225 (Current Good Manufacturing Practices (cGMPs)-for medicated feeds) mandates feed manufacturers and handlers to control the carryover of drugs from one batch or lot to the next batch through equipment at medicated feed mills and in bulk delivery trucks. Similarly, the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) had its 23rd session requesting the Food Agricultural Organization (FAO) and World Health Organization (WHO) to provide science-based advice to mitigate the unintended carryover of veterinary drugs into feed and subsequently, human food [6]. Carryover is a form of contamination involving transferring an ingredient/medication/pathogen from one batch to another and can occur during feed manufacturing, handling, transportation, and even delivery to animals on the farm [6,10]. The scope of the review is on veterinary drugs, and the incidences of drug carryover remain of interest to the global food system; hence, the Codex Alimentarius of FAO/WHO organizes a series of meetings to address residues of veterinary drugs in food. One such meeting is the 26th session of the Committee on Residues of Veterinary Drugs in Food, which occurred in February 2023 with a focus on extrapolating maximum residue limits (MLR) to one or more species [4]. It is important to mention that micro-ingredients, e.g., Copper carryover, are equally important to the animal production industry [11]. In some instances, other than the focus of this review, carryover is defined as the residual of drugs in food of animal origin at the time of execution of the animal as food or its by-products [12]. In feed manufacturing, carryover can occur in a single piece of equipment, multiple pieces, or the entire production line [13]. The phenomenon also occurs in the human food and pharmaceutical industries [14,15].

In the pharmaceutical industry, strict procedures are required to avoid patients' exposure to more than 1/1000 of the usual therapeutic dose of another active pharmaceutical ingredient (API) [12]; hence, formulation and facility design are considered for effectively cleaning drug manufacturing equipment. Under formulation, drug manufacturers consider APIs cleanability, solubility, batch size, maximum daily dose, and permitted daily exposure, whereas, with facility design, the surface area shared between the two drugs (contaminant, contaminated) gives the basis for risk assessment and validation test of cleaning efficiency [16]. In the food industry, the main concern is food allergens cross-contamination. Improper production sequencing on equipment, inadequate cleaning of shared processing and/or packaging equipment between product lines, aerosols, and airborne dust from allergens through static electricity, use of compressed air to clean equipment, and the existence of crossover points on production equipment [17]. Prevention of cross-contamination/carryover in the food industry is by the scheduling of process runs to minimize changeovers, the use of dedicated systems for allergenic products, and control of rework and work in progress. Specifically, food manufacturers are advised to design traffic patterns and airflow in the production facility to avoid cross-contact [18]. In pharmaceutical and food manufacturing, validation of cleaning programs is key to prevent carryover. Water is known as the best carryover remover, but that does not apply in dry ingredient facilities such as flour and spices and is a similar challenge to the animal feed manufacturing industry. Dry facilities should rethink traditional equipment design to increase accessibility and cleaning through vacuuming, sweeping, scraping, wiping with clothes/brushes, flushing, and dry ice [19]. Due to the difficulty in cleaning processing facilities, food manufacturers place a high emphasis on the validation of cleaning procedures through visual inspection and swabs for analytical testing such as the ATP test, Polymerase chain reaction, enzyme-linked immunosorbent assay, mass spectrometry, etc. [17,20].

In addition to veterinary drugs, micro-ingredient carryover is a persistent challenge in feed production and transportation [13]. Although there is limited public reported data by feed mills on micro-ingredient carryover in animal feed, it is evident that inorganic elements

added to animal feed in excess result in detrimental effects [21,22]. An example is Selenium, a nutrient that is necessary for the prevention of muscle disease, but concentrations between 10–25 ppm can be toxic to horses and other ruminants [23]. It is important to mention that most of the available peer-reviewed papers on drug carryover focused on developing analytical methods to analyze feed and feed ingredients [24–28]. However, a few of the peer-reviewed papers on the feed manufacturing process and management of safety [22] mostly exclude the impact of feed manufacturing equipment parameters [10,21,29,30]. From the few research papers that focused on drug carryover during feed manufacturing, the finished feed bins and bucket elevators remain where maximum drug carryover is reported [10,13,30,31]. Drugs are less quickly cleaned from the elevator boots, resulting in accumulation at the bottoms and possibly corners of the elevator. If carryover is not properly controlled, contaminated feed can harm species vulnerable to the accidental veterinary drug they eat [6,8]. Also, there is the possibility of these drug residues in food of animal origin, such as meat, milk, and eggs, which can be unsafe for human consumption. Antibiotic resistance of human and animal pathogens partly originated from excessive use of antibiotics intentionally and unintentionally from carryover to untargeted animals [6,32,33]. Economically, feed producers and animal farmers may incur financial losses due to drug carryover in feed products and subsequent product recalls. From the US FDA routine animal feed recalls, some reasons are based on elevated levels of drugs and micro-ingredients [34], although investigations findings have not been published to determine the role of drug carryover. The most effective cleanout procedure is a thorough cleaning of the feed manufacturing equipment, but the procedure is effort-demanding and time-consuming [6,10,35]. As part of the US FDA CGMPs, feed mill operators must use flushing and sequencing to control drug carryover [10,36]. Sequencing is the pre-defined succession of feed manufacturing to prevent contamination of subsequent batches, but its application is challenging for low-production facilities. This is usually done in high-production facilities with enough volume to predefine weekly production schedules. On the other hand, in both large and smaller facilities, the cleaning technique is flushing, done using the cheapest available grain (typically corn), ground to approximately 500 microns, and conveyed the same way the medicated feed is to clean equipment [10]. To prevent economic loss, facilities that use flushing as their cleanout procedure label the flush material as re-work and use it in future medicated diets [10]. The danger lies in cross-contamination if proper care is not taken in labeling and storing the flush material. The U.S. FDA recommends using 50–100 g/kg of the mixer's total capacity as the flush material, assuming that the residual drug in the feed manufacturing system will not be higher than the drug tolerance levels in subsequent feed batches [10,36].

Some pilots and industrial studies have been conducted to understand and remedy drug carryover in manufacturing equipment, but this paper is a thorough review of the mechanism of drug carryover in feed manufacturing facilities, factors resulting in varying concentrations of veterinary drug carryover in different parts of processing equipment, the impact of chemical and physicochemical properties of drugs, and the effect of equipment type and design. The paper also compares the effectiveness of equipment cleaning and drug carryover prevention methods in feed mills to methods employed by food processing companies and drug manufacturers to control allergen and drug cross-contamination, respectively.

2. Materials and Methods

The information in this review was collected through an extensive literature review by assessing the Google Scholar database on keywords such as feed technology, food allergens, pharmaceutical cleaning, classification of veterinary drugs, and validation research papers. The database search consisted of papers published from 1998 to 2023. Some articles were accessed through the Iowa State University Library database and PubMed. During the review of information, keywords and phrases searched included feed additives, drug carryover, feed manufacturing, equipment cleaning and validation of cleaning, food allergen process

control, sources of drug carryover, and process control for drug carryover. This included a combination of these words and phrases. The Food and Agriculture Organization (FAO) technical reports on veterinary drug carryover were reviewed to understand the global significance of drug carryover. In addition, the FAO/WHO Codex Alimentarius was a go-to website for reviewing the categories of veterinary drugs.

3. Results and Discussion

3.1. Veterinary Drugs as Feed Additives

Veterinary drugs are grouped into antimicrobial, coccidiostats, and growth promoters [6]. Veterinary drugs are administered to animals through the oral route and parenteral [7], but oral administration of veterinary drugs to animals is mostly preferred due to the difficulty in working with large groups of animals [6]. Medicated feeds are manufactured by adding veterinary drugs to animal feed during manufacturing and fed to the animals [26,37–41].

Antimicrobials such as antibiotics are microorganism-killing or inhibiting compounds added to animal feed for the treatment and prevention of diseases and growth promotion [1,8]. Governmental regulatory bodies around the world have set laws to control the use of antibiotics in animal feed, e.g., the ban on use for growth promotion due to instances of antibiotic resistance [42–48]. Antimicrobials added to feed include but are not limited to β-Lactams (Penicillin and Cephalosporin), tetracyclines, chloramphicols, macrolides, spectinomycin, lincosamide, sulfonamides, nitrofuranes, nitroimidazoles, trimethoprim, polymyxins, quinolinones and macrocyclines (ansamycins, glycopeptides and aminoglycosides) [1,8,40].

Coccidiostats are parasite-killing compounds used by the poultry industry to kill coccidiosis-causing protozoans [2,49]. The eleven (11) authorized coccidiostats used as feed additives include ecoquinate, diclazuril, halofuginone, lasalocid, maduramicin, monensin, narasin, nicarbazin, robenidine, salinomycin, and semduramicin [50]. Concerns are raised about using coccidiostats as feed additives in single production lines due to carryover to feed for untargeted and sensitive species such as turkeys and horses [10,50].

Although all non-nutrient feed additives, such as antibiotics, can be called growth promoters, Beta-agonists are the actual growth promoters that are added to feed to improve utilization by animals [51,52]. Growth promoters, e.g., Ractopamine and Zilpaterol, remain controversial drugs approved by countries such as the US but not others [53,54].

3.2. Veterinary Drugs Carryover in Feed Manufacturing

Drug carryover may be prevented through equipment and factory design for new facilities and by designating different equipment for specific animal species feed [38] that could come with an extra investment cost. Not many studies have been conducted to determine equipment parameters that can be modified to address the challenge for existing feed manufacturing facilities. Instead, researchers mentioned that equipment must be easily accessible for dismantling and cleaning [19]. In practice, most feed manufacturing companies are limited by time for such laborious activities, raising the question for researchers and manufacturing engineers to study equipment parameters that can be easily modified to address carryover. To compare, in the food industry, contact surfaces for manufactured foods are mostly smooth to avoid crevices, projections, and edges that can cause carryover. Ironically, food companies use surfaces of high Ra values but still must deal with carryover or cross-contamination of allergens [20].

In the feed industry, some specific locations in the processing line for drug carryover and the proposed mechanism of the carryover incidents are presented in Table 1. Although the Agricultural Extension group detailed some possible causes of drug carryover in different feed manufacturing equipment (Table 1), a greater impact can be achieved if research engineers validate the factors listed. One such factor is that drug carryover in the bucket elevator results from residual feed remaining in buckets and boots and electrostatic or moisture hang-up (Table 1). The claim is partially supported by the findings that fine

particles of feed ingredients and micro-tracer during carryover (9.8%) are affected by the feeding angles of the test bucket elevator, and conducting an up-scale industrial experiment to validate the findings is necessary [30].

Table 1. Proposed sources of drug/ingredient carryover in feed equipment by Extension Services [39].

Equipment	Form of Carryover
Dust system	The prolonged return of dust to the manufacturing line Extreme pickup of drugs and carrier Hang-up (electrostatic or moisture)
Mixer	Residual feed lingering in the mixer The buildup of material on ribbons and walls Electrostatic hang-up on walls and top Leaking mixer gate (not fully closed)
Surge bin	Partial clean-out Electrostatic or moisture hang-up
Conveyors	Same as the surge bin
Elevators	Residual feed remaining in buckets and boots Electrostatic or moisture hang-up
Bins	Bridging Residual feed from the partial cleanout
Bulk truck	Error in bin chart records Partial clean-out Bridging and hang-up

In addition to equipment type, certain feed ingredients such as processed animal by-products (PAP), including meat and bone meal, poultry by-products, blood meal, and feather meal from unspecified species can present drug carryover in non-target food-producing animals (Table 2) [6]. The implementation of the Codex Alimentarius Maximum Residue Limit (MRL) for the eighty-six veterinary drugs in different animal species [55] and other country-specific MLRs can also help to resolve the incidence of drug carryover when processed animal by-products (PAP) are used for feed manufacturing [56]. For instance, in 2008, the US FDA detected Virginiamycin and Erythromycin in distillers' dried grains (DDGs) after fermentation (Table 2). The two antimicrobials are added to the fermentation of DDGS to prevent bacterial growth but raise concerns about carryover in animal feed. Rhetorically, has the challenge been resolved to keep the grain processing and feed manufacturing industries thriving safely? The FAO/WHOs report in 2019 calls for researchers to also focus on the incidences and impact of drug carryover resulting from the non-intentional introduction of medications from feed ingredients (Table 2). It is important to mention that the information provided in Table 1 is an industrial representation of drug carryover, which necessitates the need for researchers to conduct experiments to support the claim by the industry. There is limited data on the use of PAP for feed manufacturing in developing countries, hence creating a gap for researchers to investigate the possibility of the use of PAP and drug carryover challenges. To be circumspect, bucket elevators are mentioned as the main source of veterinary drug carryover [10,13,30]. To this challenge, residual feed remaining in buckets and boots and electrostatic or moisture hang-up are proposed to be the reasons (Table 1) [30,39]. Ironically, there is limited published research to validate the claim, raising the need to conduct experiments focused on explaining the interaction of the chemistry of the veterinary drugs and engineering parameters of buckets elevators on drug carryover [39]. In perspective, it is justifiable and necessary to understand the interaction of the chemistry of veterinary drugs, feed ingredients, and engineering parameters in drug carryover for all individual feed equipment. A list of troubleshooting steps for different feed manufacturing equipment to control drug carryover in feed processing equipment, e.g., for the bucket elevator, proposed checks include adjusting bucket clearance in boots, installing air sweep jets, and remodeling boots for a more complete cleanout is provided in

Table 3 [39]. Again, as an example, how much published research data exists to support the cleanout level from air sweep jets and remodeling of boots? Considering Tables 1 and 3, more avenues exist to reignite research on the parameters of different feed equipment and the interaction with drugs and feed ingredients leading to drug carryover.

Table 2. A list of some drugs identified in processed animal by-products for feed manufacturing.

Drugs Identified	Place Identified	Source	Reference
Monensin, Flumequine, Enrofloxacin, Trimethoprim, Tylosin, Ciprofloxacin	European Union	Meat, bone meal, poultry by-products, blood meal, feather meal	[6,26,37,57,58]
Fluoroquinolones, tetracyclines, folic acid antagonists, and streptogramins	United States of America and China	Feather meal	[26,58–60]

Table 3. Proposed troubleshooting to control drug carryover by an Extension service [39].

Mode of Carryover	Proposed Corrective Action
Electrostatic hang-up	Ground wire to the equipment of interest Use a non-electrostatic type of premix Use liquid ingredients to limit dust Vibrators to shake hang-up loose
Delayed or extended dust return	Adjust air velocity at collection points allow more time for dust to clear up Use liquid ingredients to reduce dustiness Collect and discard dust following the production of medicated feeds Remodel dust system
Mixer residues	Adjust ribbons or paddles Install plastic 'wipers' on ribbons Install air sweep jet for cleaning Remodel discharge for a more complete cleanout Add drug when mixer is $^{1}/_{2}$ to $^{3}/_{4}$ full
Surge bin, conveyor residues	Adjust for a more complete cleanout Remodel bin or discharge
Elevator residues	Adjust bucket clearance in boots Install air sweep jets Remodel boot for a more complete cleanout
Bin residues	Manual inspection and cleaning when changing the kind of feed stored Install vibrator or air sweep jets
Pellet mill and dryer residues	Flush blender and dies Adjust the dryer for a more complete cleanout
Entire system	Use production schedule Allow time between kinds of feed for manual cleaning of the system

3.3. Mechanism of Drug/Micro-Ingredient Carryover

3.3.1. Chemical and Physicochemical Properties of Veterinary Drugs

The feed type and composition of the veterinary drugs are significant in determining the carryover amount [6,13]. In general, factors proposed to influence carry-over are electrostatic charge, particle size, hygroscopic nature of drugs, segregation, equipment design, and infrastructure, as well as cleaning methods of the line [27,61]. Some veterinary drugs used in feed are presented with a summary of the main characteristics of the drugs

resulting in their carryover (Table 4). The few numbers of references in Table 4 indicate that most of the papers identified hardly focused on determining the mechanism of carryover. Significantly, among antimicrobials, Tetracyclines, Sulfonamides, and Penicillin are mostly implicated with carryover in feed due to their powdered nature and high electrostatic charges [6,13]. The antimicrobials adhere to equipment surfaces and are challenging to clean. Some manufacturers are now producing granular versions of these drugs to address the problem [6,13]. Particle size and segregation fall in the same category since a high variation within the same ingredient and between different ingredients results in segregation. The possibility of controlling carryover by limiting particle size variation between ingredients used for feed manufacturing must be investigated. For coccidiostats, e.g., Monensin, the main implication is the harm caused to other non-target species, such as horses [62]. Growth promoters, e.g., Ractopamine, remain controversial drugs approved by countries such as the US but not others [53,54]. Although growth promoters are not approved in other countries, except the US, calls for research to understand the mechanism of its carryover in non-targeted feed is necessary.

Nanotechnology is an emerging technology involving the operation of constituents on an atomic or molecular scale (0.1–100 nm in size) with vast applications in diverse fields of study, such as medicine [46].

Currently, nanotechnology has been implemented in producing feed ingredients such as drugs to improve feeding efficiency and nutrition, minimize losses of animals due to diseases, and convert waste to value-added products [6,46,63]. As researchers call for the use of Nanomaterials, e.g., oxides of Magnesium oxide, Silver, and Copper nanoparticles [46,64] in place of antibiotics, there is a need for proactive studies to investigate the impact of nanomaterials in drug carryover of animal feed.

Table 4. Some veterinary drugs implicated in carryover and the proposed characteristics leading to carryover in feed.

Drug Type		Main Characteristics	Reference
Antimicrobials/Antibiotics	Tetracyclines, Penicillin, Amoxicillin, Chlorotetracycline, Doxycycline, Florfenicol, Ivermectin, Lincomycin, Tiamulin Sulfonamides	Physical characteristics High concentrations added to feed Highly electrostatic and dusty (powdered form)	[6,47,65] [6,66]
Coccidiostats	Lasalocid, maduramicin, monensin, nicarbazin, narasin, salinomycin and semduramicin, decoquinate, diclazuril, clazuril, halofuginone, nicarbazin, robenidine and amprolium	High electrostatic dusty (powdered form)	[6,61,67]
Growth promoters (β-adrenergic agonists)	Ractopamine Zilpaterol Clenbuterol Hydrochloride (not approved)	Not discussed clearly	[6,54]

3.3.2. Impact of Feed Composition and Ingredients

In the experimental setting, a full ingredient list and quantity of each ingredient for both medicated feed and non-medicated to study Nicarbazin carryover were provided [10]. Subsequent research to compare carryover in different compound feeds providing all the feed ingredients and the respective amounts can help researchers understand drug carryover more efficiently.

In the case study setting (commercial) for drug carryover, the identified research papers did not discuss the impact of feed composition and ingredients on drug carryover except for the comparison of mean % carryover about the drug doses with the nutritional composition of labels and finding low correlations with crude proteins, calcium and many

more [61]. Feed samples were from 25 feed mills in Brazil, and 63% had carryover greater than 1% of the required doses [61]. In a similar fashion, models were developed to predict drug carryover in a feed mill to the farm; variables included in the model were the probability of cross-contamination, the weight of the flush, the weight of the batch, the weight of total feed produced, the number of cross-contaminations, the flush weight of cross-contamination, and flushing per country excluding feed composition and ingredients used [29]. Future research, including feed formulation and ingredient type, will provide an in-depth understanding of reducing drug carryover in animal feed.

Although there are limited studies to understand the role of feed ingredients in drug carryover, liquids such as molasses, fat, or water added to the feed formulation are recommended to control the segregation of ingredients and drug particles [19]. Liquids aid agglomeration, but some liquids, e.g., sugar molasses, can stick to equipment and bins, leading to a high risk of carryover, while soybean molasses has a lower viscosity [28]. Conducting studies to understand the role of varieties of molasses with different viscosities in drug carryover and the means of controlling it will provide more information to support the feed industry.

3.3.3. Impact of Equipment Types and Design

The basic feed mill equipment is a hammer mill/roller mill, mixer, surge bins, elevators/conveyors, and finished feed bins [10]. Equipment flushing is the use of raw feed ingredients such as corn meal to clean out equipment in between the production of medicated feed and non-medicated feed. Sequencing is the predefined succession of feed production to possibly prevent drug carryover [13,31]. Veterinary drug carryover is traced to individual equipment, multiple equipment, and transportation of both medicated and non-medicated feed without proper steps to avoid cross-contamination [10,13,19]. In the production line, carryover is traced to some ingredients, mixers, conveyors, surge bins, elevators, and finished bins [10]. Varying time of sample collection, factory construction, place of sampling, number of samples, and their interaction on levels of carryover of some antibiotics to determine homogeneity of carryover with time [13]. The findings indicate that carryover can reduce with time and the number of runs but can also vary in the same equipment at a facility, resulting in inhomogeneity of drug carryover [13]. Establishing a system based on the homogeneity of drug carryover for feed mills is difficult, and one possible reason is the lingering of the medicated feed in corners of the equipment, e.g., the buckets of elevators, even after flushing. Although flushing can reduce carryover in the mixer to a very low level (below the Maximum Residue Limit) [10], an experiment on the effect of liquid application time and wet mix time with different mixers (double ribbon, paddle mixer, twin shaft counter poise mixer) indicated that increasing wet mix time had a greater effect on % coefficient of variation (CV) for double ribbon paddle mixer and paddle mixer but not for twin shaft counterpoise mixer [68]. While extended liquid application times are beneficial, there must be a minimum wet mix time after all the liquids have been added to the mixer. In Brazil, all the feed mills in the case study did not meet the coefficient of variation of the mixture homogeneity as required by the Brazilian government [61]. It is important to state that Brazil's standard for % coefficient of variation is 5%, which is very stringent compared to 10% of other countries such as the US. Finding the impact of the liquid application time and wet drying time on carryover in the mixer and other feed equipment is a step toward understanding drug carryover better.

Although determining the homogeneity of drug carryover is challenging, researchers have consistently mentioned that the highest concentrations of drug carryover happen in the bucket elevator and finished feed bins. Nicarbazin concentration after flushing the feed manufacturing line ranges from 1.8×10^{-4} mg/kg to 3.18×10^{-4} mg/kg in the bucket elevator and 9.10×10^{-5} mg/kg to 3.18×10^{-4} mg/kg in the finished feed bin [10]. Similarly, multiple drug carryover ranges from 0.1–154 mg/kg without indicating the specific area in the process line where samples were collected [13]. We sought to identify possible research papers that compared types of mixers, bucket elevators, and finished feed

bins on drug carryover, but we did not find any implying that the research gap must be addressed.

3.3.4. The Influence of Process Parameters

Experimental studies on industrial sites have attributed drug carryover to equipment between the mixer and pellet mill, implying that bucket elevator is a significant source of carryover, and deposits of fine particles on the walls of buckets are the culprit [10,30]. Further, the phenomenon of drug carryover is proposed in two phases, which are the separation of medicated feed particles from the first run and the collection of medicated feed into the second non-medicated feed run [30]. The head and foot areas of bucket elevators are known to have higher deposits of drugs. Interestingly, particle size analysis shows that the particle size distribution of the deposits is under 200 µm [30]. It is argued that deposits on the leg have high particle size as compared to deposits on walls and the head area. The inference is that deposits on the legs are from unpicked products from buckets and down leggings, and the first phase of drug carryover is influenced by the interaction between the discharge spout angle and discharge type (centrifugal or gravity) [30]. In the second phase, the concentration of residue collected in subsequent feed is attributed to the interaction of space between bucket walls and discharge type to this phase [30]. To further explain, these parameters are located on the head of bucket elevators and may influence airflow in this area. Unfortunately, the researchers only focused on discharge parameters to explain drug carryover, and the experiment was on a small-scale test bucket elevator. Also, airflow in bucket elevators may not only be contributed by head parameters, but an experiment to explain how modification of buckets influences airflow may help understand and reduce drug carryover through bucket elevators. The few and current review papers in feed manufacturing (e.g., Future Directions) focused on the entire feed technology to meet challenges in the world, while the current review is a specific one to address the importance of conducting research to better understand process parameters of processing equipment in controlling drug carryover. It is significant to mention that some claims are made by the extension services (Tables 1 and 3) in the feed industry, and conducting experiments to validate them will interest the entire industry in meeting feed safety regulations. It is also important to mention that the review calls for future research to be conducted in commercial/larger feed mills (if possible) together with studying the effect of process parameters on drug carryover.

3.4. Cleaning Procedures to Control Drug Carryover

Food safety regulations such as the US FDA CGMPs and Codex Alimentarius are directives to help medicated feed manufacturers prevent drug carryover. The cleaning procedures proposed to control drug carryover are full cleaning, sequencing, and/or flushing [10,31,69]. Full cleaning of production lines is the most effective choice, but considering the schedule and production rate of feed mills, routine full cleaning is not practical. Most facilities resort to a combination of flushing and sequencing of feed. Sequencing of feed is a challenge for smaller feed mills to implement. The FDA recommends using a 50–100 g/kg mixer capacity as flush material. The effectiveness of the flush size recommended by the FDA and found a significant reduction in drug carryover [10]. Yet, the concentrations of drug residue in bucket elevators and finished feed bins were relatively high, raising concerns for further studies to address the problem. This is a significant problem to address after the medicated feed is contaminated with the immediate medication used and because other researchers have found that drug carryover is inhomogeneous. Sometimes, non-medicated runs after the medicated feed are contaminated with the immediate medication used and medication used in several batches earlier [13]. Contrarily, in cattle feedlots, one sequencing decreased drug residue by 99% [31]. In support, a 1% flush size effectively avoids the remnant of narasin and monensin in poultry feed [10]. Also, the end-of-line mixers prevented drug carryover, which is not feasible for commercial feed mills [29]. In the aquaculture industry, drugs are added to pellets post-manufacturing and effectively

prevent drug carryover [38]. Experimental studies to determine the application of aquaculture techniques in producing other commercial feed while addressing its shortfalls, such as reduced palatability, can be helpful in the quest to control carryover. Could standard cleaning procedures be developed based on developed models from industry-collected data to improve cleaning procedures at feed mills?

4. Conclusions

Although future research is needed to understand and remedy veterinary drug carryover at feed mills, the phenomenon is a function of ingredients, nature of drugs, equipment type, process parameters, and cleaning procedures. Ingredients such as meat, bone, blood and feather meals, and other poultry by-products are the ingredient source of drug carryover. The electrostatic charge, particle size, and hygroscopic nature of drugs such as antimicrobials facilitate segregation, leading to drug carryover. The bucket elevator and finished feed bin are identified as major sources of drug carryover during feed manufacturing. Currently, sequencing and flushing can reduce drug carryover if applied appropriately since full cleaning can be challenging. Despite the limited information on process parameters on drug carryover, airflow in elevator buckets, discharge spout, and discharge angle were proposed to impact drug carryover in a pilot lab setting.

The gaps are the lack of commercial feed mills data on the role and interaction of nanomaterials, molasses, equipment type, and process parameters in drug carryover in animal feed. Modification of process parameters, e.g., airflow in bucket elevators and the interaction of feed ingredients, composition, equipment type, and design, need to be investigated in the commercial setting to address drug carryover. Rhetorically, can big data facilitate the standardization of cleaning procedures at feed mills? The findings can result in drug carryover prevention/control in animal feed and animal-based human food.

5. Future Directions

Future research on the list of possible causes and corrective actions of drug carryover in different feed manufacturing equipment (Tables 1 and 3) must be validated by research engineers through experiments. Policymakers can consider applying the Codex Alimentarius Maximum Residue Limit (MLR) for the eighty-six veterinary drugs, and other country-specific MLRs could be impactful in resolving some incidences of drug carryover through processed-by-products used for feed manufacturing. Also, experiments on drug carryover during feed manufacturing should factor in feed ingredients, and formulations feed forms (mash or pellets) as possible variables to be studied. Conducting studies to understand the role of varieties of molasses with different viscosities in drug carryover and the means of controlling it will provide more information to support the feed industry. As researchers call for the use of Nanomaterials, e.g., oxides of Magnesium oxide, Silver, and Copper nanoparticles in place of antibiotics, there is a need for proactive studies to investigate the impact of nanomaterials in drug carryover of animal feed. Designing experiments by varying process parameters such as airflow, discharge type, etc. of feed equipment, e.g., bucket elevator, can help research engineers identify possible means of controlling inhomogeneity in drug carryover. The research gap to identify the use of PAP for animal feed manufacturing in developing countries and to identify possible drug carryover issues will proactively protect public health. Although growth promoters are not approved in other countries, except the US, calls for research to understand the mechanism of its carryover in non-targeted feed is important. Lastly, most experiments, e.g., on process parameters, are conducted at small pilot plants or lab settings; hence, upscaling to commercial feed mills poses a non-linear relation problem. Collecting drug carryover/cross-contamination data from multiple commercial feed mills can generate models to address drug carryover and inhomogeneity and standardize cleaning protocols through big data, and machine learning.

Author Contributions: E.Y.A. is responsible for resources, writing—original draft preparation, and D.E.M. was responsible for supervision and writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Data sharing is not applicable to this article. No new data were created or analyzed in this study.

Acknowledgments: We acknowledge the authors of the papers cited in this review paper for making their research available online.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviation

A List of acronyms mentioned in the paper.

Acronym	Full Meaning
US FDA	United States Food and Drugs Administration
CFR	Code of Federal Regulations
CGMPs	Current Good Manufacturing Practices
API	Active Pharmaceutical Ingredient
ATP	Adenosine triphosphate
PAP	Processed animal by-product
DDGs	Distillers' dried grains
Ra values	Roughness average values
FAO	Food and Agriculture Organization
WHO	World Health Organization

References

1. Chantziaras, I.; Boyen, F.; Callens, B.; Dewulf, J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: A report on seven countries. *J. Antimicrob. Chemother.* **2014**, *69*, 827–834. [CrossRef]
2. Mortier, L.; Daeseleire, E.; Van Peteghem, C. Determination of the ionophoric coccidiostats narasin, monensin, lasalocid and salinomycin in eggs by liquid chromatography/tandem mass spectrometry. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 533–539. [CrossRef]
3. Roila, R.; Branciari, R.; Pecorelli, I.; Cristofani, E.; Carloni, C.; Ranucci, D.; Fioroni, L. Occurrence and residue concentration of coccidiostats in feed and food of animal origin; human exposure assessment. *Foods* **2019**, *8*, 477. [CrossRef]
4. FAO/WHO. Codex Alimentarius International Food Standards 0 Codex Committee on Residues of Veterinary Drugs in Foods. 2023. Available online: https://www.fao.org/fao-who-codexalimentarius/meetings/detail/it/?meeting=CCRVDF&session=26 (accessed on 9 June 2023).
5. FAO/WHO. Codex Alimentarius International Food Standards–Veterinary Drug Functional Classes. 2023. Available online: https://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/functional-classes/en/ (accessed on 9 June 2023).
6. FAO/WHO. Codex Alimentarius International Food Standards–Managing the Risk of Veterinary Drug Transfer through Feed to Food. 2019. Available online: https://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/en/c/1177804/ (accessed on 9 June 2023).
7. Turner, P.V.; Brabb, T.; Pekow, C.; Vasbinder, M.A. Administration of substances to laboratory animals: Routes of administration and factors to consider. *J. Am. Assoc. Lab. Anim. Sci.* **2011**, *50*, 600–613.
8. Bacanlı, M.; Başaran, N. Importance of antibiotic residues in animal food. *Food Chem. Toxicol.* **2019**, *125*, 462–466. [CrossRef]
9. Ma, F.; Xu, S.; Tang, Z.; Li, Z.; Zhang, L. Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosaf. Health* **2021**, *3*, 32–38. [CrossRef]
10. Martinez, A.; Jones, C.K.; Stark, C.R.; McKinney, L.J.; Behnke, K.C.; Paulk, C.B. Evaluating flushing procedures to prevent nicarbazin carryover during medicated feed manufacturing. *Anim. Feed Sci. Technol.* **2018**, *242*, 1–7. [CrossRef]
11. Post, L.O.; Williams, S.; Applegate, C.; Jones, B.; Herrman, T.J.; Bailey, E.M., Jr. Risk assessment of copper and molybdenum and other minerals in feed ingredients and finished feeds. *J. Regul. Sci.* **2019**, *7*, 1–9. [CrossRef]
12. Ghosh, A.; Dey, S. Overview of Cleaning Validation in Pharmaceutical Industry. *Int. J. Pharm. Qual. Assur.* **2010**, *2*, 26–30.
13. Stolker, A.A.M.; Manti, V.; Zuidema, T.; van Egmond, H.; Deckers, E.R.; Herbes, R.; Hooglugt, J.; Olde Heuvel, E.; de Jong, J. Carry-over of veterinary drugs from medicated to non-medicated feeds in commercial feed manufacturing plants. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* **2013**, *30*, 1100–1107. [CrossRef]
14. Beula, S.J.; Suthakaran, R.; Ramulu, Y.; Viswaja, M.; Venkateswaralu, G. A Review on Cleaning Validation-Regulatory Guidelines for The Pharmaceutical Industry. *Asian J. Pharm. Clin. Res.* **2022**, *12*, 167–170. [CrossRef]

15. Crevel, R.; Cochrane, S. *Allergen in Food Safety Management*; Academic Press: Cambridge, MA, USA, 2014; pp. 59–82. [CrossRef]
16. Tatli, S.; Pinar, I.; Seven, B.; Gul, B.; Seda, I.M.; Abdelfattah, Z.M.S. Nanotechnology and nano-propolis in animal production and health: An overview. *Ital. J. Anim. Sci.* **2018**, *17*, 921–930. [CrossRef]
17. Huggett, A.C.; Hischenhuher, C. Food manufacturing initiatives to protect allergies. *Allergy Eur. J. Allergy Clin. Immunol.* **1998**, *53* (Suppl. 46), 89–92. [CrossRef]
18. Jackson, L.S.; Al-Taher, F.M.; Moorman, M.; DeVries, J.W.; Tippett, R.; Swanson, K.M.; Fu, T.J.; Salter, R.; Dunaif, G.; Estes, S.; et al. Cleaning and Other Control and Validation Strategies to Prevent Allergen Cross-Contact in Food-Processing Operations. *J. Food Prot.* **2008**, *71*, 445–458. [CrossRef] [PubMed]
19. Dorne, J.L.; Fernandez-Cruz, M.L.; Bertelsen, U.; Renshaw, D.W.; Peltonen, K.; Anadon, A.; Feil, A.; Sanders, P.; Wester, P.; Fink-Gremmels, J. Risk assessment of coccidostatics during feed cross-contamination: Animal and hu-man health aspects. *Toxicol. Appl. Pharmacol.* **2013**, *270*, 196–208. [CrossRef]
20. Marengo, M.; Bonomi, F.; Iametti, S.; Ferranti, P.; Barbiroli, A. Monitoring the carryover of egg proteins in pasta making to support allergen risk management. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* **2021**, *38*, 1087–1095. [CrossRef]
21. Acedo-Rico, J.; Méndez, J.; Santomá, G. Feed manufacturing. In *Nutrition of the Rabbit*; CAB International: Wallingford, UK, 2020; pp. 222–242. [CrossRef]
22. Bouxin, A. *Management of Safety in the Feed Chain in Food Safety Management*, 2nd ed.; Academic Press: Cambridge, MA, USA, 2023; pp. 19–35. [CrossRef]
23. Desta, B.; Maldonado, G.; Reid, H. Acute selenium toxicosis in polo ponies. *J. Vet. Diagn. Investig.* **2011**, *23*, 623–628. [CrossRef]
24. Aguilera-Luiz, M.M.; Romero-González, R.; Plaza-Bolaños, P.; Martínez Vidal, J.L.; Garrido Frenich, A. Wide-scope analysis of veterinary drug and pesticide residues in animal feed by liquid chromatography coupled to quadrupole-time-of-flight mass spectrometry. *Anal. Bioanal. Chem.* **2013**, *405*, 6543–6553. [CrossRef]
25. Annunziata, L.; Visciano, P.; Stramenga, A.; Colagrande, M.N.; Campana, G.; Scortichini, G.; Migliorati, G.; Compagnone, D. Investigation of Nonionophoric Coccidiostat Residues in Feed as a Consequence of Carryover. *J. Food Prot.* **2018**, *81*, 482–489. [CrossRef]
26. Berntssen, M.H.G.; Valdersnes, S.; Lunestad, B.T.; Hatlen, B.; Alm, M.; Waagbø, R.; Buttle, L. Residue levels of enrofloxacin and ciprofloxacin in processed animal by-products used in Atlantic salmon feeds and their long-term carry-over to the edible part of the fish. *Aquac. Nutr.* **2014**, *20*, 712–721. [CrossRef]
27. Borràs, S.; Companyó, R.; Granados, M.; Guiteras, J.; Pérez-Vendrell, A.M.; Brufau, J.; Bosch, J. Analysis of antimicrobial agents in animal feed. *Trends Anal. Chem.* **2011**, *30*, 1042–1064. [CrossRef]
28. Nestmann, E.R.; Lynch, B.S. Method for calculating ADI-derived guidance values for drug carryover levels in medicated feeds. *Regul. Toxicol. Pharmacol.* **2007**, *47*, 232–239. [CrossRef] [PubMed]
29. Filippitzi, M.E.; Chantziaras, I.; Devreese, M.; Dewulf, J. Probabilistic risk model to assess the poten-tial for resistance selection following the use of anti-microbial medicated feed in pigs. *Food Addit. Contam. Part A Chem. Anal. Control. Expo. Risk Assess.* **2018**, *35*, 1266–1277. [CrossRef] [PubMed]
30. Leloup, M.; Putier, F.; Solliec, C.; Le Coq, L. Micro-ingredients carry-over during bucket elevator handling in feed industry: Influence of process parameters. *J. Food Process Eng.* **2013**, *36*, 675–685. [CrossRef]
31. Van Donkersgoed, J.; Sit, D.; Gibbons, N.; Ramogida, C.; Hendrick, S. Drug Residues Recovered in Feed after Various Feedlot Mixer Truck Cleanout Procedures. *J. Food Prot.* **2010**, *73*, 75–80. [CrossRef]
32. de Alcântara Rodrigues, I.; Ferrari, R.G.; Panzenhagen, P.H.N.; Mano, S.B.; Conte-Junior, C.A. Antimicrobial resistance genes in bacteria from animal-based foods. *Adv. Appl. Microbiol.* **2020**, *112*, 143–183. [CrossRef]
33. Toghroli, R.; Aghamolaei, T.; Hassani, L.; Sharifi, H.; Jajarmi, M. Determinants of antimicrobial resistance occurrence in animal-based food, perceived by livestock farmers: A qualitative phenomenological study. *Health Sci. Rep.* **2023**, *6*, e1160. [CrossRef]
34. U.S FDA. 2023: Recalls and Withdrawals. Available online: https://www.fda.gov/animal-veterinary/safety-health/recalls-withdrawals (accessed on 9 August 2023).
35. Paulk, C.B.; Stark, C.R.; Dunmire, K.M. Chapter 16, Feed Processing Technology and Quality of Feed. In *Sustainable Swine Nutrition*; Chiba, L.I., Ed.; John Wiley-Blackwell: Malden, MA, USA, 2022; pp. 429–444. [CrossRef]
36. U.S FDA. 2023: Practices to Prevent Unsafe Contamination of Animal Feed from Drug Carryover-Guidance for Industry. Available online: https://www.fda.gov/media/157979/download (accessed on 10 September 2023).
37. Cornejo, J.; Pokrant, E.; Carvallo, C.; Maddaleno, A.; San Martín, B. Depletion of tylosin residues in feathers, muscle and liver from broiler chickens after completion of antimicrobial therapy. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* **2018**, *35*, 448–457. [CrossRef]
38. Daniel, P. Drugs and chemicals in aquafeeds: The problems and solutions. In *The Use of Veterinary Drugs and Vaccines in Mediterranean Aquaculture*; Rogers, C., Basurco, B., Eds.; CIHEAM: Zaragoza, Spain, 2009; pp. 85–94. Available online: http://om.ciheam.org/article.php?IDPDF=801064 (accessed on 18 August 2023).
39. Harner, J.P., III; Herrman, T.J.; Falk, J.; Behnke, K. *MF-255-Avoiding Drug Carryover during Feed Processing and Delivery*; Kansas State University Agricultural Experiment Station and Cooperative Extension Service: Manhattan, KS, USA, 1996; pp. 1–6. Available online: https://bookstore.ksre.ksu.edu/pubs/mf2055.pdf (accessed on 18 August 2023).
40. Hosain, M.Z.; Kabir, S.M.L.; Kamal, M.M. Antimicrobial uses for livestock production in developing countries. *Vet. World* **2021**, *14*, 210–221. [CrossRef]

41. Rakita, S.; Banjac, V.; Djuragic, O.; Cheli, F.; Pinotti, L. Soybean Molasses in Animal Nutrition. *Animals* **2021**, *11*, 514. [CrossRef]
42. Csikó, G. Residues relating to the veterinary therapeutic or growth-promoting use and abuse of medicines. In *Present Knowledge in Food Safety*; Academic Press: Cambridge, MA, USA, 2023; pp. 96–113. [CrossRef]
43. Da Silva, R.A.; Arenas, N.E.; Luiza, V.L.; Bermudez, J.A.Z.; Clarke, S.E. Regulations on the Use of Antibiotics in Livestock Production in South America: A Comparative Literature Analysis. *Antibiotics* **2023**, *12*, 1303. [CrossRef]
44. European Commission. Veterinary Medicines-New Rules to Promote Animal Health and Fight Antimicrobial Resistance Now Apply. 2023. Available online: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32019R0006_22_663 (accessed on 10 September 2023).
45. Galhano, B.S.; Ferrari, R.G.; Panzenhagen, P.; de Jesus, A.C.S.; Conte-Junior, C.A. Antimicrobial resistance gene detection methods for bacteria in animal-based foods: A brief review of highlights and advantages. *Microorganisms* **2021**, *9*, 923. [CrossRef] [PubMed]
46. Shah, M.S.; Mirza, U.; Shubeena, S.; Gull, B.; Shafi, M.; Shaheen, S. Nanotechnology: A miniature miracle. *J. Entomol. Zool. Stud.* **2018**, *6*, 1984–1988.
47. Shimshoni, J.A.; Barel, S. Recent trends in common chemical feed and food contaminants in Israel. *J. Environ. Sci. Health C* **2017**, *35*, 189–212. [CrossRef] [PubMed]
48. U.S FDA. 2021: CVM FI#263 Recommendations for Sponsors of Medically Important Antimicrobials Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to Be Available Over-the Counter. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-263-recommendations-sponsors-medically-important-antimicrobial-drugs-approved-use-animals (accessed on 10 September 2023).
49. Martins, R.R.; Silva, L.J.G.; Pereira, A.M.P.T.; Esteves, A.; Duarte, S.C.; Pena, A. Coccidiostats and Poultry: A Comprehensive Review and Current Legislation. *Foods* **2022**, *11*, 2738. [CrossRef] [PubMed]
50. Pietruk, K.; Olejnik, M.; Jedziniak, P.; Szprengier-Juszkiewicz, T. Determination of fifteen coccidiostats in feed at carry-over levels using liquid chromatography–mass spectrometry. *J. Pharm. Biomed Anal.* **2015**, *112*, 50–59. [CrossRef]
51. Herago, T.; Agonafir, A. Growth promoters in cattle. *Adv. Biol. Res.* **2017**, *11*, 24–34. [CrossRef]
52. Parr, T.; Mareko, M.H.; Ryan, K.J.; Hemmings, K.M.; Brown, D.M.; Brameld, J.M. The impact of growth promoters on muscle growth and the potential consequences for meat quality. *Meat Sci.* **2016**, *120*, 93–99. [CrossRef]
53. Centner, T.J.; Alvey, J.C.; Stelzleni, A.M. Beta agonists in livestock feed: Status, health concerns, and international trade. *J. Anim. Sci.* **2014**, *92*, 4234–4240. [CrossRef]
54. Davis, H.E.; Geornaras, I.; Lindstrom, V.; Chaparro, J.M.; Nair, M.N.; Delmore, R.J.; Engle, T.E.; Belk, K.E.; Prenni, J.E. Effects of differing withdrawal times from ractopamine hydrochloride on residue concentrations of beef muscle, adipose tissue, rendered tallow, and large intestine. *PLoS ONE* **2020**, *15*, e0242673. [CrossRef]
55. FAO/WHO. Codex Alimentarius International Food Standards–Index of Veterinary Drugs. 2023. Available online: https://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/veterinary-drugs/en/ (accessed on 9 June 2023).
56. Léger, A.; Alban, L.; Veldhuis, A.; van Schaik, G.; Stärk, K.D.C. Comparison of international legislation and standards on veterinary drug residues in food of animal origin. *J. Public Health Policy* **2019**, *40*, 308–341. Available online: https://www.jstor.org/stable/48703566 (accessed on 18 August 2023). [CrossRef] [PubMed]
57. Nácher-Mestre, J.; Ibáñez, M.; Serrano, R.; Boix, C.; Bijlsma, L.; Lunestad, B.T.; Hannisdal, R.; Alm, M.; Hernández, F.; Berntssen, M.H.G. Investigation of pharmaceuticals in processed animal by-products by liquid chromatography coupled to high-resolution mass spectrometry. *Chemosphere* **2016**, *154*, 231–239. [CrossRef] [PubMed]
58. Van Asselt, E.D.; Arrizabalaga-Larrañaga, A.; Focker, M.; Berendsen, B.J.A.; van de Schans, M.G.M.; Van der Fels-Klerx, H.J. Chemical food safety hazards in circular food systems: A review. *Crit. Rev. Food Sci. Nutr.* **2022**, 1–13. [CrossRef] [PubMed]
59. Love, D.C.; Halden, R.U.; Davis, M.F.; Nachman, K.E. Feather Meal: A Previously Unrecognized Route for Reentry into the Food Supply of Multiple Pharmaceuticals and Personal Care Products (PPCPs). *Env. Sci. Technol.* **2012**, *46*, 3795–3802. [CrossRef]
60. Vågsholm, I.; Arzoomand, N.S.; Boqvist, S. Food security, safety, and sustainability—Getting the trade-offs right. *Front. Sustain. Food Syst.* **2020**, *4*, 1–14. [CrossRef]
61. Barbosa Da Silva, A.; Back, M.; Daguer, H.; Palmeira, M.; Antunes De Sá Ploêncio, L.; Molognoni, L.; Peripolli, V.; Bianchi, I. Carry-over and contamination of veterinary drugs in feed production lines for poultry and pigs. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* **2019**, *36*, 740–751. [CrossRef]
62. McEvoy, J.D. Emerging food safety issues: An EU perspective. *Drug Test Anal.* **2016**, *8*, 511–520. [CrossRef]
63. Singh-Sekhon, B. Nanotechnology in agri-food production: An overview. *Nanotechnol. Sci. Appl.* **2014**, *7*, 31–53. [CrossRef]
64. Tanyous, J.N. Cleaning Validation: Complete Guide for Health—Based Approach in Chemical Cross—Contamination Risk Assessment. *PDA J. Pharm. Sci. Technol.* **2019**, *73*, 204. [CrossRef]
65. Segato, G.; Benetti, C.; Angeletti, R.; Montesissa, C.; Biancotto, G. Doxycycline and sulfadimethoxine transfer from cross-contaminated feed to chicken tissues. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* **2011**, *28*, 860–868. [CrossRef]
66. McEvoy, J.D.G.; Mayne, C.S.; Higgins, H.C.; Kennedy, D.G. Transfer of sulphamethazine from contaminated dairy feed to cows' milk. *Vet. Rec.* **1999**, *144*, 470–475. [CrossRef] [PubMed]
67. Kadykalo, S.; Roberts, T.; Thompson, M.; Wilson, J.; Lang, M.; Espeisse, O. The value of anticoccidials for sustainable global poultry production. *Int. J. Antimicrob. Agents* **2018**, *51*, 304–310. [CrossRef] [PubMed]

68. Saensukjaroenphon, M.; Evans, C.E.; Jones, C.K.; Fahrenholz, C.H.; Paulk, C.B. The Effect of Liquid Application Time and Wet Mix Time with Different Mixer Types on Uniformity of Mix. *J. Anim. Sci. Res.* **2019**, *3*, 1–4. [CrossRef]
69. Cochrane, R.A.; Dritz, S.S.; Woodworth, J.C.; Stark, C.R.; Huss, A.R.; Cano, J.P.; Thompson, R.W.; Fahrenholz, A.C.; Jones, C.K. Feed mill biosecurity plans: A systematic approach to prevent biological pathogens in swine feed. *J. Swine Health Prod.* **2016**, *24*, 154–164.