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Abstract. In feed production processes, factories usually produce different mixtures within the same production line. Consequently, remainders of the first-produced feed can stay in the system and be mixed with the following feed charge. This type of transfer (carry-over) is unavoidable in the production systems currently used, and thus, non-medicated feed can be contaminated with veterinary drugs present in a previously manufactured charge of medicated feed. The carry-over of veterinary medicinal products is associated with the risk of residues remaining in the tissues of treated animals at the time of slaughter and poses a health hazard to consumers. Producing safe feed and food products is, first and foremost, a question of good management practices at each stage of the feed and food chain, from primary production to final processing. Primary responsibility for feed safety rests with the feed business operator, who must ensure that all stages of production, processing and distribution under their control are carried out in accordance with relevant legislation, good manufacturing practice and principles contained in the HACCP system. Concrete steps for feed manufacturers to prevent drug carry-over are using one or more approved cleanout procedures of manufacturing equipment, such as cleaning, flushing or sequencing.

1. Introduction

The 'farm-to-fork' approach promoted by the European Union requires the assessment and control of major components of the food production chain, with emphasis on primary production. Feeds must satisfy the nutritional requirements of the relevant animal species, and they are expected to support safe and cost-effective production of foods of animal origin, as well as to ensure the welfare of farm animals [1]. Adequate animal feedingstuffs, which are the main input into livestock production, should be used to ensure the final product reaching the market has the required quality and poses no risk to the consumer [2].

The competitiveness of the agricultural sector because of globalization has led to the need for intensified productivity of animal production systems. For this reason, the stocking rate in poultry and pig production units was increased, causing a greater frequency of disease due to higher infection pressure [3]. Although in recent years much emphasis has been placed on disease prevention through improved management and environmental conditions, intensive animal production systems still depend on drugs (antimicrobials), as shown by their continuously growing market [4]. A common means to deliver such drugs is by including them in feed, as the large-scale use of feedlots makes this easy, and as it avoids handling animals for individual drug administration. However, Dunlop et al. [5] and Varga

et al. [6] found the use of antimicrobials in feed results in a higher incidence of bacteria resistant to the active ingredients, when compared to parenteral treatments.

Also, the benefit of improved productivity from the use of veterinary medicinal products (VMPs) in food producing animals is accompanied by the risk of VMP residues remaining in the tissues of treated animals at the time of slaughter or residues in animal-derived products; such residues pose a health hazard to consumers. The major public health significances of drug residues are development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, and disruption of normal intestinal microbiota [7]. Currently, microbial antibiotic resistance is considered to be one of the greatest threats to human health. In the United States, more than 2 million people are infected with antibiotic-resistant bacteria annually, with 23,000 deaths being the direct result [8].

VMPs are critically needed to meet the challenges of providing adequate amounts of food for the growing world population [9], but they should not be used habitually to prevent disease or to compensate for poor hygiene or inadequate husbandry conditions. All antibiotics, including those administered in feed, must be prescribed by the veterinarian responsible for the animals concerned. In order to conserve the effectiveness of antibiotics in the future, it is important that wherever and whenever these medicines are used, they are used responsibly: “Use as little as possible and use as much as necessary” [10]. Even when feed containing veterinary drugs is prepared following good manufacturing practice guidelines, carry-over of active ingredients from previous formulations cannot be ruled out, because most of the mixed feed formulations are prepared in multiproduct plants. Carry-over contamination can occur during the whole production process [11], with obvious serious consequences. Risk assessment and risk management of contaminants in feeds is ultimately a key issue for veterinary public health.

2. Legal aspects of veterinary drug carry-over in feeds

After production of medicated feed, it is very difficult to completely avoid carry-over of drugs into feed that should be free from such substances (zero tolerance). From the standpoint of legislation, the veterinary drug residues in feed are not allowed and their presence, determined during official monitoring, excludes the placing of such feed on the market. Currently, this principle applies to eight countries within the EU.

However, there are alternative ways to avoid zero tolerance: direct use of orally-administered drug in powder form on the farm, top dressing or administration of drugs *via* drinking water. Each of these methods has certain application risks. Oral powders are usually not dosed into feed by specific, calibrated, devices, but are dosed manually by farmers, with evident weaknesses in such a process. The use of top dressing methods risk that strong, dominant, animals achieve over-intake, while weaker animals with less access to feed achieve lower intake than expected. In such a scenario, the target microbial pathogen in an animal is exposed to subtherapeutic dosage of the antimicrobial, so some significant number of the target pathogens survives treatment. This induces selection of drug-resistant microbial pathogens. The imprecision of delivering drugs *via* the drinking water system is reflected in the amount of water spilled and the variation in the amount of water the animals actually drink. Practical drawbacks are the creation of solid complexes in the pipes and obstruction of drinking nipples, which affect the precision of drug dosing [12].

Most countries in the European Union do not have clearly established national limits for unwanted carry-over of veterinary drugs in non-target feed, while three countries have established limit values, primarily based more on the ALARA values (As Low As Reasonably Achievable), rather than risk assessment for public health:

1. In Belgium, ALARA values are applied, but only under the conditions that the level of cross-contamination cannot cause: a) animal health disorder; b) exceeded MRL in products of animal origin, or; c) increased antimicrobial resistance. In particular, the upper limit values for contamination should never be above 2.5% of the minimum prescribed dose for antibiotics or 3% of the maximum prescribed dose for antihelmintics.

2. In France, validation of the production process is applied: the maximum permitted contamination by VMPs is 5% in the first and 1% in the second charge after production of the last medicated feed batch.

3. The legal status in the Netherlands is still in the process of adoption, but the maximum permitted contamination in non-target feed will be up to 2.5% of the lowest dose of VMP permitted in the targeted feed.

Stolker et al. [13] have shown that the percentage of veterinary medicine carry-over (in the production of medicated feed for pigs in the Netherlands) is not correlated with the percentage determined by standard Good Manufacturing Practice (GMP+) procedures. More precisely, it is not possible to predict the concentration of antibiotic in a flushing charge based on determined percentage of carry-over in the feed production plant. The inability to avoid carry-over, non-homogeneity in the production of medicated feed, and the previously stated difficulties in predicting the level of carry-over, along with increasing concern about the growing problem of microbial resistance, motivated NEVEDI, an association of Dutch feed manufacturers, to announce that they would voluntarily stop the production of medicated feed in 2011, which was the first case of this kind in Europe.

In Serbia, the Rulebook on the Quality of Feed [14] states (in Article 88) that feed mixtures must not contain antibiotics or sulphonamides, i.e. zero tolerance is applied, so these substances must not be present in feedingstuffs.

3. Legal aspects of carry-over of coccidiostatics and histomonostatics

In addition to carry-over of veterinary medicines, special attention is required to understand regulatory aspects concerning the presence of coccidiostatics and histomonostatics in non-target feed. Coccidiostats and histomonostats are substances intended to inhibition the growth or destruction of protozoa, and these substances can, *inter alia*, be approved for use as feed additives in accordance with European Regulatory Council Regulation (EC) No 1831/2003[15]. It can be a confusing fact that some coccidiostats are registered not as feed additives but as drugs, i.e. VMPs. For active substances in the VMP that are the same as a substance in a feed additive, the applicable maximum level of cross-contamination in non-target feed is the maximum content of feed additive in complete feed established in the relevant Union act [16]. A list of the named coccidiostats (registered as VMPs) is given in the Annex of Allowed Substances in Commission Regulation No. 37/2010 [17] and consists of Amprolium, Decoquinate, Diclazuril, Halofuginone, Imidocarb, Lasalocide and Toltrazuril. As such, they can be used in the production of medicated feed, based on veterinary prescription. They are most commonly used in the breakthrough of coccidiosis, where no coccidiostatics are added in feed, in cases of development of resistance, or when the vaccines are insufficiently efficacious. Carry-over of coccidiostatics and histomonostatics can lead to contamination of feed where the use of coccidiostatics or histomonostatics is not authorized, such as feed for animal species or categories not specified in the authorization of the additive. This inevitable cross-contamination can occur at every stage of production and processing of feed, as well as during storage and transport of feed. Inevitable transfer of active substances contained in approved coccidiostats and histomonostats into non-target feeds results in the presence of undesirable substances in the feed in accordance with Directive 2002/32/EC [18]. Thus, taking into account the application of good manufacturing practice, the maximum level of unavoidable carry-over should be established according to the ALARA principle. In order to allow the feed producer to manage the inevitable transfer, a transfer rate of about 3% (in relation to the maximum allowed content) should be taken into account in terms of feed for less sensitive animal species, while for feed intended for sensitive non-target species and feed with a withdrawal period, i.e. feed used in the pre-slaughter period, a transfer rate of about 1% can be considered. A transfer rate of 1% should also be established for the cross-contamination of other feed for the target species when it has no added coccidiostats and histomonostats, as well as for non-target feed for animals such as dairy cows or layer hens, where clear evidence exists of transfer from feed to food of animal origin. In the European Union, this described problem is regulated by Commission Directive 2009/8/EC of 10 February 2009 [19]. In that Directive, the maximum level of imminent carry-over in non-target feed for 11 coccidiostats has

been set: Lasalocid sodium, Narasin, Salinomycin sodium, Monensin sodium, Semumramycin sodium, Maduramycin ammonium alpha, Robenidine hydrochloride, Decoquinate, Halofuginone hydrobromide, Nicarbazine and Diclazuril. The levels are expressed in mg/kg (ppm) in feed with a moisture content of 12% (Table 1) and are aimed at avoiding excessive exposure of animals to these compounds, since most of the compounds have a relatively low safety margin and their higher concentration in feed can cause harmful effects even in the target animal species. In Serbia, in accordance with the harmonization of the regulations regarding the animal feed safety sector, in the Rulebook on the Quality of Feed [14], Article 99 (maximum permissible harmful substances) established identical levels as the EU has for these above-mentioned 11 coccidiostats, while the manner of their use and their maximum residue levels in food are given in Article 89. When interpreting this Rulebook, it is necessary to note that most coccidiostats have been registered as additives only until 2018, so the time limit for placing them on the market has already expired. However, other coccidiostats have been registered as additives for longer (until 2020, 2021, 2022, 2023, or 2025), and so all these compounds must by carefully selected for use in feeds on the basis of their being registered as additives or not.

Table 1. Maximum content levels for coccidiostats in feed as laid down in Commission Directive 2009/8/EC and Council Regulation 2010/37/EC (Adopted from O'Mahony et al., [20]).

Feed additive	Feed dose (mg/kg)	Non-target feed (mg/kg)		Withdrawal feed (mg/kg)
		Sensitive	Other species	
Lasalocid sodium	125	1.25	3.75	1.25
		D, C, R, E, DA, LB, T > 12 wks, CL > 16 wks		CF, CL < 16 wks, T < 12 wks
Narasin	70	0.7	2.1	0.7
		T, R, E, LB, CL > 16 wks		CF
Salinomycin sodium	70	0.7	2.1	0.7
		E, T, LB, CL > 12 wks		CF, CL < 12 wks, RF
Monensin sodium	125	1.25	3.75	1.25
		E, D, SR, Du, B, DC, LB, CL, T > 16 wks		CF, CL, T < 16 wks
Semduramicin	25	0.25	0.75	0.25
sodium		LB, CL > 16 wks		CF
Maduramicin NH4	5	0.05	0.15	0.05
alpha		E, R, T, LB, CL > 16 wks		CF, T < 16 wks
Robenidine HCl	70	0.7	2.1	0.7

		LB, CL > 16 wks		CF, RFB, T
Decoquinate	40	0.4	1.2	0.4
		LB, CL > 16 wks		CF
Halofuginone HBr	3	0.03	0.09	0.03
		LB, CL > 16 wks, T > 12 wks	Except CL < 16 wks	CF, T < 12 wks
Nicarbazin	50	0.5	1.5	0.5
		E, LB, CL > 16 wks		CF
Diclazuril	1	0.01	0.03	0.01
		LB, CL > 16 wks, TF > 12 wks	Except CL < 16 wks, CF, TF < 12 wks	RFB

Key: D = dogs, C = calves, R = rabbits, E = equine, DA = dairy animals, LB = laying birds, T = turkeys, TF = turkeys for fattening, CL = chickens reared for laying, CF = chickens for fattening, RF = rabbits for fattening, RFB = rabbits for fattening and breeding, SR = small ruminants (sheep and goats), Du = ducks, B = bovine, DC = dairy cattle.

4. Risk assessment of carry-over

The primary responsibility for feed safety rests with the feed business operator, who must ensure that all stages of production, processing and distribution under their control are carried out in accordance with relevant legislation and good manufacturing practice [21]. The feed producer (commercial or farm) is obligated to ensure that the exact amount of the desired drug is correctly incorporated and that there is no cross-contamination of any unwanted drug in that feed.

In feed production processes, factories produce different mixtures within the same production line. Consequently, remainders of the first-produced feed can stay in the system and be mixed with the following feed charge [19]. This type of transfer is unavoidable in the production systems currently used, and thus, non-medicated feed can be contaminated with veterinary drugs present in a previously manufactured charge of medicated feed [2]. Carry-over is (usually) expressed as the percentage of the nutrient, veterinary medicament and/or contaminant from one feed batch that ends up in the following feed batch (flushing charge). Stolker et al. [13] have documented that sometimes a flushing feed is contaminated not only with the antibiotic used directly before the production of the flushing feed, but also with an antibiotic used several batches earlier in the production process. The same authors pointed to the importance of testing the homogeneity of the flushing charge, i.e. determining whether the drug is homogeneously distributed in the feed. They found [13] that during the first 20 minutes in the production cycle, the flushing charge contained oxytetracycline at concentrations >2.5% of the allowed transfer, or significantly higher than the last part of the produced batch. If the flushing charge can be easily flushed, the concentration of the contaminant from the previous batch will be very high at the beginning and will rapidly fall, but in contrast, in the case of slow flushing, the concentration of the given substance will only gradually decrease [22]. These data must be taken into account when taking the first kilogram of this type of feed and giving it to a non-target (for the antibiotic-sensitive) animal species, as well as possible errors in the interpretation of results if a sample of such feed is sent for further analysis.

The type of drug (category I or II), the number of animal species for which the drug is intended, and the feed delivery system determine the degree of risk associated with carry-over. Feed plants producing

feed only for one type of animal and using only Category I drugs (which do not have a withdrawal period) have the least risk of contamination and the occurrence of residues in tissues of non-target animals. Since there is no withdrawal period for these products, they can be used until animals are slaughtered, and subsequent animal products can immediately be released to the market. In contrast, carry-over of Category II drugs (which have a withdrawal period) into feed could result in the unwanted presence of residues in meat, dairy products and eggs of animals. The carry-over of drugs classified as either Category I or Category II into a batch of feed intended for a species the drug is not intended for can create serious health problems for any such animal consuming the feed [23]. The carry-over of Monensin from cattle feed to horse feed which can result in lethal outcomes. The high sensitivity of horses to Monensin is associated with their lack of demethylation enzymes, which facilitate the clearance of Monensin from the animals' systems [24]. The U.S. Food and Drug Administration issued warning letters in 2018 for two feed mills in Minnesota, and Nebraska that mixed horse feed containing monensin. These firms did not adhere to Current Good Manufacturing Practice (CGMP) requirements for medicated feed mills. These incidents of monensin toxicity should be a reminder to all feed producers that make medicated feeds that they must remain vigilant in adhering to CGMP requirements by eliminating unsafe carry-over of medications into feed intended for different species. Guidance for Industry # 72 (GMPs for Medicated Feed Manufacturers Not Required to Register and Being Licensed with FDA) and Guidance for Industry # 235 (Current Good Manufacturing Practice Requirements for Food for Animals) are documents that provide explanation and examples of how to meet the FDA's requirements for safe animal feed production.

Carry-over can appear in one segment of the production line or can be a result of a combination of residues along the whole system [2]. In order to discover the cause of carry-over, all equipment must be taken into account, from the place of delivery of the medicine to the loading zone, but carry-over occurring during transport or on the farm itself must also be considered. O'Keeffe et al. [25] identified multiple potential causes for the presence of coccidiostat (Nicarbazine) residues in edible livestock tissues: contamination of feed in mixtures and/or during transport, supply of wrong feed, delivery of feed to the wrong bin on the farm, inadequate cleaning of the feeding system on farms before delivery of replacement feed, inadequately applied withdrawal period for feed with coccidiostatics, poor farm management that led to re-exposure of poultry to Nicarbazine in the period immediately prior to slaughter, and fecal recycling of Nicarbazine from the litter. McEvoy et al. [26] also pointed to the importance of particles of dust and excess material remaining during the pelleting process as an important factor in carry-over. The production practice at one factory was such that material returned to pre-press and contaminated the next production lot [26]. The most important sources of carry-over, related to production equipment, are summarized in Table 2. In Good Manufacturing Practice guidance [27], the main causes of carry-over are the dosing/grinding/mixing line, the press line, and the measurement stations within the lines. This type of carry-over is termed installation carry-over.

Table 2. Sources of carry-over regarding feed plant equipment (Adopted from Harner et al., [23])

Equipment	**Mode of Carry-over**
Dust system	-delayed return of dust to production line -excessive pickup of drug and carrier -hang-up (electrostatic or moisture)
Mixer	-residual feed remaining in mixer

Surge bin	-buildup of material on ribbons and walls -electrostatic hang-up on walls and top -leaking mixer gate (not fully closed) -incomplete clean-out -electrostatic or moisture hang-up
Conveyors	-same as surge bin
Elevators	-residual feed remaining in buckets and boot -electrostatic or moisture hang-up
Bins	-bridging -residual feed from incomplete cleanout -error in bin chart records
Bulk truck	-incomplete clean-out -bridging and hang-up

5. Risk management of carry-over

When the sources of carry-over are revealed, corrective measures can be taken. The basic principles that feed business operators should establish, implement and maintain [21] are contained in the HACCP system. HACCP principles are largely limited to the ability to carry out the following:

(a) Identify any hazards that must be prevented, eliminated or reduced to acceptable levels;

(b) Identify the critical control points at the step or steps at which the control is essential to prevent or eliminate a hazard or reduce it to acceptable levels;

(c) Establish critical limits at critical control points which separate the acceptability from unacceptability, for the prevention, elimination or reduction of identified hazards;

(d) Establish and implement effective monitoring procedures at critical control points;

(e) Establish corrective action when monitoring indicates that a critical control point is not under control;

(f) Establish procedures to verify that the measures outlined in points (a) to (e) are complete and effective. Verification procedures will be carried out regularly;

(g) Establish documents and records commensurate with the nature and size of the feed business to demonstrate the effective application of the measures set out in points (a) to (f).

HACCP principles can help feed business operators to achieve a higher standard of feed safety, but should not be considered as a method of self-regulation and do not replace official controls. Each plant must establish its own rules and manage carry-over based on their own HACCP program. Although most feed businesses are familiar with ISO 9000, it focuses on systems and procedures. However, HACCP is different, as it focuses on the product. ISO 9000 and similar standards are not an essential requirement for successful HACCP programs [28].

Concrete steps for feed manufacturers to prevent drug carry-over are set by CGMP requirements, and they are involve using one or more approved cleanout procedures for the manufacturing equipment,

such as cleaning, sequencing and/or flushing [29]. The FDA's CGMP requirements serve as guidelines for medicated feed manufacturers to ensure that their products meet identity, strength, and quality standards.

5.1. Cleaning the equipment

Equipment cleaning is still not widespread in the feed manufacturing industry, but it is potentially the most effective method of avoiding carry-over during processing and delivery of feed. It is mainly applied in high risk situations: dealing with medical premixes; when sequencing can not be included in the production schedule; with portable grinder-mixers; when the physical properties of the drug are such (adhesion strength and electrostatic properties) that sequencing and flushing do not prevent carry-over, and; if liquid ingredients (molasses or fat) are added during the feed mixture production [23]. In all of these cases, physically cleaning the production equipment (cleaning of the mixer, transport system, pellet coolers, bins) or delivery trucks is required. This involves completely stopping production, which is impractical and economically burdensome for the factory. However, GMP stipulates that all equipment should be designed, constructed, installed and maintained in such a way as to facilitate the inspection and use of cleaning procedures. In terms of cleaning efficiency, horizontal mixers have an advantage over vertical ones. A typical cross-section of a double-ribbon horizontal mixer is shown in Figure 1. When the mixer has been emptied, the residual feed will remain in the space between the outer ribbon and the housing. Some mixers can be adjusted to reduce this space to about 6 mm, which reduces the feed carry-over to an innocuous level in most cases. A typical single screw vertical mixer is shown in Figure 2, along with the location of the mixer discharge. A considerable amount of feed will remain in the mixer after the last feed leaves the discharge opening. If a clean-out opening is provided down on the boot of the mixer, the residual feed can be removed there. If it is not removed, a significant amount (18 kilos or more) of carry-over can pass into the following feed charge [30]. Some plants clean their equipment routinely, e.g. at monthly or bi-annual levels. When employees perform cleaning tasks, it is important to remove all waste and residues before the next production cycle, use safe and approved cleaning agents, use safe and clean tools, pay attention to the hygiene of the personnel involved in the task, and ensure that washing does not disseminate microbial or other contaminants in the equipment.

After cleaning, inspection should safely review all available parts of production line (such as mixers, containers, conveyors, etc.) to ensure they are clean and that carry-over will not occur. Inspection should be carried out visually, without entering the mixer or bin [31].

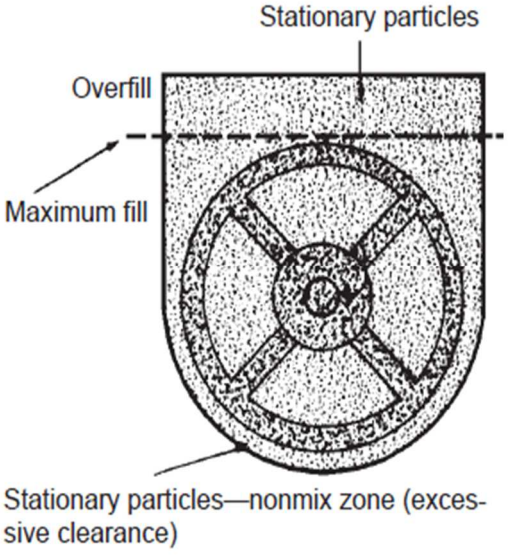

Figure 1. Double ribbon horizontal mixer from Wilcox et al., [30])

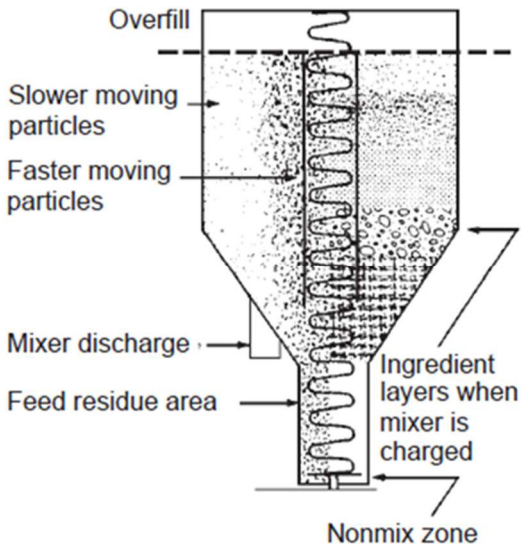

Figure 2. Single screw vertical mixer (Adopted (Adopted from Wilcox et al., [30])

5.2. System flushing

The flushing procedure involves passing a precise amount of a selected ingredient through the system to flush through any residual medicated feed produced in the previous batch. As a flushing material, grain meals are often used, most commonly ground corn of approximately 600 microns. Other suitable material that has been proven to adequately clean the production line can be used [23, 32], as can wheat [28], limestone [31], and rice hulls [33]. When material passes through the production system, it is mixed with the residual medicated feed from the previous batch, and dilutes the drug concentration to a safe level. The quantity of flushing material depends on the system; it usually amounts to about 5-10% of the mixer capacity and should not be less than 90 kilograms [23]. Some tests have shown that flushing material amounting to 1-2.5% of the mixer capacity can be effective in preventing carry-over [32]. Also, the plant should check with mixer's manufacturer for their recommendation for flushing material type, and choose the best option. Due to the degree of variability among facilities, feedmills should determine their facility's individual characteristics and apply appropriate time and volume requirements for flushing material to accomplish the intent of the procedures. The volume used should be stated in the written procedures, and should be based on documented analysis or tests of the firm's system [31].

After the flushing material is added to the mixer, the mixer should be allowed to operate for at least 1 minute before the material is removed. After the mixer is flushed, the material should pass through the whole production system along the same pathway the previously manufactured medicated feed passed. The flushing material, from that moment, must be correctly identified and stored in order to prevent contamination, and later it can be used in the production of the same medicated feed. Some plants use this flushing material to flush trucks for bulk deliveries after they make deliveries to the farm. When applying these procedures, the economic implications of the need to store the flushing material should be taken into account. Some companies choose to simply discard this material in order to avoid subsequent possible production errors, which is certainly the economically least attractive option. Manufacturers must document the applicable flushing procedures: the flushing method, the flushing time, the amount and type of flushing material and the disposal of the flushing material.

To monitor flushing, inspection must ensure that feed producers adequately apply their own procedures. It is necessary to check that the entire system is flushed (including mixer, conveyors, bins) and to visually determine whether any foreign material is not in accordance with the flushing material. Finally, quantity of flushing material released into the system must be present at the end of the flushing process [31].

5.3. Sequencing procedure

The feed industry most often uses sequencing because it minimizes discontinuation of the production line. If properly planned and executed, this method is the most cost-effective carry-over prevention procedure. The order in which the feed is prepared, processed and delivered directly determines the probability of carrying over the drug from one to the next batch and, consequently, the presence of residues in the tissues of the animals that consume such feed. This work plan involves production of all medicated feeds that contain the same drug in the sequence from the highest to the lowest level of the drug. After completion of the last batch of medicated feed, the production of non-medicated feed for the same animal species continues.

Examples of accepted principles to be considered when designing the sequencing process [34] are:

- Withdrawal feed and feed for cattle should not be produced and processed in the same equipment after the manufacture of medicated feed containing Category II drugs, unless appropriate cleaning procedures are applied. Drugs with specific toxicity characteristics, such as Monensin's toxicity for horses, require special attention.
- After the production of medicated feed containing Category II drugs, feed for the same species that are below the marketable age or weight may be produced.
- Feeds that have high potential for dangerous drug contamination (feed for withdrawal, dairy animals, etc.) should be produced first in the series, and feed with the most toxic drugs will be the last in the sequencing process, followed by complete physical cleaning of the system .

• Sequencing procedures and practices should be clearly understood by all persons responsible for the planning and production of medicated feed. They should be easily accessible for their use.

During the sequencing of feed, the age of the animal, the sensitivity to the administered drug, and the type and purpose of the drug should be considered. For example, after production of medicated feed containing oxytetracycline for broilers, non-medicated feed for layers should not be produced. Given that a very small amount of sulfamethazine consumed by pigs can lead to residues of this drug in meat, it is not acceptable to manufacture feed for pigs after the production of medicated feed with sulfamethazine [29]. Feed for pigs containing Carbodox should not be followed by unmedicated feed for gravid sows. After production of Monensin-containing feed, only non-medicated feed for cattle, poultry, or pigs can follow, but not feed for horses. If feed is produced for only one type of animal, such as pigs, the most common medicated feed is for the youngest, most vulnerable category, in this case piglets. In this case, the following order is applied: first, feed containing a drug that requires a withdrawal period for piglets, then sow, grower and finally, finisher feed. Sequencing can also be used to clean containers on trucks, but the same principles should be followed. In most feed factories, feed sequencing procedures will reduce carry-over to a level that eliminates the potential for the presence of residues in animal tissue. However, the sequencing procedure cannot reduce carry-over to a sufficiently low level unless the problems listed in Table 2 have been previously resolved. When sequencing is applied, in order to avoid cross-contamination, precise records of feed production documentation are imperative, so the last batch in a series can always be safely marked. Otherwise, the sequencing procedure could be compromised by the next feed charge preparation. Periodic evaluation of sequencing procedure should be carried out to verify and validate their effectiveness [27, 28, 31].

After the application of the described cleaning procedures, if the undesired carry-over of critical additives and VMPs can still be expected, then the company could take up the following measures: draw up a mandatory production (working) sequence; additional measures in the event of product changes; produce feeds with critical additives and VMPs on another line; switch to less critical agents [27]. When carry-over is detected in a feed plant, harmful effects can occur in people and in animals that consume contaminated feed. This type of failure is considered a violation of the regulations, with all consequences for the responsible persons. Based on the Rules on the Establishment of the Feed Safety Monitoring Program for 2018 [35], in Serbia, if the presence of contaminants in feed is detected, activities ranging from corrective measures to prohibition of operation and closure of the entire feed production facility will be implemented.

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