



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

# Carryover in feed and transfer from feed to food of unavoidable and unintended residues of approved veterinary drugs

Joint FAO/WHO Expert Meeting  
FAO Headquarters, Rome, Italy  
8–10 January 2019

FAO ANIMAL PRODUCTION AND HEALTH / **REPORT 13**



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PRODUCED BY:

Food and Agriculture Organization of the United Nations  
and  
World Health Organization

Rome, 2019

## Recommended Citation

**FAO and WHO.** 2019. *Carryover in feed and transfer from feed to food of unavoidable and unintended residues of approved veterinary drugs*. Report of the Joint FAO/WHO expert meeting – 8–10 January 2019, FAO Headquarters, Rome, Italy. FAO Animal Production and Health Report No. 13. Rome, Italy.

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ISBN 978-92-5-131833-1 (FAO)  
ISBN 978-92-4-151668-6 (WHO)

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## Acknowledgements

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) would like to express their appreciation to all those who contributed to the preparation of this report whether by providing their time and expertise, data and other relevant information, or by reviewing and providing comments on the document.

More particularly, the organizations would like to thank Patricia Dowling, for drafting the report; and the experts and resource persons for their guidance and recommendations during the meeting, as well as their valuable feedback on the report drafts: Wendy Barrantes Chaverri, Marc Berntssen, José Manuel Costa, Silvana Gorniak, David Johnson, Hui-Seung Kang, Roberto Molteni, Niall O'Brien, Folasade B. Oluwabamiwo, Oluseyi Oluwajubelo Oluwatosin, Angela Pellegrino Missaglia, Lamia Abdou Mohamed Ryad, Martinus Jacob Zeilmake, Gracia Brisco, Verna Carolissen, James Deller, Lea Pallaroni, and Gerald Shurson.

Thanks also go to Daniela Battaglia, Vittorio Fattori, Markus Lipp, Soren Madsen and Saskia Reppin, members of the FAO and WHO Secretariat, who analyzed the information received, drafted and edited the report. Thanks to Kafia Fassi Fihri and Concepcion Quevedo for the preparation of the meeting, and Enrico Masci for the desktop publishing.

Appreciation is also extended to all those who responded to the call for data that was issued by FAO and WHO and thereby drew our attention to information that was not readily available in the mainstream literature and official documentation.

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## Declaration of interest

All participants completed a declaration of interest form in advance of the meeting. In relation to the subject of this meeting, the following declarations were made: 1) Wendy Barrantes Chaverri, Niall O'Brien, Folasade B. Oluwabamiwo, Oluseyi Oluwajubelo Oluwatosin, Angela Pellegrino Missaglia, Lamia Ryad, Martinus Jacob Zeilmaker, Roberto Molteni and Hui-Seung Kang declared having paid employment and received research, technical and/or training support; 2) Marc Berntssen declared having received research support; 3) Silvana Górnjak, Folasade B. Oluwabamiwo and David Johnson reported participating in expert committees or scientific advisory groups; and 4) David Johnson provided expert opinion and made public statements as part of a regulatory, legislative, judicial, or other governmental process.

Following the FAO guidance document for declaration of interests, the declarations noted above were assessed as to the extent to which each interest could be reasonably expected to affect and exercise influence on the experts' judgment. The declared interests of Wendy Barrantes Chaverri, Niall O'Brien, Folasade B. Oluwabamiwo, Oluseyi Oluwajubelo Oluwatosin, Angela Pellegrino Missaglia, Lamia Ryad, Martinus Jacob Zeilmaker, Roberto Molteni, Hui-Seung Kang, Marc Berntssen, Silvana Górnjak, and David Johnson were considered unlikely to impair the individual's objectivity or cause significant influences on the impartiality, neutrality and integrity of the work. Meeting participation by these individuals was neither reasonably expected to create unfair competitive advantages nor were the meeting outcomes reasonably foreseen to affect the individuals' declared interests. The interests of all participants were disclosed at the beginning of the meeting to all attendees.

The participation of Gerald Shurson and Lea Pallaroni as resource persons was considered necessary because of the relevance of their knowledge and expertise for the meeting. However, a conflict of interests could not be excluded, and it was acknowledged. Therefore, as resource persons, they participated in all discussions and provided inputs during the meeting and in drafting the final report, but they were not able to provide inputs regarding the recommendations drafted as an outcome of the meeting.

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## Abbreviations and acronyms

<b>ADI</b>	Acceptable daily intake
<b>ALARA</b>	As low as reasonably achievable
<b>AMR</b>	Antimicrobial resistance
<b>ARfD</b>	Acute reference dose
<b>CCRVDF</b>	Codex Committee on Residues of Veterinary Drugs in Foods
<b>DDGS</b>	Dried distillers grains with solubles
<b>DG</b>	Distillers grains
<b>EFSA</b>	European Food Safety Authority
<b>EMA</b>	European Medicines Agency
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>GAP</b>	Good agricultural practices
<b>GMP</b>	Good manufacturing practices
<b>HACCP</b>	Hazard analysis and critical control points
<b>HARPC</b>	Hazard analysis and risk-based preventive controls
<b>HBGV</b>	Health based guidance values
<b>IFIF</b>	International Feed Industry Federation
<b>JECFA</b>	Joint FAO/WHO Expert Committee on Food Additives
<b>MRL</b>	Maximum residue limits
<b>MRPL</b>	Minimum required performance limits
<b>OIE</b>	World Organisation for Animal Health
<b>PAP</b>	Processed animal by-products
<b>RPA</b>	Reference point for action
<b>SOP</b>	Standard operating procedure
<b>WHO</b>	World Health Organization
<b>WTO</b>	World Trade Organization

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## Glossary

**Acceptable daily intake:** An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg) (FAO, WHO, 1993).

**Aquatic animals:** Species used for aquaculture including fish, crustacean species and mollusc species (FAO, 1996).

**Drug carryover:** A form of feed contamination that results when a drug is transferred from an acceptable location or feed to an unacceptable location or feed.

**Drug transfer from feed to food:** Residues of veterinary drugs in food that result from drug carryover in feed.

**Feed (Feedingstuff):** Any single or multiple materials, whether processed, semi-processed or raw, which is intended to be fed directly to food-producing animals (FAO, WHO, 2008).

**Feed additive:** Any intentionally added ingredient not normally consumed as feed by itself, whether or not it has nutritional value, which affects the characteristics of feed or the final food of animal origin. The micro-organisms, enzymes, acidity regulators, trace elements, vitamins and other products fall within the scope of this definition depending on the purpose of use and method of administration (FAO, WHO, 2008).

**Flushing:** Flushing involves taking a specific quantity of an ingredient, such as ground grain, and conveying it through the feed mill system to reduce or eliminate any residual medicated feed from the previous medicated batch.

**Hazard:** A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect (FAO, WHO, 2018a).

**Livestock:** All grown animals regardless of age, location or purpose of breeding. Non-domesticated animals are excluded under this definition unless they are kept or raised in captivity. Domestic animals included are large and small quadrupeds, poultry, insects (bees) and larvae of insects (silkworms) (FAO, 1994).

**Maximum residue limit:** The maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical, which is legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed.

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**Medicated feed:** Any mixture of a veterinary drug or drugs and feed or feeds that is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product (FAO, WHO, 2008).

**Microbiome:** The microorganisms in a particular environment, such as the human gastrointestinal tract.

**Risk:** A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food (FAO, WHO, 2018a).

**Risk analysis:** A process consisting of three components: risk assessment, risk management and risk communication (FAO, WHO, 2018a).

**Risk assessment:** A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment and (iv) risk characterization (FAO, WHO, 2018a).

**Risk management:** The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options (FAO, WHO, 2018a).

**Sequencing:** A pre-planned order of production of medicated feed designed to control veterinary drug carryover into subsequent batches of feed for target or non-target species.

**Veterinary drug:** Any substance applied or administered to any food producing animal, such as meat or milk producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour (FAO, WHO, 2018a).

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## Executive summary

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) at its 23<sup>rd</sup> session requested the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to provide scientific advice and risk management options in order to mitigate the unintended and unavoidable presence of residues of approved veterinary drugs in food of animal origin resulting from carryover of veterinary drugs in feed. Such residues when present in feed could be transferred to food of animal origin and might pose a risk to public health and/or lead to possible trade disruption. In response to this request, FAO and WHO held an Expert Meeting from 8 to 10 January 2019 at FAO Headquarters in Rome, Italy.

To help the experts to gather more comprehensive information, the meeting was preceded by a Stakeholder Consultation on 7 January 2019. The stakeholders presented on issues of drug carryover from their respective industries/organizations. This was followed by three days of discussion by the experts and resource persons on the sources of unavoidable and/or unintentional veterinary drug exposure at feed mill and farm level, human health risks due to the presence of veterinary drug residues in food from unavoidable and unintended carryover in feed, and risk management strategies for carryover of veterinary drugs. From the discussions, the Expert Meeting concluded that in some instances carryover of veterinary drugs is unavoidable to some extent even if the Codex Code of Practice on Good Animal Feeding (CXC 54-2004), Good Manufacturing Practices (GMP), and Hazard Analysis and Critical Control Point (HACCP) principles were followed. The Expert Meeting consensus was that the current Codex Code of Practice on Good Animal Feeding does not contain sufficient practical guidance on all levels to adequately address the potential for veterinary drug residues in food as a result of carryover in feed.

The Expert Meeting considered that an acceptable amount of veterinary drug in food of animal origin (i.e. action level) could be established based on residue tolerances in the subsequent food products from exposed animals, but this was feasible only if the carryover drug had established MRLs in the non-target species exposed to the drug. The Expert Meeting suggested that a suitable risk management option is to consider the establishment of action levels for veterinary drug residues in food products from non-target species. Such action levels would establish a regulatory limit below which no further enforcement action is required.

The meeting concluded that ensuring safe feed is an important component of efforts to reduce and prevent food safety hazards from veterinary drug carryover. Specific risk management options developed by the Expert Meeting include:

1. Increase awareness and provide easily accessible information about possible implications for carryover from the use of authorised veterinary drugs, as part of a structured training programme for all competent authorities, professionals and workers.

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2. Strengthen national capacities for implementation of the Codex Code of Practice on Good Animal Feeding and related measures for animal feed production.
  3. Emphasize that when possible, dedicated and separate lines for manufacturing medicated feed should be considered. However, the experts recognize that there may be practical limitations related to construction and maintenance of separate lines in feed mills.
  4. Direct prescribers and users of medicated feed to consider the appropriate selection of authorised drugs (including active ingredient, formulation and galenic form) to achieve expected therapeutic outcomes while considering carryover implications.
  5. Emphasize monitoring and control of raw feed ingredients that have potential for transfer of veterinary drugs from feed to food (e.g. identification and selection of appropriate raw feed ingredients, avoidance of hazardous raw materials).
  6. Emphasize avoidance of the need to use medicated feed by implementing the use of animal health promoting practices and ingredients (e.g. good hygiene and husbandry practices, genetic selection, animal welfare, feed constituents, feed safety and adequate animal nutrition).
  7. Include specific advice in the Codex Code of Practice on Good Animal Feeding on HACCP-identified control points for carryover during transport from feed mill to farm.

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# Introduction

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) at its 23<sup>rd</sup> session requested FAO and WHO to provide scientific advice and risk management options to mitigate the unintended and unavoidable presence of residues of approved veterinary drugs in food of animal origin resulting from carryover of veterinary drugs in feed (FAO, WHO, 2017). Such residues when present in feed could be transferred to food of animal origin and might pose a risk to public health and/or lead to possible trade disruption. In particular, the Committee requested scientific advice from FAO and WHO on the following, using residues of lasalocid sodium in eggs as working examples:

- Will the presence of residues of a veterinary drug in food at levels associated with unavoidable and unintended carryover in feed constitute a risk to human health?
- Which risk management recommendations (e.g. limit, standards, etc.) could be established to address the trade issue while protecting human health?
- Are additional measures to those in the Codex Code of Practice on Good Animal Feeding (CXC-54-2004) (FAO, WHO, 2008) available to minimise unavoidable and unintended carryover in feed?

Additionally, the Committee requested that in providing scientific advice, FAO and WHO take into consideration the discussion at the 23<sup>rd</sup> session of the Committee (as captured in the report) and the report of the physical working group that was held immediately prior to that session.

In response to this request, FAO and WHO held a joint Expert Meeting from 8 to 10 January 2019 at FAO Headquarters in Rome, Italy (the agenda of the meeting is provided in Appendix A). The meeting was preceded by a Stakeholder Consultation on 7 January 2019, with the objective of allowing stakeholders to inform the experts on the current situation in the field of animal feed production, present their position on issues involved in veterinary drug carryover in animal feed, and provide their opinions regarding appropriate risk management strategies at international, regional and national levels. More specifically, they informed on the problems they encountered regarding carryover in feed of unavoidable and unintended residues of approved veterinary drugs; the measures they apply to prevent or control it; and what they recommend addressing this problem.

The following stakeholders, which replied to a dedicated call for interest issued by FAO and WHO and provided adequate information to justify their attendance, presented from their respective industries/organizations: RIKILT Wageningen University and Research; Phibro Animal Health Corporation; Aquaculture Stewardship Council; Health for Animals; Animal Health Europe; and International Feed Industry Federation (IFIF).

The Expert Meeting was opened by Berhe G. Tekola, Director, Animal Production and Health Division of FAO, who welcomed the participants on behalf of the Directors-General of FAO and WHO. In welcoming the participants, he pointed out that the role of animal feed in the production of safe food is well recognized

and that FAO and WHO had considered it appropriate to call an Expert Meeting to review current knowledge on the unintended and unavoidable presence of residues of veterinary drugs in food of animal origin resulting from carryover of veterinary drugs in feed and its impact on food safety and international food and feed trade, and to provide orientation advice on this matter to their Members, Codex (CCRVDF) and other international organizations.

A total of 14 experts from seven regions - Africa, Asia, Europe, the Near East, North America, South America and the Southwest Pacific - were invited but one could not attend. The experts participated in their independent professional capacities and not as representatives of their governments, employers or institutions. The experts elected Marc Berntssen as chairperson. Experts provided case reports involving veterinary drug carryover in feed, which are presented in Appendix B. Other documents were submitted in response to an open call for information and data. These documents were made available to the experts, as the need arose.

## **BACKGROUND**

One of the main goals of risk management of food is to protect public health by managing and controlling known risks as effectively as possible through the selection and implementation of risk mitigation strategies. Although industry and governmental regulators strive to effectively implement production and processing systems which ensure food safety from “farm to fork”, complete freedom from risks is not attainable. Safety and wholesomeness of food are related to a level of risk that society regards as reasonable, and comparable to other risks in daily life (FAO, 1997). Manufacturers of feed and feed ingredients, producers of animals for use as human food and those involved in the distribution and sale of food of animal origin need to collaborate to identify potential hazards and assess their relative risks to consumers’ health. Collaboration between these entities enables the development and application of appropriate risk management strategies for safe production and use of medicated animal feed. FAO and WHO therefore considered it appropriate to convene an Expert Meeting to review the causes of veterinary drug carryover in animal feed, the known risks of such carryover to human health and international trade and suggest appropriate risk management strategies. The work of this Expert Meeting will be forwarded to the CCRVDF to allow the Committee to consider the risk management recommendations to address health risks from veterinary drug carryover and trade issues.

## **SCOPE AND PURPOSE OF THE EXPERT MEETING**

Within the overall role of securing food safety and protecting trade practices in the food and feed sectors, the objectives of the Expert Meeting were:

- To review the causes of veterinary drug carryover in animal feed.
- To review the known risks of veterinary drug transfer to food and impacts on human health and international trade.
- To provide guidance for further action required at the international level to address these issues.

The Expert Meeting focused on veterinary drug carryover issues that impact animal feed and human food safety, as well as international food and feed trade. The unavoidable and unintended presence of residues of veterinary drugs in food was determined to be due to one or a combination of the following:

- Carryover of residues of veterinary drugs during manufacture, storage and transport of feed (including the manufacture of medicated feed pre-mixes).
- Residues of veterinary drugs in feed ingredients, including fermentation by-products and processed animal by-products (PAP) (e.g. feather meal).

The experts did not discuss, in any depth, issues such as the impact of antimicrobials in feed on antimicrobial resistance (AMR) as these issues are under consideration in other FAO, WHO, Codex and World Organisation for Animal Health (OIE) fora. The Experts also did not consider nanomaterials or rendered animal products as there is insufficient published information to determine their role in drug carryover in animal feed.



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## Current status of knowledge on veterinary drug carryover

Drug carryover is a form of feed contamination that results when a drug is transferred from an acceptable location or feed to an unacceptable location or feed. Carryover of veterinary drugs can occur during feed processing, handling, transportation, delivery or in feeding animals on-farm. The risk of unavoidable and unintentional veterinary drug residues from feed carryover is acceptable in situations where there is no negative impact on animal or human health. But the risk is unacceptable for drug carryover that causes adverse health effects in target and/or non-target animals and/or humans consuming foods originating from these animals (Mantovani *et al.*, 2006). If carryover is not properly managed, contaminated feed can directly harm species that are sensitive to the unintended veterinary drug they consume (e.g. monensin and horses) (Doonan *et al.*, 1989), result in residues in food of animal origin such as meat, milk and eggs that render them unsafe for human consumption (Dorne *et al.*, 2013) and contribute to AMR (Peeters *et al.*, 2018). Even if residues are not a safety hazard, they can pose regulatory and global trade issue as countries/markets may enforce a “zero” tolerance for residues when appropriate maximum residue limits (MRLs) have not been established (Carnevale, 1996).

### SOURCES OF UNAVOIDABLE AND/OR UNINTENTIONAL VETERINARY DRUG EXPOSURE AT THE FEED MILL AND FARM LEVEL

#### Feed and feeding practices

To maximize productivity, most food producing animals receive nutritionally balanced diets containing various types of feed ingredients and supplements. Feed represents the largest input cost for livestock, aquaculture animal and poultry producers, accounting for up to 75 percent of total costs depending on the species. In most regions, governmental regulatory agencies evaluate and determine the acceptability and safety of ingredients that have been evaluated and are approved for manufacture, import and sale for use in animal feed (CFIA, 2018a; FDA, 2018; Council of the European Union, 2019). Good Agricultural Practices (GAP) ensure the use of suitable, safe and good quality feed and feed ingredients (FAO and IFIF, 2010). Feed grains, including corn, grain sorghum, oats, rye, and barley, are typically used as energy sources with supplemental protein-based ingredients, vitamins and minerals added to provide the necessary nutrition for animals to produce meat, milk and eggs (Sapkota *et al.*, 2007). Additional feed ingredients can include plant protein products (e.g. cottonseed and soybean meals), processed grain by-products, rendered animal by-products, and plant- and animal-based oils and fats.

The increasing demand for ethanol as fuel has led to an increase in the amount of feed grains used for ethanol production. Distillers grains (DG) is a by-product of the fuel ethanol industry (Liu, 2011). During ethanol production, the starch from the grains is converted through yeast fermentation into ethanol, while the other nutrients remain and are concentrated in the DG. This makes DG an attractive alternative feed ingredient because of its high content of energy, protein

and minerals, as well as its low cost in comparison to traditional sources of these nutrients. DG is commonly fed to beef and dairy cattle, swine, and poultry (Jolly-Breithaupt *et al.*, 2018; Linneen *et al.*, 2008; Trupia *et al.*, 2016). The dry grind process is most commonly used, and results in the production of several types of wet (e.g. wet and modified wet distillers grains with or without solubles, condensed distillers solubles) or dried (dried distillers grains with or without solubles) by-products, including dried distillers grains with solubles (DDGS). The DDGS are produced by combining the liquid and solid leftovers after the ethanol is removed. The liquid is concentrated by evaporation to form condensed distillers solubles, which is then added to the solid fraction and mixed to produce DDGS.

Processed animal by-products (PAP), including meat and bone meal, poultry by product meal, blood meal, and feather meal may be incorporated into animal feed (Sapkota *et al.*, 2007). However, data concerning the specific amounts of PAP protein that are used in animal feed are difficult to obtain because this information is neither routinely collected by regulatory agencies nor reported by the rendering industry. These ingredients are often listed on animal feed labels as “processed animal proteins” or “animal by-products”, making it difficult to discern precisely which animal protein products are included in a particular animal feed. The use of PAP from unspecified species can introduce drug residues in non-target food producing animal species (Berntssen *et al.*, 2018; Berntssen *et al.*, 2014). Wide-scope qualitative screening for permitted drug residues in commercially available European Union produced PAP showed the presence of pharmaceutical agents, including monensin, flumequine, enrofloxacin, trimethoprim, and tylosin A (Nacher-Mestre *et al.*, 2016). Similarly, earlier screening studies on feather meal from the United States of America and China showed the presence of six classes of antimicrobials including fluoroquinolones, tetracyclines, folic acid antagonists, and streptogramins (Love *et al.*, 2012). Following the outbreaks of transmissible spongiform encephalopathies in the United Kingdom in the early 1990’s, the use of all PAP in all animal feed was banned in the European Union in 2001 (Beck *et al.*, 2005). Following a bovine spongiform encephalopathy risk assessment by the European Food Safety Authorities (EFSA), the European Union set out a working plan for the re-authorization of the use of non-ruminant PAP in animal feed, initially for aquafeed in 2013 (Karapanagiotidis, 2014).

Nanotechnology involves manipulation of materials on an atomic or molecular scale. It is an emerging technology that has the potential to be used across a wide variety of applications in human and animal medicine, food, and animal feed (Sekhon, 2014; Takeuchi, Kojima and Luetzow, 2014). Improving the feeding efficiency and nutrition of food producing animals, minimizing losses from animal diseases, and turning animal by-products and waste into value-added products, are among potential uses of nanotechnology in animal production. The evaluation of nanomaterials in food producing animals is still at a very early stage, and little is known about the potential accumulation of nanomaterials in animal tissues and food of animal origin (e.g. meat, milk, eggs). Currently, there is insufficient information to determine the role of nanomaterials in drug carryover in animal feed.

Animal feed production is carried out in commercial feed manufacturing facilities and on-farm feed mills. Of the almost 1 billion tonnes of feed produced by the global feed industry annually, it is estimated that 300 million tonnes of feed is produced by on-farm mills (IFIF, 2019). Particularly in developing countries, there are numerous

small-scale animal production systems which are supplied by small scale feed mills (Parr *et al.*, 1988). The feed manufacturing process consists of some or all of the following:

- raw material procurement,
- raw material storage and selection
- raw material weighing
- raw material grinding/sieving
- mixing of dry ingredients and addition of liquids
- pelleting/extrusion of mixed feed (optional)
- blended feed bagging, storage, transport and distribution

The size and sophistication of equipment varies with the daily capacity for feed output as well as differences in manufacturers' designs (Parr *et al.*, 1988).

### **Regulation of feed production**

Worldwide, there are many different governmental regulations, systems and practices used by the feed industry to assure the safety and quality of the various feed ingredients, including veterinary drugs. Some countries have lists of banned ingredients, lists of ingredients that can be used under limitations, exclusion lists for ingredients and amounts that can be used, and positive lists that include ingredients that can be used according to limitations or intended uses (FAO and IFIF, 2010). The production, processing, storage, transport and distribution of safe and suitable feed and feed ingredients is the responsibility of all participants in the food production chain, including farmers, feed ingredient manufacturers, feed mills, and transporters. Each participant is responsible for all activities under their direct control, including compliance with all applicable regulatory requirements. In many countries, feed safety programmes have been developed by national feed industry associations to work in conjunction with regulatory agencies. The FAO and IFIF developed a feed manual to assist the feed industry to implement the Codex Code of Practice on Good Animal Feeding (CXC 54-2004) (FAO and IFIF, 2010).

### *Commercial feed manufacturing*

The Good Manufacturing Practices (GMP), Hazard Analysis and Critical Control Points (HACCP), HARPC (Hazard Analysis and Risk-Based Preventive Controls) and other quality management schemes are the practices and procedures that ensure the safety and suitability of feed and food and they should be applied throughout the food production chain. These standards are most easily applied in commercial feed manufacturing, but they may be more difficult to implement and regulate in on-farm feed production. For medicated and non-medicated feed, manufacturing equipment plays the most important role in feed safety. Storage, transport, mixing equipment, dust collectors and other utensils that come into contact with feed should be designed and constructed so that they can be adequately cleaned and maintained to avoid or minimize cross-contamination of feed. Feed should be mixed in a manner that minimizes the potential for cross-contamination between feed or feed ingredients (FDA, 2017). Standard operating procedures (SOPs) should be in place to document that feed processing, storage and handling facilities are cleaned in a manner that is sufficient to maintain feed safety at all times. Feed additives should be of a form (e.g. liquid, powder or granule) that ensures a homogenous mix within the feed. For low inclusion products, ingredient suppliers should provide evidence

that product particle size and concentration provide uniform distribution throughout the feed. The determination of the coefficient of variation of the mixture is crucial to ensure the homogeneity of the feed products. Planned maintenance of feed manufacturing facilities ensures that equipment is in safe and effective working condition (FAO and IFIF, 2010).

#### *On-farm feed production*

On-farm feed production is more difficult to regulate than commercial feed production. While all of the same GMP protocols should be followed, on-farm feed production has special challenges with the use of home-grown feed stuffs (e.g. cereals, pulses, forage crops and pasture); the use of feed or feed ingredients, including veterinary drugs, brought in from off-farm; and the processing, mixing and storage of feed on-farm (FDA, 2016; FAO and IFIF, 2010). Additionally, farmers may not be used to documented systems, process controls and testing of products and may not adequately document manufacturing conditions and process parameters.

#### *Medicated feed production*

A feed additive is any intentionally added ingredient not normally consumed as a complete, nutritionally balanced feed by itself, whether or not it has nutritional value, which affects the characteristics of feed, the biological responses of animals, or the final food of animal origin. Approved veterinary drugs make up the majority of feed additives used in production of livestock, poultry and aquaculture (Mantovani *et al.*, 2006). Veterinary drugs are incorporated into feed because it is the most practical method of administering drugs to large numbers of animals on a daily basis. Medicated feed is defined as any mixture of a veterinary drug or drugs and feed or feed that is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product (FAO and IFIF, 2010). While there is a great deal of variability in feed regulations and animal production systems between countries, the majority of veterinary drugs added to feed are antimicrobials, coccidiostats and growth promoters ( $\beta$ -adrenergic agonists) (McEvoy, 2002).

Medicated feed is usually manufactured by commercial feed mills regulated and inspected by competent authorities. However, some countries authorise on-farm production of medicated feed (European Commission Directorate General for Health and Consumers, 2010). Small feed manufacturers, generally on-farm facilities, may produce feed for only a single species and use only a small number of medicated feed ingredients. Large feed manufacturers, generally the largest on-farm operations and commercial feed mills, may use a variety of veterinary drugs to produce medicated feed for many species (e.g. poultry, cattle, swine, horses) and classes (e.g. starter, grower, finisher, breeder) of food producing animals. Large feed manufacturers have many types of equipment that are cross utilized for the production of medicated and non-medicated feed. According to GMPs, no matter the size of the feed manufacturing facility, adequate procedures should be established and used for all equipment used in the production and distribution of medicated feed to avoid unsafe contamination of medicated and non-medicated feed (AAFCO, 2017).

Veterinary drugs used in medicated feed should comply with the standards such as that of the Codex Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme Associated with the use of Veterinary Drugs in Food Producing Animals (CXG 71-2009) (FAO, WHO, 2014). Specifics of veterinary drug approval and use in animal feed varies greatly between countries/regions. For example, in the United States of America, extralabel use of veterinary drugs in feed is prohibited by the Animal Medicinal Drug Use and Clarification Act (Davis *et al.*, 2009). This is not the case in Canada; as long as it is done pursuant to a veterinarian's prescription, extralabel drug use in feed is permitted (Grignon-Boutet *et al.*, 2008). The use of veterinary drugs and medicated feed requires a prescription by an authorised veterinarian in all European Union member countries and must be done according to the label directions (European Commission Directorate General for Health and Consumers, 2010). However, in many countries veterinary drugs are available to producers for inclusion in feed with little or no veterinary oversight.

Feed containing veterinary drugs must be used in accordance with clearly defined instructions. Compounds approved as animal feed additives, including veterinary drugs, must be of verifiable quality, have proven efficacy supporting their use, be safe for animals consuming the feed and for consumers of products originating from treated animals, and be safe for the users/workers and the environment (Mantovani *et al.*, 2006). For an approved veterinary drug, risk assessors determine the acceptable daily intake (ADI) for consumers and then competent authorities determine the corresponding maximum residue limits (MRLs) in edible tissues and products (e.g. milk, eggs) (Carnevale, 1996; Codex Alimentarius, 2005; McEvoy, 2002). The ADI is expressed in milligrams of the substance per kilogram of body weight of the consumer. The higher the ADI for a substance, the lower its potential for adverse effects on human health. Therefore, ADI values provide a measure of safety for long-term exposure or repeated ingestion of approved veterinary drug residues in foods (Danaher *et al.*, 2016). From a comprehensive assessment of pharmacokinetics and toxicological studies in laboratory and target and non-target animal species and residue depletion studies, regulators establish withdrawal periods so that food products from treated animals do not contain residues unsafe for human consumption (Riviere *et al.*, 2017). However, for the presence of unintended residues in non-target species, the determination of such withdrawal times is not applicable.

Regulations and inspection of medicated feed manufacturing facilities must ensure process control systems that provide the correct and effective inclusion levels for feed additives, including veterinary drugs. Containers of veterinary drugs must be held in secure storage and under the control of authorised and trained employees. Only those products in current use are to be present in manufacturing areas. Records must be kept of all feed additives incorporated in to feed. Reconciling usage versus inventory should be done daily or on a frequent basis. Where veterinary drugs are incorporated, regular sampling must be done to demonstrate that control systems are effective in including these products into the correct feed at the correct concentration and that non-medicated feed is not contaminated at levels exceeding regulatory limits (FAO and IFIF, 2010).

### *Labelling of medicated feed*

Labelling requirements of veterinary drugs and feed additives vary greatly from country to country. But in all circumstances, labelling is designed to be clear and informative on to how to handle, store and use feed and feed ingredients (FAO and IFIF, 2010). Labels minimally contain the following:

- information about the species or category of animals for which the feed is intended;
- the purpose for which the feed is intended;
- a list of feed ingredients, including appropriate reference to additives, in descending order of proportion;
- contact information of manufacturer or registrant;
- registration number if applicable;
- directions and precautions for use, including withdrawal time(s);
- lot identification;
- manufacturing date; and
- “use before” or expiry date.

### *Traceability*

Commercial manufacturers and on-farm producers of medicated feed must maintain records of the production, distribution and use of feed and feed ingredients. This facilitates the prompt and effective trace-back to the source of a problem product and trace-forward to the recipients of the product if a food safety hazard is identified (FAO and IFIF, 2010).

### *Carryover*

During feed manufacturing, veterinary drugs may be carried over from medicated feed to non-medicated feed (Kennedy *et al.*, 1998). Carryover of a veterinary drug can occur during feed processing, handling, delivery or storage. The type of drug, number of species exposed, and feed production and delivery systems determine the hazards associated with drug carryover (Harner *et al.*, 1996). Carryover may lead to serious adverse effects on human and animal health depending on the drug and the quantity and distribution of the feed that was contaminated (Doonan *et al.*, 1989; AAFCO, 2017; Pietruk *et al.*, 2018; Vandenberg *et al.*, 2012c). Even low-level carryover of veterinary drugs may be sufficient to cause residues in the edible tissues or products (e.g. eggs or milk) from animals consuming feed containing carryover drug residues (Danaher *et al.*, 2016; Dorne *et al.*, 2013; McEvoy *et al.*, 1999; Mitchell *et al.*, 1998; Olejnik and Szprengier-Juszkiewicz, 2015; Olejnik *et al.*, 2014a; Pietruk *et al.*, 2018; Segato *et al.*, 2011; Tkacikova *et al.*, 2012; Vandenberg *et al.*, 2012a; Vandenberg *et al.*, 2012b; Vandenberg *et al.*, 2012c). Even if such residues are not an animal health or food safety concern, they may cause trade issues (Heberer *et al.*, 2007). Residues of veterinary drugs can be present in feed when ingredients of animal origin (terrestrial and aquatic) are used, but this is not considered a significant source of drug carryover (FAO and IFIF, 2010; Pinotti *et al.*, 2003).

There are a number of causes of unwanted drug carryover in medicated feed (Filippitzi *et al.*, 2016). Significant amounts of drug or medicated feed may remain in any part of the feed manufacturing and distribution system and contaminate subsequent batches of feed. Residual medicated feed can remain in mixers, surge bin conveyors and elevators, bin and bulk feed trucks. Leaking connections can cross-

contaminate feed. In a study of coccidiostat drug carryover that examined samples from feed mill equipment, packaged feed, and feed storage containers on-farm, the most contaminated sampling site was the production line and most of the positive samples were collected from a batch of non-medicated feed produced immediately following processing of the medicated feed (Annunziata *et al.*, 2018).

The type of feed and the composition of the veterinary drug are important factors determining the amount of carryover (Stolker *et al.*, 2013). The electrostatic properties of some drugs, particularly those in powder form such as the sulfonamides and coccidiostats, cause them to adhere to equipment surfaces, making it very difficult to completely clean equipment between batches of feed (Dorne *et al.*, 2013; Kennedy *et al.*, 2000; McEvoy, 2002). Some manufacturers have responded to this problem by producing granular preparations with reduced electrostatic properties, and this has reduced but not completely eliminated problems with carryover of these drugs. Other manufacturers have adopted different cleaning systems such as scraping the surfaces of the equipment, to minimize drug carryover.

Despite appropriate inclusion into a batch of feed, segregation of the veterinary drug from the feed may lead to variable drug concentrations in the medicated feed and cause carryover. Segregation can occur in pre-mixes and mixed feed. Segregation is caused by differences in particle size, shape, and density of ingredients in medicated feed. Particles tend to segregate when there is a large size difference between ingredients. In parts of the production system where particles free-fall through the air, particle shape affects the movement of materials. Flat particles tend to fall more slowly and remain where they land, while particles that are round or cuboidal fall faster and tend to roll outwards toward the container wall. Particles with high density are less affected by free-fall air resistance than those of low density. Less dense particles tend to migrate towards container walls by the air currents within the container. The processes of segregation and desegregation can cycle during the entire feed production and delivery process. Initially, feed ingredients and medications can be evenly dispersed by the mixing process, become segregated as the feed mixture drops into the surge bin, get remixed during flow from the surge bin auger to the elevator leg, then become segregated again as feed is discharged from the leg and free-falls into the holding bin over the pellet mill. Finally, the feed and ingredients become remixed as material is transferred into the conditioning chamber above the pellet mill (Harner *et al.*, 1996).

### *Sequencing*

*Sequencing* is a pre-planned order of production of medicated feed designed to control veterinary drug carryover into subsequent batches of feed for target or non-target species (CFIA, 2018b). When the order of feed production through common equipment occurs in an acceptable sequence, specific cleanout of the equipment is not required, which is a great economical savings in feed production (Van Donkersgoed *et al.*, 2010). The feed industry prefers sequencing over flushing or cleaning because it prevents downtime of the manufacturing system between batches of feed and minimizes waste of useable feed (FDA, 1995). The ordering sequence in which feed batches are processed determines the likelihood of unsafe drug carryover (CFIA, 2018b; Harner *et al.*, 1996; Van Donkersgoed *et al.*, 2010). The production of medicated feed having the same drug(s) should be scheduled in sequence so that the higher inclusion levels are produced first and ending with the lowest inclusion level.

This lowest inclusion level sequence should be followed by a non-medicated feed for the same animals before producing feed for a non-target species. When manufacturing feed for a single species (e.g. swine) with a veterinary drug with an established withdrawal time, the feed should be mixed in the following order: nursery ration containing the drug, sow feed, grower ration, and finally the finishing ration. The closer the animal species is to slaughter/harvest, the more caution must be taken with finisher feed. A sequencing procedure where a swine finishing (non-medicated) feed is mixed after production of a sulfamethazine medicated feed is not acceptable, because even a very low concentration of sulfamethazine consumed up to slaughter readily results in residues that exceed MRLs in edible tissues (Biehl *et al.*, 1981, FDA, 2017). When using a sequencing pattern to avoid unacceptable drug carryover, it is imperative that detailed feed production records are kept to identify the last batch so that human errors are minimized. Drugs with special toxicity characteristics, such as monensin with its toxicity to horses, require special risk mitigation during feed production (FDA, 1995). Whenever the planned sequencing is broken, the validated cleaning procedure should be applied.

Sequencing may also be used to clean out bins on bulk trucks but the GMP and HACCP principles need to be followed. Drivers or employees loading trucks should unload a batch of medicated feed first followed by a non-medicated feed. Depending on the type of system on the bulk truck, the feed mill and operators of the bulk trucks must carefully schedule how the trucks are loaded and the order the bins are unloaded on the truck if the truck has multiple bins. The feed manufacturer should be able to document when and how the bins on their bulk trucks are sequenced. They should also be able to demonstrate adequate cleaning of bins prior to addition of another batch of feed to the bins on the truck (AAFCO, 2017). All cleaning regimens should be properly validated to prove efficacy and fit for purpose.

### *Flushing*

Flushing involves taking an appropriate feed ingredient, usually ground grain, and moving a sufficiently large quantity of it through the feed manufacturing system to “flush” out any medicated feed that remains. It is generally recommended that the quantity of flush used be between 5 and 10 per cent of the mixer’s capacity (Van Donkersgoed *et al.*, 2010). This quantity will depend on the type of equipment and should be verified with the manufacturer as to have the best performance for the cleaning. The first portion of the flush feed will be more highly contaminated than the last portion, and this must be considered if the first flushing batch of feed is fed to a non-target animal species and when samples are taken for quality control and regulatory purposes (Annunziata *et al.*, 2018). Because of this, most countries’ medicated feed regulations dictate that “first-flush” feed is not used as feed for laying hens, lactating dairy cows, or as the finishing feed for animals before slaughtering/harvesting (Stolker *et al.*, 2013).

After the mixer is flushed, the new flush material passes through the entire production system in the same manner as the previous medicated feed. Once this occurs, the flush material must be stored in a separate bin for use in an identical medicated feed (Harner *et al.*, 1996). For bulk deliveries, some commercial manufacturers use the same flush material to flush their bulk trucks out after deliveries are

made to the farm. Some manufacturers elect to simply discard the flush material to prevent inadvertent cross-contamination (AAFCO, 2017).

#### *Physical cleanout*

The GMPs of feed manufacturing facilities stipulate that all equipment shall be designed, constructed, installed, and maintained so as to facilitate inspection and adequate cleanout procedures. Physical cleanout is done when employees enter areas of a production system and actually clean the system by sweeping, scraping, washing, and disinfecting. This is the most effective way of cleaning out portions of a production system to eliminate the risks of veterinary drug carryover. But the loss of manufacturing time is significant compared to sequencing and flushing. Some feed mills do physical cleanout only when necessary; such as when mixing feed using liquid ingredients (e.g. fat or molasses) that create residues within the system which cannot be removed through other operations (AAFCO, 2017).

#### *Contamination during storage, transport and processing*

##### **Cross-contamination at the feed mill**

Within a feed mill, different feed can be manufactured in the same production line and pass through the main mixer. The potential for cross-contamination from carryover of veterinary drugs occurs at different points throughout the production line, such as the main mixer, the surge bin, the bucket elevator, the holding bins, the pellet mill, the pellet cooler and the holding bins, before loading onto the delivery trucks (Filippitzi *et al.*, 2016; McEvoy *et al.*, 2003; Stolker *et al.*, 2013).

##### **Cross-contamination during the transport and unloading of the feed**

Cross-contamination may take place in the bin of the delivery truck during successive loading of feed into the same bin (intra-bin contamination). It may also take place in the transfer system, when traces of previously transported medicated feed remain in the conveyor screws and cross-contaminate the non-medicated feed subsequently delivered to a farm (Filippitzi *et al.*, 2016). To minimise the risk during feed delivery, the use of new trucks, the use of back bins to reduce the length of the circuit, and the careful flushing or cleaning after delivery are possible risk reduction measures (Filippitzi *et al.*, 2016).

##### **Cross-contamination at the farm**

Cross-contamination is also possible at the farm level, where carryover of veterinary drugs can occur when non-medicated feed is stored in close proximity to, or subsequently to, medicated feed. Cross-contamination may also occur during the distribution of the feed on the farm (Filippitzi *et al.*, 2016). Raising the awareness of farmers and farm workers on safe feed handling is essential to avoid cross-contamination at the farm level that may adversely affect human and animal health and international trade.

## **Veterinary drugs used in feed**

The classes of veterinary drugs most commonly incorporated in to animal feed include antimicrobials, coccidiostats and growth promoters ( $\beta$ -adrenergic agonists).

### *Antimicrobials*

Antimicrobials are extensively utilized in food animals for therapeutic, prophylactic, metaphylactic, and growth promoting purposes (Granados-Chinchilla and Rodriguez, 2017). Due to concerns over AMR, the use of antimicrobials for growth promotion has been greatly reduced (Van Boeckel *et al.*, 2017). The classes of antimicrobials permitted for use in animal feed varies widely between countries. Tetracyclines, sulfonamides (some with trimethoprim), and macrolides are the most commonly administered drugs, with some use of other antimicrobials such as  $\beta$ -lactam antibiotics, aminoglycosides, glycopeptides, pleuromutilins, and lincosamides (Dibner and Richards, 2005). Tetracyclines, sulfonamides and penicillins tend to be the most frequent veterinary antimicrobial drugs involved in residues from carryover (Segato *et al.*, 2011; Shimshoni and Barel, 2017). Risks of carryover are impacted by the physical characteristics of veterinary drug products that lead to cross-contamination of feed and the pharmacokinetic properties of the drug that determine the fate of the carryover drug in the animals consuming the feed. Oral bioavailability in animals of a drug is the most critical pharmacokinetic parameter for determining the potential for drug residues to occur in food from unintended drug carryover in feed and varies widely for different drugs and different animal species (Leeman *et al.*, 2007).

Sulfonamides are an example of a particularly problematic drug class for carryover. The concentrations in medicated feed are comparatively high; increasing the potential for contamination of other feed subsequently manufactured in the same production system (Segato *et al.*, 2011). The use of powdered sulfonamide products contributes to the problem; powder formulations are extremely electrostatic and dusty, making them practically impossible to use without significant risk of carryover. Furthermore, with good oral bioavailability in most species, even small amounts of sulfonamide carryover can result in residues in meat, milk and eggs (McEvoy *et al.*, 1999; Segato *et al.*, 2011; Vandenberg *et al.*, 2012a; Vandenberg *et al.*, 2012b). Classes of food producing animals with short finishing periods, such as “barbecue” hogs are at high risk from violative tissue residues from carryover of sulfonamides in feed (CFIA, 2018b).

Antimicrobial use in aquaculture presents unique challenges with drug carryover (Morris *et al.*, 2012; Okocha *et al.*, 2018). The most convenient way to administer antimicrobials to farmed fish and shell fish is to incorporate the drug in the feed (Daniel, 2009). The preferred dosage form for aquaculture medicated feed is a powdered premix that includes the active compound and one or more excipients that act as carriers or as diluents for the active drug. Fish premixes can be poured or sprayed on the surface of pellets (surface-coated medicated feed) or included in the premix blends or part of the oil vacuum coating of extruded fish feed. On fish farms, the mixing is generally done in a concrete mixer: the pellets are loaded first, and the powdered drug is poured and thoroughly mixed to the feed, followed by a binding agent. Fish are unique in that the potential for carryover drug residues to result in human exposure from fish products is highly temperature dependent due to the impact of water temperature on drug metabolism (Chen *et al.*, 2018; Romero Gonzalez *et al.*, 2010).

Antimicrobial residues in aquaculture-derived products can be a concern, but the contribution of drug carryover as a cause has not been specifically investigated (Done and Halden, 2015; Okocha *et al.*, 2018; Zhang *et al.*, 2018). Of greater concern for veterinary drug use in aquaculture feed is contamination of the environment and non-target species when medicated feed is not consumed and left in the water and the promotion of AMR from indiscriminate drug use (Topp *et al.*, 2018).

During fermentation of DG, antimicrobials are added during the yeast propagation and fermentation processes to combat bacterial contamination that reduce ethanol yield and DG quality. However, this antimicrobial use can lead potentially to residues in the DG or DDGS that are fed to food producing animals. The US Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM), conducted a nationwide survey in 2008 to detect antimicrobial residues in DG (Luther, 2010). Quantifiable antimicrobial residues were found in only 17 samples. Virginiamycin was estimated in 10 samples at levels of 0.1 ppm to 0.5 ppm, while erythromycin was estimated in 7 samples at levels of 0.1 ppm to 1.5 ppm. Other studies have shown low rates of detection of antimicrobial residues in DG although these residues appear to be biologically inactive (Bischoff *et al.*, 2016; Compart *et al.*, 2013; Sankarlal *et al.*, 2015). The perceived risk of antimicrobial residues in DDGS impacts trade in countries with “zero tolerance”. In addition, production of food of animal origin with labeling of “free from antibiotics” has discouraged DDGS use.

### *Coccidiostats*

Coccidiosis is a contagious disease caused by single-celled parasites that impacts the health and productivity of numerous animals, especially poultry and rabbits. Besides ensuring animal health and welfare, coccidiostats prevent economic losses caused by the disease, which on a global scale are estimated at \$3 billion annually for poultry alone (Kadykalo *et al.*, 2018). In contrast to most antimicrobials, coccidiostats need to be administered throughout the life of the food animal in order to protect against re-infection. Coccidiostats are approved as veterinary drugs or animal feed additives in many countries, including those in the European Union. The coccidiostats used in animal feed include the ionophores (lasalocid, maduramicin, monensin, narasin, salinomycin, and semduramicin), decoquinate, diclazuril, clazuril, halofuginone, nicarbazin, robenidine, and amprolium (Kadykalo *et al.*, 2018). Carryover of coccidiostats into non-target animal feed occurs for the same reasons as for the antimicrobials. Like the sulfonamides, some coccidiostats are strongly electrostatic and the use of powder formulations increases the likelihood of carryover from medicated feed to subsequent batches of non-medicated feed (Annunziata *et al.*, 2018). Residues in food of animal origin, especially liver, eggs and milk, can result in human exposure to low concentrations of coccidiostats (Clarke *et al.*, 2014; Danaher *et al.*, 2016; Dorne *et al.*, 2013; Kennedy *et al.*, 1998; McEvoy *et al.*, 2003; Olejnik and Szprengier-Juszkiewicz, 2015; Olejnik *et al.*, 2014a; Olejnik *et al.*, 2014b; Pietruk *et al.*, 2018; Tkacikova *et al.*, 2012; Vandenberghe *et al.*, 2012c; Varenina *et al.*, 2015).

For target animal species, MRLs for the coccidiostats are well established. For unavoidable carryover in to feed of non-target animal species, maximum levels in the feed have been established by EU Regulation No 574/2011 following the ALARA (As Low As Reasonably Achievable) principle (Annunziata *et al.*, 2017). The health risk to non-target animal species that results from the consumption of

feed contaminated with coccidiostats at less than maximum levels is negligible for most animal species, with the exception of ionophores in horses (Oehme and Pickrell, 1999). The health risk to humans consuming products from animals exposed to carryover levels of coccidiostats appears negligible, but the frequency of such carryover is of high regulatory concern (Clarke *et al.*, 2014; Dorne *et al.*, 2013).

*Growth promotant  $\beta$ -adrenergic agonists*

Beta adrenergic agonists are administered to livestock to increase skeletal muscle growth (Sillence, 2004). Ractopamine and zilpaterol are the  $\beta$ -adrenergic agonists that have been approved as feed additives in some countries for use in select species including cattle, swine and turkeys. The use of these growth promoters remains controversial, with many jurisdictions not approving their use. Of all the veterinary drugs used in animal feed, the  $\beta$  agonists are the most contentious for international trade of food of animal origin because there are great variations in how they are regulated in different markets (Centner *et al.*, 2014). Carryover of ractopamine and zilpaterol to feed intended for horses has frequently caused violations in racehorses and performance horses subjected to drug testing (CPMA, 2014). Proper flushing is necessary to reduce risk of carryover of these products (Holland *et al.*, 2010). Use of growth promoting  $\beta$ -adrenergic agonists is limited by trade barriers for export markets (Centner *et al.*, 2014).

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# Human health risks due to the presence of veterinary drug residues in food from unavoidable and unintended carryover in feed

Human health risks are of concern if veterinary drug residues are present in food at concentrations that exceed Health Based Guidance Values (HBGV), such as acceptable daily intake (ADI) or acute reference dose (ARfD) (JECFA, 2017; FAO and WHO, 2009). Food safety hazards associated with veterinary drug carryover in animal feed can be chemical or microbiological. Each hazard is associated with particular sources and routes of contamination and exposure. Risk management must be based on a thorough understanding of these characteristics (Dorne and Fink-Gremmels, 2013).

The risk that carryover of veterinary drugs in feed will ultimately result in detectable residues in food is influenced by the pharmacokinetics (absorption, distribution, metabolism and elimination) of the drug in the animal consuming the medicated feed. In general, food producing animals are excellent biodegraders of veterinary drugs, so that low levels of drug carryover in feed causes few instances of unsafe residues in food of animal origin (Kan and Meijer, 2007). There is a greater risk of residue transfer to milk and eggs than in meat, as these products are produced by the animals on a daily basis (Kan and Meijer, 2007; Kan and Petz, 2000; Leeman *et al.*, 2007; McEvoy *et al.*, 1999; Mitchell *et al.*, 1998; Vandenberg *et al.*, 2012c). Even if residues in food of animal origin are not a human food safety hazard, they may still cause issues with trade (Heberer *et al.*, 2007).

## CHEMICAL RISKS

Residues of veterinary drugs raise special human safety concerns primarily with regard to allergic reactions and carcinogenicity (Baynes *et al.*, 2016). Ordinary cooking procedures for meat, even to “well-done”, cannot always be considered to inactivate drug residues. High thermal exposure for canning or prolonged cooking with moist heat can inactivate the more heat sensitive compounds, such as penicillins and tetracyclines, but the toxicity of the degradation products is unknown in most cases (Moats, 1999). Allergic reactions in humans exposed to certain veterinary drugs can manifest in many ways, from life-threatening anaphylactic reactions to minor reactions such as rashes. Residues of known allergenic veterinary drugs in food do not cause primary sensitization of individuals because exposures are low and for short duration. However, veterinary drugs residues in food have the potential to cause allergic reactions in already sensitized individuals. Reports of acute adverse reactions in humans from ingestion of drug residues in food are rare (Dewdney *et al.*, 1991). Most suspicions are based on “circumstantial evidence” and drug residue involvement is anecdotal. Nearly all reports of acute adverse reactions from foodborne residues implicate penicillin as the offending agent, and the source of

penicillin residues is most often milk or other dairy products. Milk residues likely originate from intramammary infusion of penicillin used for the treatment of mastitis (Siegel, 1959). Although a substantial number of farm milk samples have been found to contain small amounts of penicillin, there have been relatively few published reports of adverse reactions from penicillin residues in milk (Boonk and van Ketel, 1982; Borrie and Barrett, 1961; Vickers, 1964; Vickers, Bagratuni and Alexander, 1958; Wicher, Reisman and Arbesman, 1969). In all instances, the patients reported a history of penicillin allergy or skin disease unrelated to penicillin allergy. Symptoms varied in intensity from mild skin rashes to exfoliative dermatitis. Many drugs other than penicillin, including other  $\beta$  lactams, streptomycin (and other aminoglycosides), sulfonamides, and to a lesser extent, novobiocin and tetracyclines are known to cause allergic reactions in sensitive people; however, there is only a single published report of an allergic reaction to meat suspected of containing streptomycin residues (Tinkelman and Bock, 1984).

Other potential adverse human effects from antimicrobial residues in food of animal origin include carcinogenicity and bone marrow suppression. While there is no direct evidence that consuming food of animal origin that contains residues causes these impacts on human health, a number of drugs are banned from veterinary use in many countries because of concerns (Baynes *et al.*, 2016). Chloramphenicol, nitroimidazoles (e.g. metronidazole, dimetridazole), nitrofurans (e.g. nitrofurazone) and carbadox are banned for veterinary use in most jurisdictions due to carcinogenicity potential.

Risk assessments for humans consuming products from animals exposed to carryover levels of coccidiostats have found no appreciable risk for consumers (Clarke *et al.*, 2014; Dorne *et al.*, 2013). Although these drugs are currently not considered as important for human medicine, there is new interest in their potential as chemotherapeutics and antimicrobials that may give cause to re-evaluate their use in food animal production (Dorne *et al.*, 2013).

There have been no reported cases of adverse health effects in humans exposed to food of animal origin containing zilpaterol or ractopamine residues (Baynes *et al.*, 2016; Sakai *et al.*, 2016).

Clenbuterol is not an approved veterinary drug feed additive, but illicit use has been associated with direct human toxicity from residues in food of animal origin (Chan, 1999; Doerge *et al.*, 1996).

## **MICROBIOLOGICAL RISKS**

### **Antimicrobial resistance**

While the risks to human health from chemical hazards of veterinary drug carryover appear negligible, microbiological risks are much more complicated and significant (Hoelzer *et al.*, 2017). Scientific evidence is growing that there are risks that are significant to human health from the use of antimicrobials in food producing animals. A recent systematic review concluded that exposing animals to antimicrobials results in higher resistance rates to those antimicrobials than exposing animals to no (or a lower dose of) antimicrobials (Scott *et al.*, 2018). Resistant bacteria and/or resistance genes can spread to humans through direct exposure from infected or contaminated animals, such as on farms or in processing facilities and through food (Castillo Neyra *et al.*, 2012; Dohmen *et al.*, 2017; Hoelzer *et al.*, 2017; Price *et al.*, 2007; You *et al.*, 2016). While most of the current evidence is from investigations regarding

the therapeutic use of antimicrobials in animal feed, an in vitro study of doxycycline at cross-contamination concentrations selected for plasmid-mediated resistance in porcine commensal *E. coli* strains (Peeters *et al.*, 2018).

### **Foodborne disease**

Antimicrobial susceptible and resistant bacteria from animals can reach humans through the food supply, by direct exposure to antimicrobial resistant pathogens that directly cause foodborne disease or to commensal bacteria harbouring transmissible resistance genes that are then spread to the human microbiome. Production practices that group large numbers of animals together for feeding and transport and modern slaughter practices increase the risk of bacterial contamination of food products (Noyes *et al.*, 2016; Wasyl *et al.*, 2013). In food animals, AMR in foodborne zoonotic pathogens such as *Salmonella*, *Campylobacter* and *E. coli* have long been of concern and have led to regulatory interventions. For example, the association between the use of ceftiofur *in ovo* in hatcheries and the rise of resistant *Salmonella* isolates causing human disease led to the suspension of this use in the United States of America and Canada (Parmley *et al.*, 2013). But the risk of foodborne illness directly impacting human health from veterinary drug carryover needs to be considered in a broader context. In a recent report from the European Union, approximately 200 deaths were attributed annually to cases of salmonellosis and campylobacteriosis, while 25,000 deaths were attributed to other antimicrobial resistant infections (EFSA and ECDC, 2014). And even those 200 deaths are not necessarily related to AMR, as most zoonotic *Salmonella* and *Campylobacter* strains are susceptible to many antimicrobials. But where it occurs, AMR complicates treatment of these foodborne illnesses and is of increasing concern for human health (Florez-Cuadrado *et al.*, 2018; Hoelzer *et al.*, 2017).

### **CONCLUSIONS OF THE EXPERT MEETING**

Veterinary drug residues in food following drug carryover in feed are unlikely to be at concentrations high enough to result in human food safety hazards as expected exposure of non-target animals from carryover is less than the therapeutic dose for target animals. However, human health risks cannot be ruled out in all circumstances. Therefore, specific risk assessments may be required to determine if the level of carryover results in food residues that exceed HBGV's such as the ADI or ARfDs. Risk assessments for antimicrobial uses and antimicrobial residues at carryover concentrations in animal feed may require additional consideration for AMR.



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## Trade issues from residues in food at detectable levels in the absence of suitable regulatory provisions

The regulation and use of veterinary drugs vary widely between countries/regions and concerns over the risk of residues may be used as trade barriers (Carnevale, 1996; Centner *et al.*, 2014; Heberer *et al.*, 2007). Approximately 200 veterinary drugs are regulated in a variety of food matrices such as milk, meat and eggs (Delatour *et al.*, 2018). International emphasis has been on trade liberalisation and barriers to trade frequently cause trade disruption. The lack of international harmonization of MRLs can result in obstacles to trade (Carnevale, 1996; Heberer *et al.*, 2007; Wilson *et al.*, 2003). In this respect, the WTO strongly encourages countries to harmonise their sanitary and phytosanitary measures with international standards, such as those of Codex, OIE and the International Plant Protection Convention (IPPC). Under the Agreement on Sanitary and Phytosanitary Measures of the WTO, countries may set a higher level of health protection than that reflected in international standards, providing their measures are based on an appropriate assessment of risks and the approach is consistent, not arbitrary.

Trade issues may also arise due to veterinary drug carryover even though MRLs have been set, for example, when zero tolerances are applied to non-target species or food of animal origin (e.g. milk, eggs) where no MRL has been established even though MRLs are established in other species and/or other food products (Carnevale, 1996; Vandenberghe *et al.*, 2012c). Codex Alimentarius has established Risk Management Recommendations for veterinary drugs for which JECFA could not establish an ADI and/or recommend MRLs due to safety concerns (FAO, WHO, 2018b).

Due to the increasing sensitivity of analytical methodology, the analytical limits of detection and quantification of veterinary drug residues are continuously being lowered (Delatour *et al.*, 2018). This means that more and more substances, which could not be detected before, can now be detected at lower concentrations. Detection of drug residues is therefore largely dependent on technological progress and the equipment available in a laboratory, but the differences in performance of the laboratories involved leads to enforcement difficulties (Heberer *et al.*, 2007).



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## Risk management strategies for carryover of veterinary drugs

The Expert Meeting focused their discussions on risk management recommendations that could be established to address trade issues resulting from veterinary drug carryover and transfer from feed to food, while still protecting human health.

### SIGNIFICANT RISKS

While there are clear examples of drugs that are toxic to animal species for which they are not approved (e.g. monensin fed to horses) or contraindicated to be mixed with other drugs (e.g. tiamulin with ionophores), carryover of veterinary drugs and subsequent feed to food transfer is most significantly an international trade issue. The most efficacious way to avoid unintended carryover of veterinary drugs is by reducing the production and use of medicated feed (Filippitzi *et al.*, 2016). For some of the drugs involved in carryover, such as the coccidiostats, elimination of use is not in the best interest of animal health and welfare, and the risks to human health appear negligible (Kadykalo *et al.*, 2018). For antimicrobials in animal feed, there is growing consensus that therapeutic and disease prevention use needs to be reduced and their use as growth promoters eliminated because of AMR. Following the lead of the European Union, the United States of America and Canada are revoking approvals of antimicrobials for growth promotion purposes and changing the marketing status from “over-the-counter” to requiring a veterinary prescription for all antimicrobials deemed important in human medicine (Government of Canada, 2018; FDA CVM, 2018). But not all countries follow these restrictions on the use of antimicrobials. With the growing global human population and increasing consumer demands for foods of animal origin, any decrease in the relative amounts of antimicrobials used in foods animal production maybe counteracted by the increase in the absolute amount of antimicrobials administered. Therefore, even restrictions to only “prudent use” of veterinary antimicrobials may be insufficient to prevent the occurrence of AMR bacteria and resistance genes (Van Boeckel *et al.*, 2015).

### ANALYTICAL CAPABILITY

The Expert Meeting recognized that analytical methodology for the detection of veterinary drug residues in feed and food of animal origin is advancing rapidly (Borràs *et al.*, 2011). Advances in analytical chemistry have resulted in methods capable of detecting large numbers of pesticides and veterinary drug residues in animal feed at very low concentrations (Aguilera-Luiz *et al.*, 2013; Cronly *et al.*, 2010, Cronly *et al.*, 2011; Love *et al.*, 2012; Molognoni *et al.*, 2018; Moreno-Bondi *et al.*, 2009; Nacher-Mestre *et al.*, 2016; Song *et al.*, 2018; Stolker *et al.*, 2013). As a result, the ability of regulatory authorities to detect drug carryover in feed is constantly improving, and while the amount of detected residues may be too low to be toxicologically relevant, they may still have regulatory and trade implications. There is great variability in global access to such advanced and often expensive methodologies. Appropriate validation of regulatory laboratories carrying out such analyses is also challenging on a global basis.

## **RISK ASSESSMENT**

It is not possible to generate specific information for carryover of every veterinary drug for every feeding situation, especially considering all the possible differences in bioavailability, metabolism/elimination, feed composition, feed concentrations, production systems and exposure periods for each type of food producing animal. Therefore, decisions need to be based on the concentration of carryover veterinary drugs in feed that poses a human health hazard. The most intuitive and consumer acceptable target is zero tolerance, where no detectable amount of drug is present in the animal feed. While this gives consumers the greatest safety protection, the advances in analytical chemistry allow for detection of drugs and their metabolites at increasingly smaller concentrations, to the point where they are no longer physiologically or toxicologically significant (Heberer *et al.*, 2007). In addition, differences in the ability of analytical laboratories to detect drugs at their lower analytical limits leads to difficulty in enforcement. In the EU, Minimum Required Performance Limits (MRPLs) that must be met by all official laboratories have been established for some substances as an approach for achieving zero residues. This is in order that the Reference Point for Action (RPA) set for the aforementioned banned, pharmacologically active substances can be monitored as part of the statutory residues surveillance programme. If MRPLs are not established, then enforcing compliance with zero tolerances for prohibited or non-approved veterinary drugs depends on the performance capability of the individual laboratory doing the testing.

A recent European Commission Regulation on medicated feed calls for a scientific assessment by the EFSA in cooperation with the European Medicines Agency (EMA), as well as taking into account the application of good manufacturing practice and the ALARA principle (EU Regulation 2019/4 of the European Parliament and of the Council). Until the completion of that scientific risk assessment, national maximum levels of cross-contamination for active substances in non-target feed, regardless of its origin, should apply, taking into account the unavoidable cross-contamination and the risk caused by the active substances concerned, on the maximum permitted levels of cross-contamination due to carryover.

## **GOOD ANIMAL FEEDING**

There is a great deal of variability in regulation of animal feed production between countries. For effective control of safe feed production, all regulations should be demonstrably effective and enforced in accordance with production programmes that include GAPs, GMPs and HACCP principles.

Risk-based governmental regulatory programmes are designed to ensure that feed and feed ingredients are produced, distributed and used in such a way that foods of animal origin are safe for human consumption. According to recommendations from sources such as the manual of *Good Practices for the Feed Industry-Implementing the Codex Alimentarius Code of Practice on Good Animal Feeding* (FAO and IFIF, 2010), feed and feed ingredient manufacturers and other all other parts of the feed production chain should practice self-regulation/auto-control to ensure compliance with required regulations for production, storage and transport. Internal and external inspection and process control procedures should be used to verify that feed and feed ingredients meet requirements in order to protect consumers against hazards from food of animal origin. Regulators should employ risk

assessment methodology that is based on currently available scientific evidence and be consistent with internationally accepted approaches.

Animal feed ingredients must be obtained from safe sources or be subject to a risk analysis if the ingredients are derived from processes or technologies that have not been evaluated from a food safety risk assessment. Risk analysis procedures must be consistent with the working principles for risk analysis applied by Codex set out in the Procedural Manual of the Codex Alimentarius Commission (FAO, WHO, 2018a) and the Codex Guidelines on the Application of Risk Assessment for Feed (CXG 80-2013) (FAO, WHO, 2013). Manufacturers of feed additives need to provide clear information to the users to ensure proper use. Monitoring of feed ingredients includes inspection and sampling and analysis for contaminants using risk-based protocols (FDA, 2000; FDA, 2016; FDA, 2017; FAO and IFIF, 2010; Mantovani *et al.*, 2006).

Avoidance of veterinary drug carryover begins with standardized feed production practices (CFIA, 2018b; FDA, 2016; FDA, 2017; FAO and IFIF, 2010). Regardless of whether feed is produced commercially or on-farm feed, regulations must stipulate that equipment be suitable for manufacturing animal feed. Routine inspections are to be carried out and written maintenance and cleaning records kept. For example, the CFIA requires feed mills to determine carryover rates at least once every ten years to establish the benchmark for the facility. Additionally, carryover is checked after any installation, major repair or modification to any manufacturing equipment from the mixer to the end of the production line (CFIA, 2013a). The biggest challenge for regulators is finding ways to adequately carry out the inspection requirements for the large number of facilities, both on and off farm, involved in feed and ingredient manufacture and distribution.

Facilities and equipment to be used for mixing medicated feed must be routinely checked, in accordance with written procedures pre-established by the manufacturer for the products. All scales and metering devices used in the manufacture of feed must be appropriate for the range of weights or volumes to be measured and regularly tested for accuracy. All mixers used in the manufacture of feed must be appropriate for the range of weights or volumes mixed and be capable of manufacturing suitable homogeneous mixtures (VMD, 2019). The assessment of homogeneity should be considered as an integral part of the equipment requirements and GMPs of each establishment manufacturing feed additives, premixtures, compound feed or medicated feed. Mixing inhomogeneity is mainly a technical problem resulting from inadequate equipment used on farms (European Commission Directorate General for Health and Consumers, 2010).

Unwanted drug carryover can be avoided by using separate delivery systems for the feeds or effectively minimized by proper sequencing, flushing, and cleaning feed processing equipment. Proper sequencing and flushing protocols are very effective in preventing drug carryover. In cattle feedlots using mixing trucks, a single sequence reduced veterinary drug residues by 99 percent (Van Donkersgoed *et al.*, 2010). Studies with narasin and monensin in poultry feed demonstrated that even a 1 per cent flush size was effective in preventing carryover of these medicated feed additives (Martinez-Kawas, 2008). The use of an end-of line mixer for the production of medicated feed at the feed mill and the use of a separate silo for medicated feed and non-medicated feed are other ways to reduce cross-contamination of medicated feed (Filippitzi *et al.*, 2018).

In case of medicated feed production, GMPs (e.g. regular cleaning of equipment) must be followed at the feed mill, during transport and unloading as well as during storage and distribution at the farm. Although cleaning remains the most effective method of limiting carryover, there is reluctance to employ it widely in the feed industry because the thorough cleaning of the manufacturing equipment following every batch of medicated feed can only be accomplished by completely shutting down the facility. This is both impractical and not economically feasible. A complete manufacturing system cleanout is typically only done under high-risk situations such as handling a high potency form of a drug with high toxicity potential, when physical properties (e.g. adhesive strength, electrostatic properties) of drugs are such that sequencing and flushing are insufficient, when the manufacturing equipment is inaccessible, or when liquid ingredients (e.g. fat, molasses) are used in the diet (Martinez-Kawas, 2008).

The amount of segregation that may occur in feed and feed ingredients can be addressed by implementing GMPs. Monitoring the grain after grinding ensures the desired particle size and uniformity. Other feed ingredients may come in granular form and purchasing specifications can be placed on particle size. Production of medicated feed as pellets will reduce ingredient segregation, but pellet mills are uncommon for on-farm feed production due to the capital and operating costs. Another commonly used technique to reduce drug segregation is to add a liquid, such as molasses, fat, or water, to the feed formula. Liquids act to unite small and large particles into agglomerates, which maintain their homogeneity through the subsequent processing and handling. However, the added liquid may cause feed to adhere to equipment and bins, thereby increasing the risk of carryover (Harner *et al.*, 1996).

From a HACCP standpoint, monitoring and verification are used to check whether the control measures (at each process step) are being adhered to and are operating as intended. Most countries have well defined regulations establishing appropriate inspection and validation of good feed production. Validation is the process of demonstrating that the feed processing steps adequately control identified hazards to produce a safe feed product (CFIA, 2013b). Inspectors (governmental or third party) should verify that feed manufacturers' procedures are adequate, validated and documented. For example, how they flush, when they flush, how much and what material is being used to flush, and the disposition of the flush material (AAFCO, 2017).

## **CONCLUSIONS OF THE EXPERT MEETING**

### **Action levels**

Since carryover of veterinary drugs is unavoidable to some extent even if the Codex Code of Practice on Good Animal Feeding, GMP, and HACCP principles are followed, the Expert Meeting believes that an acceptable amount of drug could be established based on the residue tolerances (i.e., MRLs) in the subsequent food products from exposed animals. This works as long as the carryover drug has established MRLs in the non-target species exposed to the drug. For many veterinary drugs added to feed, MRLs for non-target species/products have not been established, so alternative methods of determining acceptable carryover levels are needed.

The Expert Meeting suggests that a suitable risk management option is to consider the establishment of action levels for veterinary drug residues in food. Such

action levels would establish a regulatory limit below which no further enforcement action is required. The establishment of these action levels should be based on a documented risk assessment that considers:

1. Drug carryover in feed or drug residues present in feed ingredients.
2. Identify action level in feed for non-target species.
3. Determine transfer factors from feed to food.
4. Determine action level for food products from non-target species.

The Expert Meeting participants agreed that the intended use of a veterinary drug added to the unintended use of the drug should not result in an exposure that exceeds HBGVs. It is expected that the action level will be set at levels significantly below MRLs set for an approved use. Based on the different circumstances of the source of drug exposure in food animals (approved drug use versus unintended carryover in feed), different principles might be applied to establish standards in these two scenarios. For example, the ALARA principle would be more appropriate for the latter as setting standards for unintended carryover situations is not a substitute for good feed manufacturing practices.

### **Code of Practice on Good Animal Feeding**

The Expert Meeting considered the question, “Are additional measures to those in the Codex Code of Practice on Good Animal Feeding available to minimize unavoidable and unintended carryover in feed?” The group consensus was that the current Codex Code of Practice on Good Animal Feeding does not contain sufficient practical guidance on all levels to adequately address the potential for veterinary drug residues in food as a result of carryover in feed. FAO collaborated with the IFIF to produce the manual *Good Practices for the Feed Industry - Implementing the Codex Alimentarius Code of Practice on Good Animal Feeding*. It provides expanded information on good feed production, but specific practical guidance for minimising veterinary drug carryover in the feed production industry (technical and organizational measures including suitable facilities and equipment, production planning and sequencing, line flushing and criteria and requirements for cross-contamination testing) are lacking. Specific recommendations from the Expert Meeting include:

1. Increase awareness and provide easily accessible information about possible implications for carryover from the use of authorised veterinary drugs.
2. Strengthen national capacities for implementation of the Codex Code of Practice on Good Animal Feeding and related measures for animal feed production.
3. Emphasize that when possible, dedicated and separate lines for manufacturing medicated feed should be considered. However, the experts recognize that there may be practical limitations related to construction and maintenance of separate lines in feed mills.
4. Direct prescribers and users of medicated feed need to consider the appropriate selection of authorised drugs (including active ingredient, formulation and galenic form) to achieve expected therapeutic outcome while considering carryover implications.

5. Emphasize monitoring and control of raw feed ingredients that have potential for transfer of veterinary drugs from feed to food (e.g. identification and selection of appropriate raw feed ingredient, avoidance of hazardous raw materials).
6. Emphasize reduction of the need to use medicated feed by the use of animal health promoting practices and ingredients (e.g. good hygiene and husbandry practices, genetic selection, animal welfare, feed constituents, feed safety and adequate animal nutrition, vaccination).
7. Include specific advice in the Code on HACCP-identified control points for drug carryover during transport from feed mill to farm.

While the Expert Meeting did not consider the following issues in detail, it was noted that implications for environmental sustainability, biosecurity provisions and animal health and welfare may need further consideration for inclusion in the Code. In addition, the Expert Meeting considers that the delivery of a veterinary drug through water or top dressing is not an appropriate measure to mitigate the presence of undesirable drug residues in food.

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## Appendix A

# Agenda of the meeting

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### TUESDAY 8 JANUARY 2019

09:00 – 09:30	<b>Opening of the Expert Consultation Meeting</b> <ul style="list-style-type: none"><li>• Welcome remarks</li><li>• Declaration of interests</li><li>• Approval of the agenda</li><li>• Selection of Chair, co-chair and rapporteur</li><li>• Meeting objectives</li></ul>	<i>Plenary FAO/WHO Secretariat</i>
09:30 – 10:30	Summary of stakeholder meeting discussion and conclusion Summary of information received and response to the call for data General comments on background paper and items/topics still to be addresses	<i>Trisha Downing and FAO/WHO Secretariat</i>
10:30 – 11:00	<i>Refreshment break</i>	
11:00 – 12:30	<b>Sources of unavoidable and/or unintentional veterinary drug exposure at feed mill and farm level</b>	<i>Plenary discussion/ Breakout groups</i>
12:30 – 14:00	<i>Lunch break</i>	
14:00 – 15:30	Discussion in breakout groups	<i>Breakout groups</i>
15:30 – 16:00	<i>Refreshment break</i>	
16:00 – 17:30	Report from breakout sessions (groups)/ discussion and preliminary conclusions	<i>Plenary discussion</i>

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### WEDNESDAY 9 JANUARY 2019

09:00 – 10:30	<b>Human health risks due to the presence of veterinary drug residues in food from unavoidable and unintended carryover in feed</b>	<i>Plenary discussion/ Breakout groups</i>
10:30 – 11:00	<i>Refreshment break</i>	
11:00 – 12:30	Discussions in breakout groups	<i>Breakout groups</i>

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*Carryover in feed and transfer from feed to food  
of unavoidable and unintended residues of approved veterinary drugs*

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12:30 – 14:00	<i>Lunch break</i>	
14:00 – 15:30	Report from breakout sessions (groups)/ discussion and preliminary conclusions	<i>Plenary discussion</i>
15:30 – 16:00	<i>Refreshment break</i>	
16:00 – 17:30	<b>Risk management strategies for carryover of veterinary drugs</b>	<i>Plenary discussion/ Breakout groups</i>

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**THURSDAY 10 JANUARY 2019**

09:00 – 10:30	Discussions in breakout groups	<i>Breakout groups</i>
10:30 – 11:00	Refreshment break	
11:00 – 12:30	Report from breakout sessions (groups)/ discussion and preliminary conclusions	<i>Plenary discussion</i>
12:30 – 14:00	Lunch break	
14:00 – 15:30	<b>Initial discussions on recommendations and final conclusions</b>	<i>Plenary</i>
15:30 – 16:00	Refreshment break	
16:00 – 17:30	<b>Finalize conclusion and recommendations</b> Agreement on next steps	<i>Plenary</i>
17:30	Close of Meeting	

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## Appendix B

# Case reports of veterinary drug carryover

### IONOPHORES IN EGGS

*David Johnson, Canadian Food Inspection Agency*

In Canada, feed is manufactured both on-farm and in commercial feed mills. It is estimated that medicated feed accounts for approximately 30 per cent of all complete feed produced. Small feed manufacturers, generally on-farm facilities, may be dedicated facilities producing feed for only a single species and using a small number of medicating ingredients (often dilute premixes). Large feed manufacturers, generally the largest on-farm operations and commercial mills, use a variety of medicating ingredients and concentrated premixes, to produce medicated feed for many livestock species (e.g. poultry, cattle, swine, etc.) and production classes (e.g. starter, grower, finisher, breeder, etc.). Large mills have many pieces of equipment that are cross-utilized for the production of a variety of medicated and non-medicated feed. This cross-utilization of equipment can lead to carryover residues of medications: cross-contamination between batches of feed.

Between 2004 and 2007, the Canadian Food Inspection Agency (CFIA) identified an increasing prevalence of detected residues of the ionophore drugs lasalocid, monensin, narasin, and salinomycin in domestic and imported shell eggs. These ionophores are not approved for use in laying hens. The detectable residues ranged from 0.3 to 94 ppb in approximately 10 per cent of all eggs tested. Analytical methods in CFIA and its contract labs, at the time, had limits of quantification (LOQs) for ionophore residues ranging from 0.2 to 0.5 ppb in eggs and 1 to 2 ppm in feed: 3 to 4 orders of magnitude less sensitive. It became clear that non-detectable residues of these ionophores in feed from carryover cross-contamination were resulting in detectable residues in eggs. As the use of these drugs was not approved for laying hens no maximum residue limit (MRL) had ever been set and therefore any detectable residue in eggs was considered to be an adulteration and a violation.

A review of the scientific literature and residue surveillance reports from other jurisdictions revealed that this issue was not unique to Canada and a risk assessment of the detected residues was undertaken by Health Canada. Health Canada concluded that the residues detected in domestic or imported eggs, conservatively considering an intake of 500 g of egg/day would result in exposure levels at fractions of the ADI, and therefore not pose a health risk. However, they recommended the following:

1. The CFIA should consider improving the methodology for detecting these ionophores in feed to minimize the differences in LOQ between feed and eggs in order to identify the source of contamination and take appropriate actions in case of any adulteration.
2. The CFIA ensure that there is no deliberate use of these unapproved products in breeding, replacement, or laying chickens and take appropri-

ate actions to ensure that cross-contamination is eliminated as much as possible at the feed mills to minimize carryover of the drugs between the batches of feed for different species.

### **Feed Analytical Methods – Response to Recommendation 1**

In response to Health Canada’s first recommendation, the CFIA laboratory responsible for feed drug residue analysis developed and validated a new liquid chromatography tandem mass spectrometry (LC-MS/MS) method for ionophore residues in feed capable of detecting concentrations as low as 10 ppb. Additional methods for other in-feed drug residues were also reviewed and more sensitive methods have since been developed for a number of analytes. The CFIA aims to develop feed drug residue methods with LOQs of 1-2 per cent of the lowest approved use rate in feed. These LOQs are intended for monitoring purposes to characterize cross-contamination in feed rather than for taking compliance action.

Recognizing that the reduced LOQs would result in detections of cross-contamination that may not represent an immediate risk to animal health or food safety the CFIA and Health Canada developed:

1. Risk-based feed maximum levels (MLs) considering unintentional exposure due to cross-contamination for non-target livestock species (i.e. those species where drug approvals and MRLs do not exist).
2. Risk-based food MLs for tissue, egg, and/or milk residues from non-target livestock species.

The magnitude of the food MLs for unintentional exposure from carryover cross-contamination represent a much smaller fraction of the ADI than would be considered for an MRL developed for an approved use of a drug. Unintended carryover MLs have been derived for monensin, lasalocid, salinomycin, narasin and nicarbazin (Table 1). Additional non-target MLs could be evaluated in the future on a case-by-case basis within the existing framework.

**Table 1:** Maximum Limits (MLs) for lasalocid, monensin, narasin, nicarbazin, and salinomycin in feed, eggs, and liver for non-target species

Drug	Feed ML (ppm)	Egg ML (ppm)	Liver ML (ppm)
Lasalocid	0.5 (layers) 1.0 (others)	0.03	0.01
Monensin	1.0	0.025	0.01
Narasin	1.0	0.01	0.005
Nicarbazin	2.0	0.15	0.05
Salinomycin	0.5 (horses) 0.9 (turkeys) 1.0 (others)	0.01	0.035

## Management of Cross Contamination – Response to Recommendation 2

To respond to the second recommendation, the CFIA developed the medication sequencing guide (CFIA, 2018b) for the production of medicated feed as a risk management tool. It was designed to help the feed industry manage the order of production of medicated feed and non-medicated feed to limit carryover residues to feed for species where low-level residues would not result in a food violation. Initially this meant sequencing to target possible carryover residues into feed for approved species and production classes of livestock with some additional considerations:

- Withdrawal times (i.e., not sequencing for finishing animals).
- Animal health concerns where cautions are indicated (e.g. ionophores and horses).
- Drug incompatibilities (e.g. tiamulin and ionophores)

When a valid production sequence is not possible, feed mills are expected to use a validated flushing or physical cleanout process to eliminate carryover. Flushing material could then be used to manufacture feed containing the same medicating ingredient.

Additional sequencing flexibility was requested by the Feed Industry as the volumes of flushing materials generated presented handling, storage, and disposal challenges. As such, the CFIA and Health Canada continued to assess the risk of additional sequencing options using data in the peer reviewed literature and information available from foreign drug approvals. The current sequencing guide includes several additional sequencing options that were a result of this process. Assessments have not been completed for all in-feed drugs; however, the risk assessment framework is available to address new data or issues on a case-by-case basis.

## NICARBAZIN IN EGGS

*James Deller, Australian Pesticides and Veterinary Medicines Authority*

In May 2016, the Australian Pesticides and Veterinary Medicines Authority (APVMA), the national regulator of pesticides and veterinary medicines in Australia, supported the establishment of an MRL for nicarbazin in eggs. The purpose of this MRL for eggs was to cover residues arising from low-level carryover of nicarbazin into non-medicated feed for laying poultry.

In Australia, products containing nicarbazin are only approved for use in broiler chickens and MRLs were established for chicken kidney, liver, muscle and skin/fat at 20, 35, 5 and 10 ppm. Products carry instructions that they are not to be used in birds that are, or may, produce eggs for human consumption and therefore an egg MRL was not established. Nicarbazin is administered to broiler chickens orally via medicated feed with a mix rate of up to 125 mg nicarbazin/kg of complete feed.

Residue monitoring identified low levels of nicarbazin residues in eggs. Trace back investigations which investigated the production of the eggs in which residues were observed confirmed that the egg producers were not intentionally treating their laying chickens with nicarbazin-medicated feed. The trace back investigations also confirmed that the feed mills for which the egg producers were sourcing their feed did produce nicarbazin medicated feed for broiler chicken producers. These mills were complying with the principles of good manufacturing practice and were employing sequencing practices to reduce the likelihood of nicarbazin occurring in un-medicated feed. The results of the trace back investigations pointed to unintended carryover

from medicated feed into un-medicated feed and the subsequent transfer into eggs of laying hens as the likely cause of the low-level residue detections in eggs.

The APVMA considered the results of the monitoring data and trace back investigations as well as available information relevant to the occurrence of nicarbazin residues in eggs following a literature search such as that published by the European Food Safety Authority. It was determined that an MRL of 0.3 mg/kg for nicarbazin in eggs was appropriate to cover the occurrence of nicarbazin residues in eggs that may result from carryover in feed following the implementation of good manufacturing practice in feed mills. Before finalising its MRL recommendation the APVMA conducted a dietary exposure estimate that confirmed that the dietary exposure associated with nicarbazin residues in eggs at the proposed MRL should not result in a consumer safety concern.

This nicarbazin in egg case was the first time the APVMA formally considered establishing MRLs to cover residues that may occur in food commodities as a result of carryover. The APVMA consulted with other relevant Australian National and State departments on the issue of carryover from medicated to un-medicated feed and the subsequent transfer to food and it was acknowledged that:

1. In some cases, residues of medicinal feed additives carryover over to untreated feed at levels high enough to cause residues in animal commodities regardless of practicable cleaning and sequencing procedures.
2. Establishment of MRLs in relevant commodities should be considered as an option in these cases, acknowledging:
  - a There should not be a public health or trade risk
  - b Such MRLs should not condone or support poor manufacturing practice
  - b Residue monitoring data and trace back information should be used wherever possible to assist in determining if these MRLs are required in practice, and to assist in determining the level of the MRL.
3. The establishment of MRLs should be seen as secondary to good manufacturing practice in managing such residues. Sequencing, cleaning and other best practice guidance should be available, and industry is best placed to lead development and maintenance of this information.

The primary outcome of the APVMA's assessment of the issue of carryover of nicarbazin from broiler feed (an approved use) to layer feed (not approved) was the establishment of a nicarbazin MRL for eggs at 0.3 ppm. The other outcome was the development of a framework for considering carryover issues of other veterinary drugs that are mixed in feed in Australia that involves investigations to confirm that poor manufacturing practice or off label use was not the cause of the issue, utilizes available monitoring data and other relevant literature to inform an appropriate MRL, and a dietary exposure estimate to confirm consumer safety is protected.

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14. Hazards associated with animal feed – Joint FAO/WHO expert meeting  
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Carryover of veterinary drugs in feed can occur during feed processing, handling, transportation, delivery or in feeding animals on-farm. The risk of unavoidable and unintentional veterinary drug residues from feed carryover and/or transfer from feed to food of animal origin is unacceptable when it causes adverse health effects in target and/or non-target animals and/or humans consuming food originating from these animals. If carryover is not properly managed, contaminated feed can directly harm species that are sensitive to the unintended veterinary drug they consume, and /or can result in residues in food of animal origin such as meat, milk and eggs that render them unsafe for human consumption. Even if residues are not a safety hazard, they can pose regulatory and global trade issue as countries/markets may enforce a “zero” tolerance for residues when appropriate maximum residue limits have not been established.

Upon request of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), FAO and WHO convened an Expert Meeting to review the causes of veterinary drug carryover in animal feed and the transfer from feed to food, as well as the known risks to human health and international trade, and suggest appropriate risk management strategies. This report shows the results of the expert discussions, conclusions and recommendations.

ISBN 978-92-5-131833-1



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CA6296EN/1/10.19