Revision of Council Directive 90/167/EEC – current and future legal situation regarding medicated feed in the European Union as compared to the United States of America and Canada

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LIST OF ABBREVIATIONS

AVM-GSL	authorised veterinary medicine – general sales list
CFIA	Canadian Food Inspection Agency
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CMIB	Compendium of Medicated Ingredient Brochures
DG SANCO	Directorate General for Health and Consumers (now DG SANTE – Directorate General for Health and Food Safety)
DIN	Drug Identification Number
EDR	Emergency Drug Release
EEC	European Economic Community
e.g.	for example (exempli gratia)
ESC	Experimental Studies Certificate
esp.	especially
EU	European Union
FCEC	Food Chain Evaluation Consortium
FDA	U.S. Food and Drug Administration
HACCP	Hazard Analysis and Critical Control Points
IND	Investigational New Drug
i.e.	that is (id est)
MFML	Medicated Feed Mill License
MIB	Medicating Ingredient Brochure
NFA-VPS	non-food animal – veterinarian, pharmacist, suitably qualified person
No	Number
PCP	Preventive Control Plan
PCU	population correction unit
POM-V	prescription-only medicine – veterinarian, pharmacist
POM-VPS	prescription-only medicine – veterinarian, pharmacist, suitably qualified person
SmPC	Summary of Product Characteristics
SQP	suitably qualified person
TSE	Transmissible spongiform encephalopathy
VCPR	Veterinarian-client-patient relationship
VFD	Veterinary Feed Directive
VMP(s)	Veterinary medicinal product(s)

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1. INTRODUCTION

The long-term trends in farm animal production verge towards a gradual decrease in the number of livestock farms in combination with a steady increase of the numbers of animals per farm in order to increase the profit by reducing the costs per animal[1]; this trend is visible in the European Union[1–3] as well as in the United States of America[4,5] and Canada[6,7]. The resulting husbandry conditions with large numbers of animals consequently lead to the necessity of treating many animals at a time in case of illnesses.

Therefore, the treatment option of single animal treatment via injection or oral dosing with e.g. tablets or capsules is often discarded due to the immense effort of such an individual medication. Thus, other ways of orally treating the whole herd or flock are used in the majority of cases[8]. One option is the so-called "top-dressing", where proprietary medicinal products are put on top of the concentrated feedingstuffs offered to the animals[9]. Another option is the use of medicated feed, where a pharmaceutical pre-mix is mixed into a concentrate feed and the ready-to-use concentrates are then offered to the animals to be treated[9,10].

The latter procedure has been regulated by the European Union (EU) in 1990 via Council Directive 90/167/EEC laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community[11]. The directive[11] is based on Article 43 of the Treaty establishing the European Economic Community[12]. It had to be implemented into national law; consequently, each member state found its own interpretation of the legal contents of the directive which lead to considerably differing legal situations in almost all EU member states[13]. As the technical and scientific knowledge in the area of medicated feed has increased significantly in the meantime[13] and the directive has never been substantially updated or amended until today, a report was commissioned by the Directorate General for Health and Consumers (DG SANCO – now DG SANTE – Directorate General for Health and Food Safety) to be carried out in 2009/2010. This report was to "evaluate the production and use of medicated feed in the EU, taking particular attention to the additional costs of manufacturing medicated feed compared with manufacturing compound feed and to the costs of using medicated feed for farmers"[14]. The results of the report were intended as a basis of decision-making for the European Commission on how to proceed further – i.e. whether to leave the current legislative framework unchanged, to revise the existing directive or to repeal the directive and replace it by a regulation which is directly legally binding in all member states at once.

The aim of this thesis is to compare the current legal situation regarding medicated feed in the European Union with the situation in North America (i.e. the United States of America and Canada) and to assess the future prospects of the European Union's legislation as compared to the current state.

2. LEGISLATIVE FRAMEWORK FOR MEDICATED FEED IN THE EUROPEAN UNION

2.1. BACKGROUND DATA

The Food Chain Evaluation Consortium (FCEC), which was assigned the task to compile this report[14], is composed of four companies and "is working under a framework contract with DG SANCO for the evaluation of policies related to the food chain"[15]. It consists (amongst others) of economists, political analysts, scientific and veterinary experts, thereby uniting "multi-disciplinary and cross-sectoral skills" from various member states of the EU and claims to have a "long track record of policy evaluation in the areas of agriculture, food, and feed, for the European Commission and national administrations in the EU"[15].

Some content of the FCEC's report[14] will be presented in the first part of this thesis, complemented by some new data gathered in the more recent years since the report was finished.

2.1.1. ANIMAL HUSBANDRY IN THE EUROPEAN UNION

2.1.1.1. LIVESTOCK, POULTRY AND AQUACULTURE

In 2014, all the 28 member states of the European Union together held 23.556.660 dairy cows with Germany housing the greatest number, followed by France and Italy[16]. The number of cattle amounted to 88.387.620 animals with France accounting for the largest number, followed by Germany and the United Kingdom[16]. The United Kingdom was the EU member state with the largest number of live sheep in 2014 (> 23 million), followed by Spain and Romania, the total number EU-wide summing up to 55.429.830 animals[16]. The EU pig herd counted 148.309.930 heads in 2014, 41.828.020 of which were piglets[16]. Germany, Spain, France, Poland and The Netherlands were the most important producers for fattening pigs, whereas Germany, Spain, Denmark, France and Poland were the major piglet producing countries[16].
In 2014, the animal output in the EU valued in basic prices (i.e. the price received by the producer, after deduction of all taxes on products but including all subsidies on products) amounted to approximately 170 billion Euros[16].

According to Eurostat (the statistical office of the European Union), the aquaculture production (i.e. fish, crustaceans, molluscs and other aquatic organisms cultivated in aquaculture – "fish-farming") amounted to more than 680.000 tons live weight in 2013 (the total amount probably being notably higher, since some countries treat the respective data as confidential)[16].

2.1.1.2. COMPANION ANIMALS

In 2012, the European Union's pet population (including dogs, cats, small mammals, ornamental birds, reptiles and ornamental fish) amounted to at least 204.947.400 animals[17]. In 2012, approximately 24% of all households owned at least one cat, 25% at least one dog, with approximately 72 million households owning at least one pet animal; the total European Union's dog population amounted to around 60.5 million pet dogs, the EU's cat population to 66.5 million animals (stray animals not included)[17].

2.1.2. PRODUCTION OF ANIMAL PRODUCTS AND PRODUCTION SYSTEMS

7.3 million tons of beef[18] as well as 22.1 million tons of pork[19] were produced in the EU in 2013 along with 0.7 million tons of sheep meat[20], and 141.2 million tons of cow's milk[21]. 13.2 million tons of poultry meat were generated in the EU in 2014 with Poland, France, the United Kingdom, Germany and France being the largest producers[22]. In 2012, 1.25 million tons of aquaculture products were brought forth in the EU[23].

2.1.3. DATA ON THE MARKET OF ANIMAL FEED AND VETERINARY MEDICINAL PRODUCTS

2.1.3.1. SALES OF COMPOUND FEED

The production of compound feed in the 28 EU-member states was estimated to be about 153.8 million tons in 2013, which means a slight decrease compared to the year before[24]; in 2014 the production decreased further to 153.4 million tons[25]. Farm animal feed accounted for approximately 141 million tons in 2014[26]. Poultry feed was the leading segment in EU's compound feed production, followed by pig feed[24]. Europe produced 3.2 million tons of aquatic feed in 2014[27].

According to the FEDIAF (European Pet Food Industry), pet food product sales had a volume of 8.5 million tons equalling a turnover of 13.8 billion Euros in 2012[17]. A private research company specialising in industry analytics states that markedly smaller scales of pet food sales were sold in 2012, with cat food sales amounting to 1.9 billion Euros in 2012, 1.23 billion of which were apportioned to wet food and 0.5 billion Euros allotted to dry food, the rest accounting for snacks[28]. According to this source, dog food sales amounted to 1.4 billion Euros, and other pet food accounted for 91 million Euros in 2012[28].

2.1.3.2. SALES OF VETERINARY ANTIMICROBIALS

Antimicrobials are by far the most important veterinary medicinal products (VMPs) used for the production of medicated feed in the European Union[14]. In many member states

approximately ¾ of all pre-mixes authorised for the preparation of medicated feed are antimicrobials (e.g. 75% of authorised pre-mixes in Bulgaria, 71% in Finland, 85% in Germany)[14]. In 2012, 8.064 tons of antimicrobials (weight of active substance) were sold in the EU/European Economic Area (EEA), 64 tons of which were tablets (mostly used in companion animals), thus representing 0.8% of total sales, whereas the rest was used in form of other pharmaceutical forms such as injectables[29]. Pre-mixes used for the production of medicated feed represented 35.5% of the sales of antimicrobials' active substances in 2012 in total[29]. The share of pre-mixes in the overall sales varied considerably from country to country, though, with Germany and Luxemburg having used practically no pre-mixes at all whereas, on the other hand, in Cyprus almost 80% of overall antimicrobially active substance sales were represented by pre-mixes, followed by Spain, Hungary, the United Kingdom and Portugal with around 65% of total sales being pre-mixes[29].

Tetracyclines represented 37% of antimicrobial agents sold for food-producing animals in the EU/EEA in 2012, followed by penicillins with 22% and Sulphonamides with 10%[29]. The type of penicillins used differed between countries – the Nordic countries used mainly beta-lactamase-sensitive penicillins, whereas in the other countries the majority of penicillins sold were penicillins with extended spectrum[29]. Critically important antimicrobials according to the World Health Organization's definition[30], such as 3rd and 4th generation cephalosporins, fluoroquinolones and macrolides, accounted for 0.2%, 1.7% and 8%, respectively, of the total sales[29]. 45.7% of all tetracyclines sold were used for pre-mixes, 17.2% of the penicillins and 35.6% of the sulphonamides; as much as 36.9% of the macrolides sold were used for pre-mixes as well, whereas neither cephalosporins nor fluoroquinolones were used for preparing medicated feed in the EU/EEA in 2012[29].

In relation to the food-producing animals' population (expressed as "population correction units (PCU)", i.e. the "animal units" (number of animals) kept in a certain country related to the animals' body weight, since different species are taken into account) there were large differences in antimicrobial use between the member states: Cyprus, for example, used as much as 396.5 mg/PCU, followed by Italy with 341.0 mg/PCU and Hungary, Spain and Germany with 245.5, 242.0 and 204.8 mg/PCU, respectively. The lowest amount sold per PCU were found in Scandinavia with Norway (3.8 mg), Iceland (5.9 mg), Sweden (13.5 mg) and Finland (23.8 mg) representing the lower end of the sales statistics per PCU[29]. 85.5% of the total sales of product presentations used for group treatment (i.e. pre-mixes, oral powders, oral solutions) contained one antimicrobially active ingredient, 14.2% contained two and 0.3% three active ingredients[29]. The differences were attributed to differences in the animal population (e.g. more pigs than cattle etc.) as well as differing treatment regimens depending on the antimicrobial agent or formulation used[29]. In addition to this, some countries focus on disease prevention by management, vaccines or implementation of responsible-use campaigns, thereby reducing antimicrobial usage[29].

The sales patterns of antimicrobially active substances sold in tablet form, which are usually used in companion animals, varied considerably between the EU/EEA countries in 2012;

35% were penicillins, 27% 1st and 2nd generation cephalosporins, 13% sulphonamides and 7% macrolides[29].

2.1.4. PRODUCTION AND USE OF MEDICATED FEED IN THE EUROPEAN UNION

In general, it can be said that only very small numbers of medicated pre-mixes are newly authorised per year in the EU member states and they usually concern generic products with old substances as active ingredient[14]. The total number of medicated pre-mixes authorised differs considerably between countries with France having a number of authorisations in 2008/2009 as high as 312 authorised pre-mixes, whereas other countries such as Finland, Luxembourg, Slovenia or Sweden show numbers as low as 11 – 14 authorised pre-mixes at the same point in time[14].

Production of medicated feed varies substantially between EU member states. In 2008 Spain produced the highest amounts with 2 to 3 million tons, Italy's production amounted to 1.3 million tons and France's to 0.8 to 1 million tons[14]. Considerable amounts were also produced in Belgium (300.000 tons)[14], though production there decreased to approximately 215.000 tons until 2013[31]. Other EU countries such as Denmark or Germany are only of minor importance with production figures in 2008 of 12.000 tons, respectively, and in some member states such as Slovenia, medicated feed is hardly used at all[14]. Still, those numbers have to be interpreted with caution since official statistics on production of medicated feed are rare and in some EU member states are based on the estimates of only a few large manufacturers[14]. Italy appears to be the country where the relevance of medicated feed is highest since it reached a market share (i.e. relation of produced amounts of medicated feed to compound feed production) of around 9% in 2008, whereas other countries with larger production figures only have market shares of 3 – 7% for medicated feed; in Denmark or Germany, where production of medicated feed is of minor importance and "top dressing" or incorporation of ready-to-use VMPs in feed or the drinking water is a major way of administering oral antimicrobials or other drugs, the market shares are very low with 0.2 and 0.1%, respectively[14].

The report[14] revealed rather large differences in the additional costs of producing medicated feed in comparison to compound feed depending on the varying national requirements. If overall production levels of medicated feeds are low and therefore preclude the realisation of economies of scale and especially if national legislative frameworks require high investments in special technology such as end-of-line mixers in Germany, high additional production costs for medicated feed are the result[14]. Case studies carried out in Denmark, France, Germany and the United Kingdom by the FCEC revealed a range of additional production costs as broad as plus 0.4% in France and up to plus 25% in Germany[14].

According to a survey carried out by the FCEC[14] amongst stakeholder organisations such as national feed manufacturers' associations or farmers' associations, medicated feed is used most commonly in intensive livestock production. Nevertheless, it was emphasised by

some stakeholders that medicated feed is practically the only way to treat animals such as e.g. iberic pigs in extensive production systems and that the major factors influencing the use of medicated feed are not the type of production systems, but species, age and group size of animals[14]. Also, according to stakeholders, pigs are the species for which the use of medicated feed is considered to be most common, followed by poultry and rabbits[14]. On the other hand, feed for animals reared under extensive conditions such as game is medicated to an extent of up to 90%, at least in Scotland, according to the National Farmers Union Scotland[14].

Other alternatives to medicated feed for oral administration of VMPs to livestock animals are represented by mixing ready-to-use veterinary medicines into the animals' drinking water or using ready-to-use veterinary medicines either for "top dressing" on the feed or mixing them into feed manually by the farmer[14]. Those alternatives are not regulated by Directive 90/167/EEC[11]. Their relevance of use as compared to the use of medicated feed is only known to a limited extent due to the lack of data on that issue[14]. In Germany, for instance, probably due to the very limited relevancy of medicated feed already mentioned before, the German Federal Ministry of Food and Agriculture issued a guidance note regarding the oral administration of veterinary medicines in the livestock sector through feed or drinking water[10]. This guidance note[10] is intended to facilitate correct administration of oral medications to animals and imparts information on selection, dosage and dispensing of veterinary medicines along with guidance on administration, storage, prevention of cross-contamination and other aspects. The main focus is on ready-to-use VMPs, since the responsibility for the correct mixing and dosage lies with the veterinarian or animal owner[10]. Therefore, the animal owners should have a risk management plan in place which ought to be developed individually for their livestock farm in cooperation with the supervising veterinarian[10]. Overall, the market share of medicated feed used for the administration of oral antimicrobials appears to be decreasing in the EU compared to other administration routes[9,14].

2.2. CURRENT LEGAL SITUATION IN THE EUROPEAN UNION

2.2.1. DEFINITIONS

2.2.1.1. VETERINARY MEDICINAL PRODUCT

In accordance with Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products[32] a "veterinary medicinal product" (VMP) is "(a) any substance or combination of substances presented as having properties for treating or preventing disease in animals; or (b) any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis".

2.2.1.2. MEDICATED PRE-MIX AND MEDICATED FEED

Directive 90/167/EEC[11] defines "authorized medicated pre-mix" as "any pre-mix for the manufacture of medicated feedingstuffs as defined in Article 1(2) of Directive 81/851/EEC[33] which has been granted an authorization in accordance with Article 4 of that Directive". Since Directive 81/851/EEC[33] has been repealed and replaced by Directive 2001/82/EC[32], the definitions of this successive directive apply: pursuant to Directive 2001/82/EC[32], "medicated feedingstuffs" is defined as "any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing, because of its curative or preventive properties or other properties as a medicinal product covered by point 2" (i.e. a veterinary medicinal product); a "pre-mix for medicated feedingstuffs" is defined in the same directive[32] as "any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs".

2.2.2. MARKETING AUTHORISATION FOR MEDICATED PRE-MIXES

The authorisation of medicated pre-mixes is regulated mainly in Directive 2001/82/EC[32]. Pursuant to Article 3(1) of Directive 2001/82/EC[32], medicated feedingstuffs may only be prepared from pre-mixes authorised under this directive, i.e. the national, the decentralised or the mutual recognition procedure. This is slightly deceptive since the authorisation of medicated pre-mixes is not completely restricted to those procedures, but there are (few) pre-mixes authorised under the centralised procedure as well[14]. Pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[34], VMPs are only eligible for authorisation under the centralised marketing authorisation procedure, if they represent a significant therapeutic, scientific or technical innovation or if their authorisation would be in the interest of animal health. The centralised procedure is mandatory for VMPs intended as growth or yield enhancers[35]. Since, according to an interview of the FCEC with a representative of the European Medicines Agency, the majority of medicated pre-mixes comprises older active substances, there are only a few medicated pre-mixes authorised via the centralised procedure[14].

The subsequent preparation of the medicated feedingstuff itself is regulated by Council Directive 90/167/EEC[11]. Pursuant to Article 3 of Directive 90/167/EEC[11], the EU member states have to prescribe that medicated feed may be manufactured from authorised medicated pre-mixes. By way of derogation they may also authorise intermediate products which are prepared from such an authorised medicated pre-mix and one or more feedingstuffs and intended for the manufacture of ready-to-use medicated feeds[11]. Still, those intermediate products may only be produced in authorised establishments[11].

2.2.3. GOOD MANUFACTURING PRACTICE

In almost every EU member state there are rules for Good Manufacturing Practice (GMP) in force, which are stipulated by Article 4 of Directive 90/167/EEC[11]. Only Estonia, Lithuania, Luxembourg, Latvia and Sweden are lacking mandatory rules, according to their competent authorities, as is stated in the FCEC report[14] and shown in Table 1.

Table 1: Rules of Good Manufacturing Practices in the different EU member states (Source: FCEC[14])

	Rules of good manufacturing practice	Details
AT	✓	Rules in force include the *Fütterungsarzneimittelbetriebsordnung 2006, BGBl II Nr. 394/2006* and others (see Annex 7) [(a)]
BE	✓	The concrete application of the rules is mandatory by law. [(b)]
BG	✓	Medicated feed manufacturers are required to apply the GMP and HACCP of the Bulgarian feed manufacturers association. [(a)]
CY	✓	The concrete application of the rules is not mandatory by law. [(a)]
CZ	✓	The concrete application of the rules is mandatory by law. [(a)]
DE	✓	The concrete application of the rules is mandatory by law. [(a)]
DK	✓	In Denmark the manufacturing process must conform to the rules of good manufacturing practice of the EU GMP on the rules governing medicinal products in EU; however, some exceptions from these rules are allowed. [(a)]
EE		No rules of good manufacturing practice exist in Estonia. [(a)]
ES	✓	A new Royal Decree amending Royal Decree 109/1995 which introduces hygiene rules in compliance with Council Regulation 183/2005 is officially available since September 2009 and it includes an approach to rules of good manufacturing practice and specific requirements for Intermediate (feed) products among other considerations. [(a)]
FI	✓	The concrete application of the rules is not mandatory by law. [(a)]
FR	✓	The concrete application of the rules is mandatory by law. [(a)]
GR	✓	Commission Directive 91/412/EEC has been implemented in Greece by the 94/313314/GMD Greek Ministerial Decision. Circular 98/310584 refines particular matters. [(a)]
HU	✓	The concrete application of the rules is mandatory by law. [(a)]
IE	✓	The Regulations in Ireland transposing EU Directive 90/167 are entitled 'European Communities (Animal Remedies and Medicated Feedingstuffs) Regulations 1994'. Regulation 6(1)(e) of the aforementioned regulations gives effect to Article 4(1d) of the Directive. [(a)]
IT	✓	*Circolare 23 gennaio 1996 n.1* and the document "Production of medicated feed, measures for reducing cross- contaminations" provide indications about the way to put into practice the requirements of national and Community law. Most requirements of these guidelines are mandatory by law. [(a)]
LT		There are no approved rules for good manufacturing practise for medicated feed in Lithuania. [(a)]
LU		No rules of good manufacturing practice exist in Luxembourg. [(a)]
LV		There are no rules for good manufacturing practice in Latvia. [(a)]
NL	✓	Rules are established in the GMP Standards by the Product Board Animal Feed. The concrete application of the rules is not mandatory by law. [(a)]
NO	✓	The concrete application of the rules is mandatory by law. [(a)]
PL	✓	The principles of good practice for medicated feed (production and distribution) are included in national regulations. [(a)]
PO	✓	The concrete application of the rules is not mandatory by law. [(a)]
RO	✓	The concrete application of the rules is not mandatory by law. [(a)]
SE		No specific rules for good manufacturing practice are established in Sweden. [(a)]
SI	✓	The concrete application of the rules is not mandatory by law. [(a)]
SK	✓	The concrete application of the rules is mandatory by law. [(a)]
UK	✓	There are no nationally approved Industry Codes in the UK. However manufacturers are required to comply with the Veterinary Medicines Regulations. [(a)]

Information from either (a) the member state's competent authority or (b) a National Feed Manufacturers Association

According to the same source, some other member states such as Cyprus, Finland, The Netherlands, Portugal, Romania, and Slovenia, do not enforce the concrete application of the rules in force. Spain, one of the major producers of medicated feed in the European Union, did not have GMP rules until September 2009[14]. The contents of the GMP rules vary between the member states: in France, for example, the manufacturers have to fulfil the requirements for pharmaceutical establishments, whereas in Denmark the GMP rules for medicated feed manufacturing practice allow some exceptions to the GMP rules governing medicinal products in the EU[14].

In Germany the pharmaceutical law also applies for medicated feed production with for instance the requirement to have the end-of-line mixing technology authorised in order to be allowed to produce medicated feed[14].

2.2.4. CONTENTS OF COUNCIL DIRECTIVE 90/167/EEC

As mentioned before, medicated feed is regulated currently under Council Directive 90/167/EEC[11], which has come into force on the 6th of April 1990 and has not been amended ever since. The directive[11] set the outline that had to be implemented into national law by the EU member states by 1st of October 1991.

2.2.4.1. APPROVAL OF MANUFACTURING FACILITIES

Article 4(1) of Directive 90/167/EEC[11] lays down that the EU member states have to ensure that medicated feeds are only produced by manufacturers whose premises have been approved previously, with suitable technical equipment, adequate storage and inspection facilities, staff who are sufficiently knowledgeable and qualified regarding mixing technology. Producers have to make sure that only (combinations of) feedingstuffs are used which comply with Community regulations and result in a homogenous and stable mix with the authorised medicated pre-mix[11].

2.2.4.2. RESPONSIBILITIES OF MEDICATED FEED MANUFACTURERS

The manufacturer is to be held responsible for using the pre-mix only under the authorised conditions without any undesired interactions between the VMP used, any additives and the feedingstuffs, for not using feedingstuffs containing the same antibiotic or feedingstuff used in the medicated pre-mix and for the medicated feed keeping its stability over the stipulated period[11]. Furthermore, it has to be ensured that the entire manufacturing process complies with the rules of good manufacturing practice the member state has in place[11]. Premises, staff and equipment have to conform to the manufacturing hygiene rules and principles of the respective member state[11]. The medicated feeds have to be checked on a regular basis, especially by laboratory analyses, by the manufacturer (who is supervised and controlled regularly by the appropriate official department) particularly regarding their

homogeneity, stability and storability[11]. With regard to record keeping, the manufacturers are to keep daily records regarding the types and quantities of medicated pre-mixes and feedingstuffs used and medicated feeds manufactured, held or dispatched, along with the names and addresses of the breeders or holders of animals, and, where appropriate, of the authorised distributors and the prescribing veterinarian[11]. The records must be kept for at least three years after the last entry and must be available for checking by the competent authorities at all times[11]. Storage of pre-mixes and medicated feeds shall occur in suitable separate and secured rooms or hermetic containers specifically designed for the storage of such products[11]. Member states are to prescribe that packaging and sealing of medicated feed occur in a way that, when opened, the closure or seal is damaged; road tankers or similar containers have to be cleaned thoroughly before re-use to avoid subsequent undesirable interaction or contamination[11]. Pursuant to Article 6 of Directive 90/167/EEC[11], labelling of medicated feed has to comply with Regulation (EC) No 767/2009 of the European Parliament and of the Council of 13 July 2009 on the placing on the market and use of feed[36]; additionally, the medicated feed has to be marked clearly as "medicated feedingstuffs"[11]. In case of shipping the medicated feed in road tankers or similar containers the labelling mentioned above has to occur in accompanying documents[11]. The EU member states are to ensure that medicated feeds are only supplied to animal owners following the presentation of a prescription of a registered veterinarian which is made out on a form containing the heading set out in Annex A of Directive 90/167/EEC[11]. Pursuant to Article 9 EU member states have to ensure that medicated feed is only issued directly to the stock farmer or animal holder by either the manufacturer or a specifically approved distributor[11]. The amounts delivered may not exceed the quantity prescribed by the veterinarian and may additionally not exceed one month's requirements[11]. In special cases EU member states may authorise distributors who are specially approved for that purpose to issue, based on a veterinary prescription, small quantities of prepacked and ready-to-use medicated feed[11]. The distributors must comply with the requirements set out above for the manufacturer regarding record keeping, storage, transport and issue of the products concerned and they are subject to special controls by the competent veterinary authority[11]. The prepacked medicated feed has to have in particular the indication of the withdrawal period on the packaging or the containers, along with instructions for use[11].

2.2.4.3. VETERINARY PRESCRIPTION

The original form of the veterinary prescription has to stay with the manufacturer, whereas the member states can specify the number of copies, the persons who are to receive them and the record keeping period of the original and the respective copies[11]. Medicated feed may only be used for one treatment per prescription with the prescription being valid for a period of time set out by the member state's competent authority, but not exceeding a three months period[11]. The veterinary prescription may only be issued for animals under the direct care of the veterinarian, who must be satisfied that the treatment is medically indicated, that there is neither incompatibility with previous treatment(s) nor any contra-indication or interactions where several pre-mixes are used nor that other feedingstuffs used

currently to feed the animals contain the same antibiotic or coccidiostat[11]. Only medicated feed in quantities necessary for the purpose of the treatment may be prescribed and the daily dose of medicinal product is contained in a quantity of feedingstuff which is corresponding to at least half the daily feed ration of the animals treated or, in the case of ruminants, to at least half the daily requirement of non-mineral supplementary feed[11]. Veterinarians shall be authorised by the member states to prescribe under their own responsibility medicated feeds containing more than one authorised medicated pre-mix on condition that no specific medicated pre-mix for this purpose exists that is authorised for the disease to be treated or the species concerned[11].

Annex A[11] contains a sample form for veterinary prescriptions. The required information comprises name and address of the manufacturer or supplier of the medicated feed and of the stock farmer or the holder of the animals; furthermore, identification and number of the animals to be treated as well as the diagnosed disease and the designation of the authorised medicated pre-mixes[11]. Along with the quantity of medicated feed special instructions for the stock farmer like the percentage of medicated feed in the daily ration, the frequency and duration of treatment as well as the withdrawal time before slaughtering or the waiting period before placing products from treated animals on the market have to be indicated[11].

2.2.4.4. ON-FARM MIXING

Per derogation laid down in Article 4(2) of Directive 90/167/EEC[11] it is possible for member states to authorise farms to manufacture medicated feed using authorised medicated pre-mixes as long as the requirements of Article 4(1) are complied with. The FCEC gathered information from the competent authorities of the EU member states regarding the use of this derogation in their country; on-farm production of medicated feed is prohibited in all member states other than Austria, Cyprus, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Portugal, Slovenia, Spain, Sweden and the United Kingdom[14]. The countries making use of the derogation have authorised approximately 5.700 on-farm producers for medicated feed production; some of those countries such as Austria and Cyprus do only have authorised on-farm producers and no commercial feed mills authorised for manufacturing medicated feed[14]. The rules for on-farm production of medicated feed are similar to those for commercial feed mills manufacturing medicated feed, but in some countries additional requirements may apply. For instance, in the United Kingdom, the Veterinary Medicines Regulations[37] which implement, amongst other directives, also Directive 90/167/EEC[11] into national law, set out in Schedule 5 all requirements relating to medicated feedingstuffs in the United Kingdom. Therefore, manufacturers of medicated feed have to comply as well with the conditions set out in Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene[38], especially its Annex II, as to operate in accord with Schedule 5 of the United Kingdom's Veterinary Medicines Regulations[37]. A detailed guidance for manufacturers and suppliers of medicated feed facilitates the overview over the rules that have to be adhered to when preparing medicated feed, e.g. on-farm[39].

2.2.4.5. RESPONSIBILITIES OF THE LIVESTOCK FARMER

The livestock farmer or holder of the animals has to ensure that treated food-producing animals are not slaughtered for human consumption before the end of the withdrawal period; products from those animals from before the end of the withdrawal period have to be disposed of in way to prevent them from being used for human consumption[11].

2.2.4.6. INSPECTIONS

Article 13 of Directive 90/167/EEC[11] sets out that EU member states have their competent authorities make sampling checks at all stages of the production and marketing of the products referred to by this Directive[11] to ensure compliance with the provisions, especially focusing on farms and slaughterhouses to ensure compliance with the conditions of use and withdrawal periods.

2.2.4.7. INTRA-UNION TRADE AND IMPORT FROM AND EXPORT TO THIRD COUNTRIES

Furthermore, the directive[11] makes provisions regarding the free trade between EU member states by ordering that there may not be any prohibitions, limitations or obstacles regarding the trade of medicated feed produced in accordance with Directive 90/167/EEC[11]. The directive[11] also stipulates that safeguard measures and rules and requirements concerning veterinary controls set out by Council Directive 89/662/EEC[40] shall be applied to trade within the community with authorised medicated pre-mixes and medicated feeds.

Imports of medicated feeds shall be subjected by the EU member states to measures at least equivalent to those laid down in Directive 90/167/EEC[11].

There are no specific conditions laid down in Directive 90/167/EEC[11] for the exportation of medicated feed to third countries, i.e. to countries not part of the EU or EEA; therefore, the export conditions set out for the respective country apply. More detailed information on the requirements for the export to an individual country can be found on the European Commission's website[41], where market access prerequisites are specified.

2.3. IMPLEMENTATION INTO NATIONAL LAW IN SELECTED EU MEMBER STATES

As opposed to EU regulations, which are used for unification of law, EU directives are used for harmonisation of legislation[42], i.e. for bringing different national laws in line with each other. They set out results that all EU member states must achieve, whereby the national authorities have the choice of form and method to attain this result[43]. Consequently, there can be more or less big differences in the implementation of a directive into national law, although the European Commission examines the national transposition measures to ensure

that they attain the results required by the directive[42]. In order to show the variations between national implementation in the different EU member states, two examples were chosen for illustration with Germany representing the probably strictest interpretation of Directive 90/167/EEC[11] and the United Kingdom's national implementation of that directive[11] belonging to the most lenient interpretations within the EU[9].

2.3.1. GERMANY

Council Directive 90/167/EEC[11] was transposed into German law by implementing the contents in the Medicinal Products Act ("Arzneimittelgesetz")[44] and its subsequent ordinances such as the Medicinal Products and Active Substance Production Ordinance[45]. Hence, in German legislation medicated feed is treated under the same regulations as medicinal products.

2.3.1.1. DEFINITIONS

The definitions of medicated feed and medicated pre-mixes are found in the Medicinal Products Act[44] in Section 4(10) and (11), stating that "medicated feeding stuffs are medicinal products in the form of ready feeding stuffs, manufactured from medicated pre-mixes and mixed feed and intended to be placed on the market for administration to animals". Medicated pre-mixes are "medicinal products intended exclusively for use in the manufacture of medicated feeding stuffs. They shall be regarded as finished medicinal products"[44].

2.3.1.2. MARKETING AUTHORISATION FOR MEDICATED FEED

Medicated pre-mixes are required to have a marketing authorisation in accordance with either the Medicinal Products Act[44] (national marketing authorisation), Directive 2001/82/EC[32] (decentralised authorisation procedure or mutual recognition procedure) or Regulation (EC) No 726/2004[34] (centralised procedure) in order to be produced and sold. Medicated feeds do not need to have a marketing authorisation of their own as long as they are manufactured in accord with their designated purpose from medicated pre-mixes for which a marketing authorisation has been issued[44].

Pursuant to Section 23 of the Medicinal Products Act[44], marketing authorisation documents on medicated pre-mixes intended for the use in food-producing animals are required to comprise some additional information compared to other VMPs: the particulars of the mixed feed intended to be used as carrier along with proof of the homogenous and stable distribution of the active substance in the medicated feed and information on the manufacturing methods required to achieve this are to be given[44]. Furthermore, details on the shelf-life of the medicated feeds and on reliable and routinely feasible quantitative and qualitative analysis methods are required[44].

2.3.1.3. APPROVAL OF MANUFACTURING FACILITIES

Pursuant to Section 13 of the Medicinal Products Act[44], each manufacturer must be authorised in order to be allowed to produce medicated pre-mixes or medicated feed. Before an authorisation is issued, an inspection by the competent authority has to take place[44], the requirements for the inspectors of companies manufacturing medicated feed being laid down in the "Procedural instruction – qualification of GMP inspectors"[46]. The information required for the authorisation application is shown in Table 2.

Table 2: Information required for the application for obtaining a medicated feed manufacturing authorisation in Germany pursuant to the Medicinal Products Act[44], the Medicinal Products and Active Substance Production Ordinance[45] and the Instruction leaflet for application for a manufacturing authorisation for medicated feed[47]

Information required	**Legal basis for the respective requirements**
Name, address, trade register excerpt and business registration of company (and production site, if applicable – e.g. mobile mixers are considered a production site[48])	Section 13(1) Medicinal Products Act[44] and Section 3.2.3.2 Procedural instruction – manufacturing authorisation[48]
Name, address, phone number of o Qualified person o Person responsible for supervising the technical side of the manufacturing procedure o Graduated plan officer o Information officer	Section 14(1) No 1 Medicinal Product Act[44] Section 14(1) No 5a Medicinal Product Act[44] Section 63a Medicinal Product Act[44] Section 74a Medicinal Product Act[44] Required qualifications specified in Medicinal Products Act[44] and Procedural instruction – audit of qualification of staff[49]
Detailed map of premises used for manufacturing, analysis and storage of medicated feed and pre-mixes and information on flow of material and staff	Section 14(1) No 6 Medicinal Product Act[44] and Section 5 Medicinal Product and Active Substance Production Ordinance[45]
Information on suitability of facilities, i.e. o on mixing accuracy of the machines o on critical control points in the manufacturing process for validation of operational steps and testing o Storage rooms for pre-mixes and retention samples	Section 14(1) No 6 and 6a Medicinal Product Act[44] and Sections 5 and 30(2), (3) and (7) Medicinal Product and Active Substance Production Ordinance[45]

Information required	Legal basis for the respective requirements
Information on the type of production of medicated feed (i.e. production with stockpiling or on demand based on singular formulae)	Section 56(1) Medicinal Product Act[44]
If applicable: details on external analysis facilities (especially for homogeneity testing)	Section 14(4) No 3 Medicinal Product Act[44] and Section 9 Medicinal Product and Active Substance Production Ordinance[45]
If applicable: List of service contractors (shipping companies) and the respective contracts	Section 3.3.2.3.3 Procedural instruction – manufacturing authorisation[48]
Quality assurance system	Section 3 Medicinal Product and Active Substance Production Ordinance[45] an Chapter 1 of Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use[50]
Duties of the responsible staff	Sections 4 and 12 Medicinal Product and Active Substance Production Ordinance[45]
Labelling	Sections 10, 11, 15 and 56(4) Medicinal Products Act[44] and Section 30(5) Medicinal Product and Active Substance Production Ordinance[45]
Batch release by the qualified person pursuant to Section 4 Medicinal Products Act[44]	Section 19 Medicinal Products Act[44] and Section 16 Medicinal Product and Active Substance Production Ordinance[45]
Documentation of o Manufacturing directions o Inspection directions and protocols o Cleansing directions o Validation procedures	Section 3.4.3 Procedural instruction – GMP inspections[51]

2.3.1.4. RESPONSIBILITIES OF MEDICATED FEED MANUFACTURERS

Section 43 of the Medicinal Products Act[44] sets out that medicated feeds are exempt from the rule that veterinary medicinal products which are not released for trade outside from pharmacies may solely be dispensed by veterinarians or pharmacists. Pursuant to Section 56 (1)[44], medicated feed may only be dispensed from the manufacturer (distributors are not

mentioned) directly to the animal holder, and only if the medicated feed is prescribed by a veterinarian. It is prohibited to repeatedly dispense on the same prescription[44].

The percentage of the feed requirement the medicated feed is intended to cover has to be made clearly visible on the label along with the word "Fütterungsarzneimittel" (medicated feed)[44]. The minimisation of carry-over has to be ensured by using techniques in accord with the current state of science, therefore rendering e.g. an end-of-line mixing technology mandatory[48]. Cleaning procedures have to ensure that not more than 0.1% of the product produced before is carried over into the following batch of medicated feed[47]. Testing for homogeneity has to occur on a sample basis; in contrast to Directive 90/167/EEC[11] a representative sampling technique and tolerance ranges are specified[47].

2.3.1.5. VETERINARY PRESCRIPTION

A veterinarian may only prescribe medicated feeds, if they are intended for animals under their direct care and for the animal species and therapeutic indications specified in the package leaflets of the medicated pre-mixes[44]. Their use in accordance with the therapeutic indications and quantity prescribed must be justified by the current veterinary standards to achieve the treatment objective and the amount prescribed for food-producing animals is intended for a maximum of 31 days after dispensing unless an antimicrobial effective substance is contained, which reduces the time after dispensing to a maximum of seven days, unless the authorisation of the pre-mix provides for a longer period of treatment[44]. Since this differentiation is made for food-producing animals it implicates that producing medicated feed for non-food-producing animals such as pets is at least theoretically possible in Germany, though it is not stated explicitly. The prescription for medicated feed must be made on a form complying with the sample form set out in Annex 1 (for medicated feed produced in Germany) and 1a (for medicated feed produced in a member state of the EU or EEC) of the Veterinary Pharmacy Ordinance[52] and comprise the original and two carbon copies.

If the therapy of an animal or herd cannot be achieved by a medicated feed authorised for the species and therapeutic indication, a veterinarian may, pursuant to Section 56a (2)[44], prescribe a medicated feed in accordance with the "treatment cascade" laid down in that Section. The stipulation is that this does not result in danger for the health of humans or animals and that there are no other special provisions laid down by the Commission on Veterinary Medicinal Product Use set up by the Federal Ministry of Food and Agriculture which are prohibiting the use of the active substance concerned in animals other than indicated in the authorisation of the medicated pre-mix[44].

Only medicated pre-mixes which are either authorised or exempt from authorisation may be used for manufacturing medicated feed[44]. Upon prescription by a veterinarian up to three authorised medicated pre-mixes may be incorporated into one medicated feed provided no authorised medicated pre-mix for the therapeutic indication and animal species in question is available, the resulting mixture ensures a homogenous and stable distribution of the

active substances in the final product and at maximum two of the pre-mixes contain an antimicrobially effective substance or only one of the pre-mixes contains several such substances[44]. The compound feed used as a carrier for the medicated feed has to comply with the feeds legislation as well before as after the mixing procedure and it may not contain any antibiotic or coccidiostatic feed additive[44].

2.3.1.6. ON-FARM MIXING

Medicated pre-mixes may not be prescribed to an animal holder, thereby prohibiting on-farm mixing of medicated feed[44].

2.3.1.7. RESPONSIBILITIES OF THE LIVESTOCK FARMER

Animal holders keeping dairy cows, cattle or calves, pigs, or poultry have to inform the competent authority every six months about the use of medicinal products (which also comprises the use of medicated feed) containing antimicrobially effective substances[44]. The livestock farmer receives a copy of the veterinary prescription for the medicated feed from the medicated feed manufacturer together with the medicated feed[52,53]; pursuant to Article 1 of the "Tierhalter-Arzneimittelanwendungs- und Nachweisverordnung"[53], which sets out the obligations of the animal keeper to produce proof on the usage of medicinal products in their animals, the copy has to be retained for five years and must be available in case of an inspection by the competent authority.

2.3.1.8. INSPECTIONS

Facilities producing medicated feed are subject to inspections by the competent authorities. The qualifications required for inspectors of medicated feed-producing facilities are set out in the procedural instruction on the qualification of GMP inspectors[46]. The inspection frequency follows a risk-based approach[44]. Samples have to be taken and analysed officially[44]. Further requirements are laid down in the procedural instruction on GMP instructions[51].

2.3.1.9. INTRA-UNION TRADE AND IMPORT FROM AND EXPORT TO THIRD COUNTRIES

Pursuant to Section 56(1) of the Medicinal Products Act[44], medicated feed manufactured in another EU member state or a country which is part of the EEA with authorised medicated pre-mixes either authorised in Germany or having the same qualitative and comparable quantitative composition as pre-mixes authorised in Germany may be dispensed directly to the animal holder by the manufacturer, but only upon a veterinary prescription. Those pre-mixes have to abide by all provisions laid out in the Medicinal Product Act[44] and must have an accompanying document based on the Federal Ministry of Food and Agriculture's sample certificate[44]. The prescribing veterinarian has to

immediately send a copy of the prescription to the competent authority, which is responsible for the control of compliance with pharmaceutical legislation[44]. Since countries besides the EU member states and the EEA are not mentioned specifically, third country importation from outside the EEA is not permitted for medicated pre-mixes or medicated feed[44].

Pursuant to Section 73a of the Medicinal Product Act[44], veterinary medicinal products, hence also authorised medicated pre-mixes or the resulting medicated feed, may be exported to third countries, if the competent authority of the country of destination does not oppose to it. Upon request, the German competent authority can issue a certification in accordance with the World Health Organization's certificate system, if the manufacturer of the product has either requested the certification or assented to it[44].

2.3.2. UNITED KINGDOM

In the United Kingdom, the superordinate EU legislation has been implemented into national law by laying down the Medicated Feedingstuffs Regulations[54], which have been revoked in 2006 and replaced by the Veterinary Medicines Regulations[37].

Schedule 5 of the Veterinary Medicines Regulations[37] addresses medicated feed along with feed additives. The Schedule[37] represents the enforcement of several EU regulations concerning European feed law, which also have to be abided by when producing medicated feed: topics addressed in those regulations are food safety[55], feed additives[56], official controls on compliance with feed and food law, animal health and animal welfare[57], feed hygiene[38] and labelling[36].

2.3.2.1. DEFINITIONS

Pursuant to Schedule 3 Part 1 of the Veterinary Medicines Regulations[37], there are four different types of veterinary medicinal products: POM-V, which is prescription-only medicine that may solely be supplied by a veterinarian or a pharmacist, POM-VPS, a prescription-only medicine which may be supplied by a veterinarian, a pharmacist or a "suitably qualified person" (SQP) pursuant to Schedule 3 paragraph 14[37], i.e. a person who has passed a specific examination and is registered as SQP. Furthermore, there are NFA-VPS, which are medicinal products for non-food-producing animals and supplied by either a veterinarian, a pharmacist or a suitably qualified person, or AVM-GSL, i.e. authorised veterinary medicine which is listed on a general sales list[37]. The classification of a VMP is specified by the Secretary of State when granting the marketing authorisation, though the classification can still be changed later on in certain cases[37]. POM-V-classified products either contain narcotic or psychotropic substances or require a diagnosis or clinical assessment by a veterinary surgeon before administration[37]. All VMPs for food-producing animals or products requiring special precautions to avoid unnecessary risks to the target

species, to the persons administering the drug or to the environment or which are newly authorised have to be classified either as POM-V or POM-VPS[37]. Further characteristics of veterinary medicines affecting their classification in one of the four groups are set out in Schedule 3 of the Veterinary Medicines Regulations[37].

In accord with the Veterinary Medicines Regulations[37] "'premixture' means a mixture of a veterinary medicinal product or a specified feed additive with feedingstuffs materials, intended for further mixing with feedingstuffs before being fed to animals".

2.3.2.2. MARKETING AUTHORISATION FOR MEDICATED FEED

Pursuant to Sections 8(a) and 10(a) and (c) of Schedule 5 of the Veterinary Medicines Regulations[37], veterinary medicinal products incorporated into animal feed must have a marketing authorisation. The incorporation into animal feed may only occur in accordance with the said marketing authorisation, unless it was prescribed under the "cascade", or in accord with a veterinary prescription[37].

2.3.2.3. APPROVAL OF MANUFACTURING FACILITIES

In accordance with Section 7(2) of Schedule 5 of the Veterinary Medicines Regulations[37] manufacturing and distribution of medicated pre-mixes and medicated feeds has to be approved by the competent authority, which is the Secretary of State. The conditions for approval of feed business establishments set out in Annex II of Regulation 183/2005[38] and incorporated into the Veterinary Medicines Regulations[37] also apply for manufacturers of medicated pre-mixes and medicated feed[37].

2.3.2.4. RESPONSIBILITIES OF MEDICATED FEED MANUFACTURERS

Section 11 of Schedule 3 of the Veterinary Medicines Regulations[37] lays down who may be supplied with veterinary medicinal products intended for incorporation into feed. VMPs for use in medicated pre-mixes or medicated feed are either classified as POM-V or POM-VPS (in case of deworming agents[9,39]). The supply of the VMP to a pre-mix manufacturer or a feed manufacturer (or to an end-user approved for manufacturing) can occur by the marketing authorisation holder, an authorised manufacturer of the product, an authorised wholesale dealer or a veterinarian, a pharmacist or, in case of POM-VPS-classified products, by a suitably qualified person[37].

The manufacturer has to ensure an as homogeneous as possible incorporation of the VMP[37]. When producing a medicated pre-mix the manufacturer has to ensure that the Summary of Product Characteristics (SmPC) of the VMP is abided by, the VMP is incorporated in accord with its marketing authorisation (if not prescribed under the "cascade") and the prescription and that no other additive contains the same active substance[37]. Promotion of "top dressing" of products, i.e. sprinkling them onto food without thoroughly incorporating them into the feed, is prohibited unless specifically permitted by the SmPC[37]. The daily

dose of the VMP has to be contained in an amount of medicated feed equivalent to at least half the daily feed ration (or non-mineral complementary feed in case of ruminants) of the animals to be treated[37]. Section 11 of Schedule 5 of the Veterinary Medicines Regulations[37] sets out the record keeping requirements for medicated feed manufacturers. Records have to be kept for five years[37]. Medicated pre-mixtures as well as medicated complete feed or medicated complementary feedingstuff must be clearly labelled as such, along with information on the name of the VMP and the active substance, acceptable inclusion rates with the words "refer to the prescription for the exact inclusion rate" and warnings and contra-indications[37]. Furthermore, the withdrawal period (of the active ingredient with the longest withdrawal, if more than one is contained) together with a statement that a longer withdrawal period applies, if stated on the prescription, the expiry date, special instructions for storage, if applicable, and a statement, if the resulting medicated feed is prescription-only, must be shown on the label[37]. Medicated feed additionally has to indicate the target species and a statement that the feed may only be fed in accordance with the prescription[37]. A prescription may be for a period longer than one month, but if this is the case, the supplier may provide the animal holder only with a supply sufficient for one month at a time, which also has to be clearly indicated on the prescription[37]. VMPs and medicated pre-mixes have to be stored in suitable, locked storage areas or hermetic containers; medicated feed that is packaged has to be sealed or, if transported in road tankers, the accompanying documentation must obey the labelling requirements[37]. Thorough cleaning of road tankers transporting medicated feed has to be ensured and the driver has to be provided with written instructions as to how to avoid cross-contamination[37].

2.3.2.5. VETERINARY PRESCRIPTION

The mandatory contents of the prescription are set out in Section 19 of Schedule 5 of the Veterinary Medicines Regulations[37]. The prescription is valid for three months, if no shorter period is specified and the amounts prescribed may only be sufficient for one treatment course[37]. The prescription must be issued in three copies – one for the person prescribing the medicated feed, one for the manufacturer of the medicated feed and one for the animal holder[37].

2.3.2.6. ON-FARM MIXING

Pursuant to Section 11 of Schedule 3 of the Veterinary Medicines Regulations[37] mentioned above, VMPs or authorised medicated pre-mixes may only be supplied to end-users (i.e. livestock farmers) if they are approved as manufacturers and if they merely receive amounts in accord with the prescription. By way of derogation, animal owners may manufacture medicated feed from a VMP supplied to them by a veterinarian, a pharmacist or (in case of a POM-VPS) by a suitably qualified person, on their premises without being approved; the precondition is that the produced medicated feed is used for feeding either non-food-producing animals or food-producing animals directly on those premises, and that the animals or their products are not sold or supplied commercially[37]. The prescription may either be oral or written in those cases[37]. Consequently, production of medicated feed for

non-food-producing animals is theoretically possible in the United Kingdom. Persons breeding or selling ornamental fish not used for human consumption are exempt from the regulations on medicated feed provided they use a maximum of 1 kg of a VMP annually for medicated feed[37].

2.3.2.7. RESPONSIBILITIES OF THE LIVESTOCK FARMER

In accordance with Part 3 of Section 17 of the Veterinary Medicines Regulations[37] livestock farmers have to keep proof of purchase (or documentary of how else they were attained) of all veterinary medicinal products, hence as well of medicated feed containing a veterinary medicinal product, acquired for their animals.

2.3.2.8. INSPECTIONS

Inspections have to be carried out with a risk-based inspection frequency[37]. Section 22 of Schedule 5 of the Veterinary Medicines Regulations[37] lays down the tolerance levels for analysis of the active substance in the medicated feed. The tolerances range in between ±50% for levels ≤50mg/kg and ±10% for levels ≥50g/kg[37].

2.3.2.9. INTRA-UNION TRADE AND IMPORT FROM AND EXPORT TO THIRD COUNTRIES

Medicated feed from other EU member states may only be imported, if the VMP contained has the same qualitative and quantitative composition as a VMP authorised in the United Kingdom; importation from a third country is prohibited[37].

Pursuant to Section 29 of Schedule 5 of the Veterinary Medicines Regulations[37], manufacturers of pre-mixes or feed may import a veterinary medicinal product authorised in another member state or third country for the purpose of incorporating it into pre-mixes or feed for export, even if that veterinary medicinal product is not authorised in the United Kingdom. Once the veterinary medicinal product is incorporated into feed, it is prohibited to place the resulting medicated feed on the market in the United Kingdom[37].

2.4. RESULTS AND CONSEQUENCES OF THE FCEC REPORT

The FCEC Report[14] showed quite marked differences between the EU member states regarding the implementation of Directive 90/167/EEC[11] into national law, as has been demonstrated above by the examples of the national regulatory framework in Germany and the United Kingdom. It stated that size and recent evolution of the medicated feed market vary drastically between EU member states and that, in all, the importance of medicated feed as a route of administration is decreasing[14]. The "Executive summary of the impact assessment"[58] identified four major problems concerning the current legislation represented

by Directive 90/167/EEC[11]: firstly, it was pointed out that several EU member states have "lax national requirements" eventuating in "generous tolerance levels for the carry-over of antibiotics from medicated feed into compound feed" and consequently, an increased risk for the development of antimicrobial resistance and, in member states without carry-over limits, a "burdensome case-by-case evaluation […] combined with legal uncertainty for operators"[58]. A second problem was discovered to be imprecise dosage of VMPs, either resulting from inhomogeneous incorporation of a VMP into medicated feed due to lax rules in an EU member state or due to a lower than expected feed intake or because of the use of less precise and controllable administration routes than medicated feed, such as top-dressing of oral VMPs or application via the drinking water with the risk of either over- or under-dosage of a VMP[58]. Thirdly, the current regulatory framework was identified to pose barriers to expand the production and intra-EU trade of medicated feed due to the differences in national implementation, which lead to high regulatory burdens for operators not limited to the local market and an unsatisfactory manufacturing quality in member states with more lenient rules as opposed to excessive costs for medicated feed in member states with very high standards[58]. Another problem stated in the executive summary of the impact assessment[58] was the lack of market access of medicated feed for pets, for some member states regard the medicated feed legislation as only applicable for livestock animals, since Directive 90/167/EEC[11] is based on Article 43 (Common Agricultural Policy) of the Treaty of Rome[12]. According to the European Commission's Impact Assessment[59], medicated pet food is available in only three member states and many member states feel unable to authorise medicated pre-mixes for use in non-food producing animals due to the Directive's[11] being derived from Article 43 (Common Agricultural Policy) of the Treaty[12]. Furthermore, the requirement for a prescription having to be available before production instead of delivery (several member states prohibit anticipated manufacturing of medicated feed and require a direct distribution from the feed mill to the animal keeper) impedes centralised production and distribution[58].

Therefore, the executive summary of the impact assessment[58] phrased several objectives of the EU initiative to modernise the medicated feed legislation: While ensuring a smooth functioning of a competitive and innovative internal market for medicated feed together with a high protection level of human and animal health, it was considered necessary to "overcome the zero-tolerance for unavoidable carry-over of VMPs", to provide farmers as well as pet owners with medicated feed at a competitive price, to reduce the risk of antimicrobial resistance from residual or sub-therapeutic administration of antimicrobials, to improve animal health via precise dosage of oral VMPs and to eliminate barriers for innovative medicated feed[58].

The impact assessment[58] considered three options for modernising the current regulatory framework, i.e. maintaining the status quo, amending Directive 90/167/EEC[11] combined with "soft law" or establishing a new EU regulation with detailed rules which is directly legally binding for all EU member states. After weighing the different options with regard to the objective mentioned above, the new EU regulation was favoured as having the most positive impact regarding the achievement of those objectives since it was considered to

improve cost efficiency and economic growth, encourage innovative applications of VMPs, improve animal and public health by establishing safe maximum residue levels and EU-wide valid product criteria, thereby also facilitating inspections[58].

2.5. FUTURE LEGAL SITUATION IN THE EUROPEAN UNION

The European Commission criticises that Directive 90/167/EEC[11] "gives no indication on what standards to apply in approving plants or the acceptable techniques to produce medicated feed, whether standards should be technology-based or results-based, it does not provide for homogeneity criteria, it is totally silent on the concept of carry-over of medicated feed between batches, on the specific labelling of medicated feed and on medicated feed for pets and it is vague on whether feed may be prepared in advance of prescription in the feed mill, allowing member states to arrive with different interpretations"[60]. Due to those rather vague provisions in Directive 90/167/EEC[11] it is not surprising that national implementations vary considerably between member states with all the consequences for e.g. intra-union trade or safety aspects in countries with lower standards regarding drug residues and over- and under-medication, but also safety issues in countries with high standards, since veterinarians and animal owners may resort to even less accurate methods such as top-dressing or mixing veterinary medicinal products manually into feeds.

Therefore, it was necessary to draw up a solution to overcome those issues. In accordance with the results from the medicated feed report[14], it appears to be the most consequent approach to issue a regulation which is immediately binding in all EU member states and does not allow for different interpretation in the various countries.

A proposal for a Regulation of the European Parliament and of the Council on the manufacture, placing on the market and use of medicated feed and repealing Council Directive 90/167/EEC[60] was adopted by the European Commission on September 10th, 2014. The new regulation will be based on the articles 43 and 168(4)(b) of the Treaty on the Functioning of the European Union[61], which cover the implementation of the Common Agricultural Policy of the EU and measures in the veterinary and phytosanitary fields concerned with the protection of public health. The aim of the review of the European medicated feed legislation is "to harmonise at a high safety level the manufacture, marketing and use of medicated feed and intermediate products in the EU and to reflect technical progress in this field"[60]. The draft proposal permits the anticipated production of medicated feed, and mobile and on-farm mixing, while simultaneously establishing the parameters for these schemes[60]. The provisions comprise measures for the disposal of unutilised medicated feed on farm[60]. A system for the collection of those unused or expired products shall be introduced in order to control any risk that such products might raise with regard to the protection of animal or human health or the environment[60]. EU-wide limits are laid down for the carry-over of veterinary medicines in feed that should be adapted

based on an assessment of the risk for animals and humans with respect to the different types of active substances[60].

The general manufacture requirements set out in Regulation 183/2005 are going to apply, along with the veterinary medicinal products legislation[32] (which is currently under revision as well) for the medicinal component of the medicated feed[60]. The proposed regulation[60] will also set rules for the approval of feed business operators and for the manufacturing of medicated feed. The regulation proposal[60] lays down rules for the homogenous incorporation of the veterinary medicinal products into the medicated feed and requirements in order to avoid carry-over of active substances from veterinary medicinal products into non-target feed. The general labelling rules for animal feed set out in Regulation 767/2009[36] will apply as well for medicated feed, supplemented by additional rules addressed in the new regulation such as deviation limits of the labelled content of medicated feed from the actual content[60]. Specific rules for prescription and its validity, the use of medicated feed containing antimicrobials in food-producing animals and the quantities of medicated feed which are required for the treatment are set out; manufacturers, distributors and users of medicated feed have to keep daily records in order to be able to effectively trace medicated feed[60]. For veterinary medicinal products authorised at national level, the regulation[60] sets intra-Union rules for trade of medicated feed in order to prevent distortions in competition. The regulation proposal[60] lays down that feed business operators manufacturing, storing, transporting or selling medicated feed are obliged to develop, implement and maintain a written "hazard analysis and critical control points (HACCP) system"; furthermore they have to ensure that no interaction between the veterinary medicinal product and the feed used as a carrier occurs and no feed additive for which a maximum content is set out and that is already used as active substance in the medicated feed is incorporated. Homogeneity criteria for the incorporation of the veterinary medicinal product into the intermediate product or the medicated feed laid down by the European Commission will have to be abided by the manufacturers[60]. Specific carry-over limits are set for all active substances for which no limits have been set yet; for antimicrobial active substances the limit is set at 1% of the amount incorporated into the last batch of medicated feed or intermediate product before producing non-target feed and 3% for all other active substances[60]. Anticipated production of medicated feed or intermediate products will be allowed except for on-farm mixing or for veterinary medicinal products that have been re-designated under the "cascade" pursuant to Article 10 or 11 of Directive 2001/82[32,60]. Medicated feed and intermediate products will have to be packed in containers or packages whose seals are irretrievably damaged when opened for the first time[60]. When medicated feed is to be used in a member state other than where it was manufactured, the medicinal compound used has to be authorised under Directive 2001/82[32] in the member state of use, i.e. a purely national authorisation will not suffice, since an authorisation in the member state of manufacture is mandatory is well[60]. All medicated feed-manufacturers have to be approved prior to starting production in accordance with the provisions of the Feed Hygiene Regulation[38] and the suitability of their production system has to have been demonstrated to the government's inspectors by an on-site visit[60].

Medicated feed may only be issued upon presentation or, in case of on-farm mixing, possession of a prescription; only for non-food-producing animals the same prescription may be used for more than one treatment with a validity of the prescription of six months for non-food-producing animals and three weeks for food-producing animals[60]. The prescribing veterinarian may only issue a prescription for animals under his direct care for a therapeutic indication justified by the diagnosis and has to ensure that there are neither incompatibilities with other treatments nor contra-indications nor interactions with other medicinal products used[60]. The prescription has to comprise the information set out in Annex V and shall, in line with the veterinary medicinal product's Summary of Product Characteristics, indicate the inclusion rate calculated on the basis of relevant parameters; the original (for the manufacturer) and two copies (for the veterinarian and the animal holder) shall be kept for three years[60]. For food-producing animals, medicated feed manufacturers or on-farm mixers may only supply or mix quantities for a treatment duration of one month (or two weeks in case of antimicrobials), but either way not exceeding the quantities prescribed; antimicrobials shall not be used for disease prevention or growth promotion[60]. The livestock farmer has to ensure adherence to the withdrawal period of the medicated feed's active substance as provided with the veterinary prescription; record keeping requirements for medicated feed manufacturers concerned with food-producing animals have to be in accord with Article 69 of Directive 2001/82[32,60]. An appropriate collection system for unused or expired medicated feed or intermediate products, be it on-farm or at the manufacturer's premises, has to be established[60].

The annexes of the regulation proposal[62] set out specifically the requirements for medicated feed; Annex I[62] is concerned with requirements for feed business operators, addressing the prerequisites regarding facilities and equipment, staff and their qualifications (such as the need for a qualified person for the manufacture of medicated feed and intermediate products and one responsible for quality control), manufacture (HACCP concept, avoidance of carry-over, presence of undesirable substances, storage etc.) and quality control (e.g. sampling for carry-over, homogeneity testing etc.), storage and transport conditions, record keeping requirements as well as recall procedures.

Pursuant to Annex II[62], mobile and on-farm mixers may only incorporate medicinal compounds at inclusion rates above 2kg/ton of feed. The daily dose of the veterinary medicinal product has to be incorporated into a quantity of feed that ensures the complete uptake by the target animal taking into account the prospected feed uptake of a diseased animal in comparison to a normal daily ration[62]. The provision that medicated feed has to comprise at least 50% of the daily ration (50% of the complementary feed in case of ruminants) has been adopted from Directive 90/167/EEC[11,62]. Annex III[62] sets out labelling requirements and combines requirements laid down in Regulation 767/2009[36] with specific rules for medicated feed adopted from Directive 90/167/EEC[11]. Annex IV[62] contains the permitted tolerances for the compositional labelling of medicated feed and intermediate products; regarding antimicrobial active substances a maximum deviation of 10% between labelled and actual content is permitted, independently of the concentration, whereas for all other active substances permitted tolerances between 10 and 40% depending on the

intended concentration apply. Annex V[62] sets out the information required to be comprised in the veterinary prescription; therefore, the approach from Directive 90/167/EEC[11] with a predefined form to be used for prescription has been abandoned[62].

Currently, the discussions regarding the contents of the regulation proposal are still ongoing; several parties have sent comments and statements to the European Commission demanding corrections or clarifications. For instance, the German Federal Chamber of Veterinarians criticises the tolerances for drug carry-over laid down in the regulation proposal[60] as being too high, especially for active substances with high potency and therefore low inclusion rates[63], whereas, by contrast, in the UK an ad hoc working party representing the feed, farming, veterinary and pharmaceutical industries regards the planned tolerances as too restrictive, as does the European Feed Manufacturers Association[64,65]. The European Parliament's Committee on Environment, Public Health and Food Safety (COMENVI) recommends a shorter prescription duration for antibiotic medicated feed, whereas the UK's working party mentioned before postulates a much longer one (as well as the European Economic and Social Committee in its opinion paper[66]) and the German Federal Chamber of Veterinarians demands to adjust the prescription duration to the treatment recommendation of the respective veterinary medicinal product[63,64]. Similarly, there are several other aspects with contrasting opinions, e.g. as to whether preventative use is acceptable or not[64,66] or is currently banned already anyway by EU legislation[65] (a point of view which is strengthened by a press release[67] published by the European Commission in 2005 stating that "an EU-wide ban on the use of antibiotics as growth promoters in animal feed enters into effect on January 1, 2006").

Therefore, several issues still will have to be solved before the final regulation can come into effect.

3. LEGISLATIVE FRAMEWORK FOR MEDICATED FEED IN THE UNITED STATES OF AMERICA

3.1. BACKGROUND DATA

3.1.1. ANIMAL HUSBANDRY IN THE UNITED STATES OF AMERICA

3.1.1.1. LIVESTOCK, POULTRY AND AQUACULTURE

In 2014 the cattle population in the United States amounted to around 88 million animals[68,69], beef cows counted 29 million animals[69] and dairy cows 9.3 million animals[69]. 5.3 million sheep and lambs and 1.7 million goats were counted in 2011; the pig population counted 66.9 million heads in 2015[69,70], the poultry population amounted to 350.7 million layer hens, 110 million pullets, 1.5 billion broilers, 100.7 million turkeys[71] in 2012. The aquaculture catfish inventory in 2015 counted approximately 849 million animals[72], whereas about 53 million trouts from aquaculture were sold in 2011[73].

3.1.1.2. COMPANION ANIMALS

According to The Humane Society of the United States approximately 62% of all households owned at least one pet animal in 2012 with a total number of around 164 million pets, which means that pet ownership has tripled since the 1970s[74]. Regarding the dog and cat population 47% of the households owned at least one dog in 2012, amounting to 83.3 million pet dogs in total, whereas there were 95.6 million owned cats in the same year's statistics[74]. The American Veterinary Medical Association states slightly lower numbers for the same time frame, with the dog population being around 70 million animals and 36.5% of all households owning one or more dogs; the number of cats is indicated with 74 million animals and, accordingly, 30.4% of all households in the United States are said to be owning one or more cats[75]. 8.3 million ornamental birds, 57.8 million ornamental fish, approximately 7 million small mammals as well as 4.6 million reptiles were owned in 2012 in the United States[75].

3.1.2. PRODUCTION OF ANIMAL PRODUCTS AND PRODUCTION SYSTEMS

In 2014, 30.1 million cattle and 566.000 calves were slaughtered, amounting to a total of approximately 11 million tons of meat[68,76,77]. 106.9 million hogs, 2.3 million sheep and lambs, 8.5 billion broilers, 144.2 million other chicken as well as around 240 million turkeys were used for meat production[77,78]. In total 11.4 million tons of pork were produced in 2014[79], 78.000 tons of lamb and mutton[80], 19.3 million tons of broilers (live weight)[81] and 260.500 tons of other chicken[82] along with 2.9 million tons of turkey carcasses[83]. 70.7 million fish were sold in 2014 with a total weight of approximately 3.550 tons and a value of 8.9 million US$[84].

3.1.3. DATA ON THE MARKET OF ANIMAL FEED AND VETERINARY MEDICINAL PRODUCTS

3.1.3.1. SALES OF COMPOUND FEED

Feed concentrates for livestock and poultry fed in the United States amounted to 188.1 million tons in 2011[85]. Production of compound feed in the United States was reported to be 168.5 million tons in 2012, with 23.6 million tons being for use in pigs, 19.5 million tons for use in dairy cows and 23.4 million tons for use in cattle[86]. Production of poultry feed in 2012 amounted to 23.1 million tons for use in layer hens, 57.2 million tons for use in broilers and 6.5 million tons for use in turkeys[86]. Of the 1 million tons of compound feed produced for aquaculture in 2012[86], 477.762 tons were used for catfish in aquaculture in 2012[87].

In 2014 US American citizens spent 22.26 billion US$ on pet food[88]; 5.7 million tons of dog food worth 12.6 billion US$ and 2.1 million tons of cat food with a worth of 6.4 billion US$ were sold in 2012, along with 34.669 tons of bird food, more than 3.000 tons of fish food and more than 44.000 tons of reptilian and small mammal food[89]. Pet food production in total amounted to 8 million tons in 2012, along with 6 million tons of horse feed[86].

3.1.3.2. SALES OF VETERINARY ANTIMICROBIALS

In 2013 a total of 14.789 tons of antimicrobial active substances intended for use in food-producing animals (though a certain amount may also have been used in non-food-producing animals, since some drugs are approved for use in several different species, food-producing and non-food-producing) were sold in the USA, with tetracyclines administered via feed representing the major group with 5.700 tons per year[90]. Administration via feed was the most used route, followed by administration via the water; administration using other routes such as intramammary administration, injection or orally administered finished dosage forms played only a comparatively minor role[90]. Tetracyclines represented the majority of antibiotics used in total (6.515 tons per year), followed by ionophores with 4.435 tons[90].

3.1.4. PRODUCTION AND USE OF MEDICATED FEED IN THE UNITED STATES OF AMERICA

According to the American Feed Industry Association, the U.S. Food and Drug Administration (FDA) announced the number of feed mills in April 2015 to be 6.012 in total with 541 manufacturing pet food and 1.005 facilities holding a medicated feed mill license (MFML)[91]. In 2007, approximately 5.183 feed mills produced medicated feed without requiring a MFML[92].

For production purposes such as growth promotion or improvement of feed efficiency, antibiotics in the United States are administered at sub-therapeutic levels, generally via medicated feed[93]. In 2006 57.5% of dairy operations provided 49.9% of pre-weaned heifers with medicated milk replacer; this was especially common in small- and medium-sized dairy farms as compared to larger farms[93]. In 2006, 26.8% of dairy farms fed 40% of dairy cows at these operations coccidiostats in feed to promote growth; at least half of dairy operations fed either antibiotics or ionophores to weaned heifers to prevent disease or promote growth[93]. In 2010, 77.3% of heifer farms (representing 87.3% of heifers at such operations) included ionophores in their weaned heifers' feed[93]. In 2007/2008, 15.8% of cow-calf operations reported adding antibiotics to cattle feed for disease prevention and/or growth promotion, 2.6% used medicated feed for promoting growth in replacement heifers weaned, but not yet calved; 90.5% of large feedlots used feed with ionophores for their cattle in 2011, whereas the percentages in medium and smaller operations were 28.7 and 17.1%, respectively[93]. 48% of cattle in large feedlots received antibiotics other than ionophores and coccidiostats in their feed in 2011, while smaller feedlots only fed a total of 38% of their cattle with those antibiotics[93]. In 2006, 24.5% of sites with nursery-age hogs administered antibiotics in feed for growth promotion and 50.9% for disease prevention; in 2000, 82% of farms with nursery-age pigs provided antibiotics in feed for growth promotion purposes[93]. 55.1% of sites with grower/finisher hogs used antibiotics via feed for growth promotion in 2006[93].

3.2. CURRENT LEGAL SITUATION IN THE UNITED STATES OF AMERICA

In the United States of America, medicated feed is addressed in the Federal Food, Drug and Cosmetics Act that is contained in Title 21 Chapter 9 of the Code of Laws of the United States of America (United States Code, U.S.C.); the U.S.C. is "a consolidation and codification by subject matter of the general and permanent laws of the United States"[94]. Further ordinances concerning medicated feed are laid down in the Code of Federal Regulations (CFR)[95] which is "the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government"[96]. Title 21 of the CFR[95] which is concerned with Food and Drugs deals in its Chapter I Subchapter E with animal drugs, feeds and related products. Part 558 of Subchapter E of Title 21 CFR[95] is devoted to new animal drugs for use in animal feeds, while Part 515 addresses medicated feed mill licenses. Medicated feed legislation is solely concerned with medicated feed for food-producing animals[97,98].

Subpart B of 21 CFR 558[95] gives information on specific new animal drugs for use in animal feeds, such as instructions on concentrations and combinations, indications for use and limitations, whereas subpart A (§§ 558.3 – 558.15) lays down general provisions.

The regulatory framework on medicated feed in the United States also covers liquid medicated feed and free-choice medicated feed (i.e., "medicated feed that is placed in

feeding or grazing areas and is not intended to be consumed fully at a single feeding or to constitute the entire diet of the animal", such as medicated blocks, mineral mixes, and liquid feed tank supplements), which are addressed in 21 CFR 558.5 and 510.455[95].

3.2.1. DEFINITIONS

3.2.1.1. DRUG

Pursuant to 21 USC 321(g)(1)[94], the "term 'drug' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)".

21 CFR 558.3 defines two categories of new animal drugs with Category I-drugs requiring no withdrawal period at the lowest use level in each species for which they are approved and Category II-drugs requiring "a withdrawal period at the lowest use level for at least one species for which they are approved, or are regulated on a 'no-residue' basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required"[95].

3.2.1.2. MEDICATED FEED

Additionally, definitions regarding medicated feed are given in 21 CFR 558.3[95]: a 'Type A medicated article' is "intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. It consists of a new animal drug(s), with or without carrier (e.g., calcium carbonate, rice hull, corn, gluten) with or without inactive ingredients. […] A 'Type B medicated feed' is intended solely for the manufacture of other medicated feeds (Type B or Type C). It contains a substantial quantity of nutrients including vitamins and/or minerals and/or other nutritional ingredients in an amount not less than 25 percent of the weight. It is manufactured by diluting a Type A medicated article or another Type B medicated feed. […] A 'Type C medicated feed' is intended as the complete feed for the animal or may be fed "top dressed" (added on top of usual ration) on or offered "free-choice" (e.g., supplement) in conjunction with other animal feed. It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A medicated article or a Type B medicated feed."[95]. Therefore, the term "Type A medicated article" is more or less equivalent to the term "medicated pre-mix" used in the European Union, whereas the term "medicated feed" as defined in 21 CFR 558.3(b)(8)[95] means either a "Type B medicated feed" (a medicated feed based on a supplemental or mineral feed) or a "Type C medicated

feed" (a complementary feed containing a medicating ingredient). A Type B medicated feed is not intended to be fed "as is", but has to be further diluted to a Type C medicated feed[99] and can be considered corresponding to the term "intermediate product". Therefore, only a "Type C medicated feed" is more or less equivalent to the term "medicated feed" as it is used in the European Union.

3.2.1.3. VETERINARY FEED DIRECTIVE DRUG

Another definition in 21 CFR 558.3(b)(6) and (7)[95] deals with the term "veterinary feed directive (VFD) drug", which means "a drug intended for use in or on animal feed which is limited […] to use under the professional supervision of a licensed veterinarian. Use of animal feed bearing or containing a VFD drug must be authorized by a lawful veterinary feed directive", which "is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the Food and Drug Administration"[95].

During their approval process, animal drugs can either be classified as VFD drugs (if veterinary supervision is required and the drug is intended for use in or on animal feed[97]), prescription drugs (not for use in or on animal feed[97]) or over-the-counter drugs. Currently, drugs used in medicated feeds are either over-the-counter drugs or VFD drugs[100,101]. VFD drugs are not considered prescription drugs in order to provide veterinary supervision without invoking state pharmacy laws for prescription drugs that were deemed "unworkable for the distribution of medicated feed"[97]. In order to ensure the judicious use of medically important antimicrobials a Guidance for Industry with the title "New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209"[102] was issued that applies to all current VFD drugs; with effect of January 1st, 2017 all medically important antimicrobials authorised for use in or on animal feed will require a VFD, whereas for those to be used in drinking water a prescription will be required. Therefore, their current over-the-counter marketing status will have to be switched to a VFD marketing status[98]. Until December 2016 the drug sponsors are supposed to change the use conditions of their drug products affected[103], thereby abolishing all approved indications for VFD drugs regarding growth promotion or improvement of feed efficiency[98,104]. Therapeutic uses under veterinary supervision will remain allowed for VFD drugs[98,104].

3.2.2. DRUG REGISTRATION FOR MEDICATED ARTICLES AND MEDICATED FEED

The animal drug intended for use in whichever type of medicated feed must be approved for this use under 21 USC 360b of the Federal Food, Drug, and Cosmetic Act or index listed under 21 USC 360ccc–1 (index of legally marketed unapproved new animal drugs for minor species)[94], i.e. either an approval under an original new animal drug application (NADA), a supplemental NADA or an abbreviated NADA pursuant to the respective legislation is required. New drug applications for animal drugs to be used in liquid medicated feed have to contain either additional information on chemical and physical stability of the drug in liquid medicated feed under field conditions or labelling of the feed with recirculation or agitation directions if the liquid feed is not stable over a longer period of time under field conditions[94,95].

Each drug registered for use in Type A medicated articles and Type B or Type C medicated feeds is listed in 21 CFR 558.4(2)(d)[95] with identification of the drug's category, the maximum level of drug in Type B medicated feeds, and the assay limits for the drug in Type A medicated articles and Type B and Type C medicated feeds.

Drug sponsors of Type A medicated articles have to include in the NADA representative labelling proposed to be used for Type B and Type C medicated feeds containing the new animal drug (21 CFR 514.1(b)(3)(v)(b)[95]), which is referred to by the FDA's Center of Veterinary Medicine as "Blue Bird Label" and supposed to function as a guide to manufacturers of medicated animal feeds in the preparation of final printed feed labels[105]. They have to contain information on the name of the medicated feed, the indication(s) for use, the active drug ingredient(s), the guaranteed analysis, other ingredients, mixing directions, caution and warning statements, manufacturer information, a weight statement and possibly other information; details on the FDA's current thinking on the recommended content and format of those Blue Bird Labels are given in a Guidance for Industry on Blue Bird Medicated Feed Labels[99]. Pursuant to 21 CFR 515.10(7)[95], manufacturers intending to produce Type B or Type C medicated feed have to have the Blue Bird Labels corresponding to the Type A medicated articles they want to use at hand in advance, before being allowed to start production. Current Blue Bird Labels are published on the website of the FDA and updated regularly[105].

3.2.3. CURRENT GOOD MANUFACTURING PRACTICES (CGMP)

Medicated feed manufacturers have to abide by the current Good Manufacturing Practice Regulations, which are set out by the FDA in order to have a "preventive approach" rather than an "after the fact" sampling and testing programme to uncover existing problems, which is appreciated by the industry to be more effective and efficient[101]. If the cGMP rules are adhered to by the medicated feed manufacturers, this should result in finished products containing the correct drug at the intended concentration with accurate labelling, while

maintaining as well the integrity of the product as that of other products produced at the same facility[101]. In 21 CFR 225[95] the rules for cGMP for medicated feeds are set out addressing topics such as general provisions for cGMP and personnel, construction and maintenance of facilities and equipment, product quality control and product quality assurance, packaging and labelling, as well as records and reports. Manufacturers requiring a MFML are to adhere to the regulations laid down in 21 CFR 225.10 through 225.115[95], whereas for facilities manufacturing solely medicated feeds for which no approved MFML is necessary §§ 225.120 through 225.202[95] apply, the provisions of which are less detailed.

3.2.4. REGISTRATION AND LICENSING OBLIGATIONS OF MEDICATED FEED MANUFACTURERS

Depending on which type of drug is used in a medicated feed or for which purpose a medicated feed or a Type A medicated article is intended, a manufacturer may require a MFML.

A feed manufacturer who uses Category II, Type A medicated articles to produce Type B or Type C medicated feed has to possess a MFML; manufacturers producing Type B or Type C medicated feed using Category I, Type A medicated articles or Category I, Type B or Type C medicated feeds are exempt from applying for a MFML, as are manufacturers of Type B or Type C medicated feed using Category II, Type B or Type C medicated feeds with the exception of certain liquid or free choice medicated feeds for which Category II-animal drugs are used or for which a proprietary formula and/or specifications are used with a Category I-drug[95,106].

If a facility is required to apply for a MFML, the registration as a drug establishment pursuant to 21 CFR 207.20[95], which has to be renewed annually, is necessary before applying; the establishment has to be registered within 5 days of beginning of the operations (21 CFR 207.21(a) and 207.40[95] and 21 U.S.C 510(c), (d) and (i)[94]). Manufacturers only producing Type B or Type C medicated feed are not required to submit a drug list (i.e. a list of all drugs in commercial distribution of the facility) along with the drug establishment registration (21 CFR 207.20(a)[95]).

The licensing requirements are the same for using VFD- or over-the-counter drugs in the medicated feeds produced[106] and are laid down in 21 CFR 515.10[95]. The application has to contain the full business name, address and FDA registration number of the manufacturing facility along with name, title and signature of the facility's responsible individual(s), a certification that the medicated feed is manufactured and labelled in accord with the respective regulations and a certification of adherence to cGMP and to correct record keeping[95]. Furthermore, a commitment has to be made to renew the drug establishment registration annually and to have the current approved or index listed Type B and/or Type C medicated feed labelling for each Type B and/or Type C medicated feed ("Blue Bird

Labels") in the possession of the feed manufacturing facility prior to receiving the Type A medicated article containing such a drug[95].

3.2.5. VETERINARY FEED DIRECTIVE DRUGS

VFD drugs are addressed in 21 CFR 558.6[95]. Animal feed that contains a VFD drug or a combination of drugs with at least one VFD drug may be fed to animals only upon a lawful VFD issued by a licensed veterinarian who has a valid veterinarian-client-patient-relationship (VCPR); this information must also be displayed prominently and conspicuously as a cautionary statement on the labelling[95]. The minimum requirements for the VCPR are laid down in 21 CFR 530.3(i) – those requirements have to be adhered to even if the state the licensed veterinarian is practicing in has VCPR requirements in place that do not include those key elements[95].

3.2.5.1. VETERINARY FEED DIRECTIVE

A VFD has to comprise the following information: the name, address and telephone number of the issuing veterinarian and the client, the premises, where the animals to be treated are located, the date of the VFD issuance and the expiration date, which indicates the maximum period of time the VFD is valid (at maximum the period of time indicated in the NADA or 6 months after issuance); after the expiration date of the VFD the medicated feed must not be fed to animals[95]. Furthermore, the name of the VFD drug(s), the species and production class of the animals to be fed, the approximate (potential) number of animals to be fed at the premises during the period of validity, i.e. until the expiration date, the therapeutic indication of the VFD, the level of VFD drug in the feed and the duration of use (that is the time period one individual animal to be treated is to receive the medicated feed) as well as the withdrawal time and further special instructions and cautionary statements. The VFD has to be signed by the veterinarian electronically or in writing and must be non-verbal[95]. For combinations of (a) VFD drug(s) with other over-the-counter drugs, further information has to be given by the veterinarian on the VFD, which is set out as different "affirmations of intent" in 21 CFR 558.6(b)(6), depending on which drug combinations the veterinarian intends to authorise with this specific VFD.

3.2.5.2. RESPONSIBILITIES OF THE MANUFACTURER AND VETERINARIAN

Extralabel use of a VFD drug, i.e. in a manner other than directed on the label, is prohibited and has to be indicated in the VFD as a cautionary statement[95]. Refills, i.e. reorders of the VFD drug are not permitted unless explicitly specified in the drug (conditional) approval or index listing[95]. The veterinarian, the distributor and the client have to retain a copy of the VFD for 2 years and make it available along with other records (e.g. receipt and distribution information on VFD medicated feed and VFD medicated feed manufacturing records) specified in 21 CFR 558.6[95] upon request of the FDA. A distributor of VFD

medicated feed has to notify the FDA of those activities one-time-only prior to the first distribution of a VFD medicated feed[95].

3.2.6. OVER-THE-COUNTER DRUGS IN MEDICATED FEED

All drugs authorised for the production of medicated feed which are not classified by the FDA as VFD drugs are categorised as "over-the-counter (OTC) drugs" (as mentioned above, the classification as a prescription drug is not prohibited, but it is de facto not used by the FDA for medicated feed)[97]. An OTC drug product is "a drug product marketed for use by the consumer without the intervention of a health care professional in order to obtain the product"[107]. With OTC animal drugs it is deemed to be "possible to prepare 'adequate directions for use' under which a layperson can use the drugs safely and effectively"[108]. In consequence, medicated feed containing OTC, but no VFD drugs can be purchased by an animal owner without veterinary prescription or veterinary oversight. Currently, almost all drugs used for medicated feed are OTC drugs, but with the revision[98] of the Veterinary Feed Directive Regulation (21 CFR 558[95]) the antimicrobials deemed critically important for human use by the FDA are supposed to have their OTC status switched to VFD by their sponsors by the end of 2016[102]. After this switch only not critically important antimicrobials and other drugs such as for instance antiparasitic agents which are authorised for use in medicated feed will have OTC status and only those antimicrobials will be permitted to be used for production purposes, i.e. growth promotion or improvement of feed efficiency[98,102].

3.2.7. RESPONSIBILITIES OF THE LIVESTOCK FARMER

The livestock farmer's responsibilities are specified, if he uses animal feed containing (a) VFD drug(s). Pursuant to 21 CFR 558.6(a) and (b)[95], the animal owner must ensure that VFD feed is only fed upon a VFD issued by a licensed veterinarian, that the animals concerned do not receive the VFD feed after the expiration date specified in the VFD and the animal owner must maintain a copy of the VFD order for at least 2 years and must provide those orders to the distributor of the feed, if the licensing veterinarian has not already done so[95]. Upon request the VFD orders have to be presented to the FDA for inspection and copying[95]. The animal owner has to follow the instructions given by the veterinarian; if the state the animal owner has his premises in has state-defined VCPR rules in place, the animal owner is obliged to abide by them in accord with 21 CFR 530.3(i) and 558.6(b)(1)(ii)[95,106].

3.2.8. ON-FARM MIXING

On-farm mixing is permitted, but the on-farm mixer is subjected to the same requirements as other medicated feed manufacturers, i.e. depending on the type of drug used in the medicated feed, a MFML and drug establishment registration may be required[101,109,110]. Mobile mixers have to be registered in the same way as stationary manufacturing locations[110].

3.2.9. INSPECTIONS

Licensed feed mills are inspected routinely by the FDA once every two years, whereas non-licensed facilities do not undergo routine inspection by the FDA (but they may be inspected on a regular basis by state officials); the FDA Safety & Innovation Act Section 705[111] demands a risk-based approach regarding the inspection frequency[100,110]. All facilities may be inspected in response to specific incidences such as adulterated feed or illegal drug residues[110]. The FDA has developed Guidance Manuals for their inspectors regarding inspections of facilities that produce Type A medicated articles[112] and facilities manufacturing feed (including medicated feed)[112]; those Guidance Manuals are made publicly available in order to facilitate it for manufacturers to meet the requirements for their specific situation by being able to check the aspects covered by a cGMP- or non-cGMP-inspection as set out in those manuals.

3.2.10. IMPORT AND EXPORT REGULATIONS

New animal drug substances (or bulk drug substances labelled for further manufacturing or processing and indicated for veterinary use) which are intended for the production of Type A medicated articles may only be legally imported if they have an approved NADA, an abbreviated or conditional NADA or an investigational new animal drug exemption[113], otherwise they are considered adulterated or misbranded pursuant to 21 USC 351 and 352[94]. For feed and feed ingredients of foreign origin the adulteration and misbranding standards and therefore the requirements including feed mill licensing and new animal drug approval are the same as for domestic products, but the burden of proof to consider a product as violative is much less for imported products, since the FDA must only establish that the product "appears" to be violative[114]. However, the enforcement procedures are different, as imported products are subject to inspection at the time of entry into the country; shipments found to be non-compliant are subject to detention and, if they cannot be brought into compliance, they must be either destroyed, or re-exported[114].

For the export of FDA approved medicated feed to foreign countries the FDA issues a "certificate to foreign government", which indicates that the products concerned can be legally marketed in the United States of America[115].

4. LEGISLATIVE FRAMEWORK FOR MEDICATED FEED IN CANADA

4.1. BACKGROUND DATA

4.1.1. ANIMAL HUSBANDRY IN CANADA

4.1.1.1. LIVESTOCK, POULTRY AND AQUACULTURE

In Canada, cattle, sheep, horses, chickens, turkeys, geese, ducks, swine, rabbits, fish, mink and foxes are defined as livestock[116]. In 2014 the pig population comprised about 13 million pigs[117] with pig production amounting to 19.6 million animals, which is a slight decrease compared to 2013[118]. The cattle population counted between 12 and 13 million heads during 2014[68,117] and the sheep population amounted to around 1 million animals[117]

4.1.1.2. COMPANION ANIMALS

In Canada, around 57% of all households own pets; 37% of the households own at least one cat, 32% at least one dog and 9% owned other pet animals such as ornamental fish, ornamental birds, small mammals or reptiles[119]. In 2013 approximately 5.9 million dogs lived in Canadian households, along with 7.9 million cats[119].

4.1.2. PRODUCTION OF ANIMAL PRODUCTS AND PRODUCTION SYSTEMS

In 2014 2.8 million cattle and 249.000 calves were slaughtered in Canada, resulting in a total meat production of 1.1 million tons[68]. 21.1 million hogs were slaughtered in Canada in 2012, 0.88 million of which were exported to the United States[120]. Regarding poultry, more than 5.6 million ducks and geese[121] were slaughtered in 2015 along with 629 million broiler chickens[122] and around 35 million mature chickens[123], as well as 20.5 million turkeys[124]. The Canadian aquaculture produced an output of 172.097 tons in 2013[125].

4.1.3. DATA ON THE MARKET OF ANIMAL FEED AND VETERINARY MEDICINAL PRODUCTS

4.1.3.1. SALES OF COMPOUND FEED

The total compound feed production in Canada amounted to 19.642 million tons in 2012[86]. 4 million tons were produced for pigs, 10 million for dairy cows, 0.78 million for cattle and 0.18 million tons for small ruminants; compound feed for the poultry industry comprised 800.000 tons for layer hens, 0.96 million tons for broilers and 0.18 million tons for turkeys and other poultry, respectively[86]. For aquaculture, 0.76 million tons were produced in 2012,

along with 1.2 million tons for pets and 0.58 tons for horses[86]. According to Agriculture and Agri-Food Canada, the sales of cat food (dry and wet food) amounted to 150.500 tons with a value of 594.5 million C$ in 2011, the value of the 290.000 tons of dog food (dry and wet food) sold in 2011 equalled 750.2 million C$[126]. 5.400 tons of other pet food for small mammals, reptiles as well as ornamental fish and ornamental birds were sold in Canada in 2011[126].

4.1.3.2. SALES OF VETERINARY ANTIMICROBIALS

The Canadian Government states that in 2013 1.4 times more antimicrobials were distributed in Canada for use in animals than in humans (adjusted for weight and population)[127]. In 2013, 1.600 tons of antimicrobial active ingredients were sold for use in animals in Canada, 99.4% of which were used in food-producing animals and 0.6% were used in companion animals[127]. 32% of the antimicrobials distributed belonged to classes not used in humans[127]. Most of the antimicrobials were administered via feed rather than administration via the water and were used for disease prevention, treatment and for production claims, i.e. growth promotion purposes[127,128]. Tetracyclines were the predominantly used antimicrobials, followed by ionophores, ß-lactams and macrolides[127]. Tylosin, ionophores, lincomycin and chlortetracycline were used for production claims (i.e. growth promotion purposes)[127].

4.1.4. PRODUCTION AND USE OF MEDICATED FEED IN CANADA

According to the Animal Nutrition Association of Canada, the annual total feed production amounts to just over 30 million tons with 10 million tons produced on-farm and 20 million tons produced commercially[129]. There are 511 known commercial feed mills in Canada, the majority of which (66%) is located in Quebec and Ontario[130,131]. 468 feed-mills have been categorised for their risk regarding use of medications (a high risk meaning that either medicating ingredients with a defined withdrawal period are used in the manufactured feed or that feed (some of which is medicated) is produced for multiple species or classes of animals, whereas a low risk is defined as only medicating ingredients without a withdrawal period being used)[131]. 297 mills have been identified as high-risk for medications; 311 are regarded as high risk for medications as well as the use of prohibited material for other species while producing ruminant food, which increases the risk for transmissible spongiform encephalopathies (TSE)[131]. 25.000 out of the approximately 200.000 livestock farmers use on-farm mixing for medicated feed[131]. According to the CFIA in 1998 for instance in the Atlantic Area of Canada, around 4% of manufactured fish feed representing approximately 3.600 metric tons, was medicated and accounts for around 85% of the medicated fish feed produced in Canada for that year[132].

Data available regarding the use of medicated feed in Canada are rather scarce. In 2014, the Ministry of Agriculture of British Columbia published a report on the use of over-the-counter antibiotics in livestock and poultry in their province[128] which stated that

approximately 95% of the antimicrobials used in British Columbia were administered via feed, around 5% via the drinking water and all other administration routes added up to less than 1% of total usage. Antibiotics authorised for use in poultry, cattle and poultry or poultry and swine accounted for 83% of total usage[128]. The use of antibiotics by category of importance as classified by Health Canada (category I representing very high importance, category IV low importance, since those products are not used in human medicine) are shown in Figure 1; the data refer to the amount of active substance used per ton of biomass, i.e. per ton of livestock live weight in the respective period of time in British Columbia[128]. Since British Columbia has, on average, the most lenient legislation regarding medicated feed in Canada (as explained further below), those data may only be interpreted with caution regarding the extrapolation to the situation in other regions of Canada.

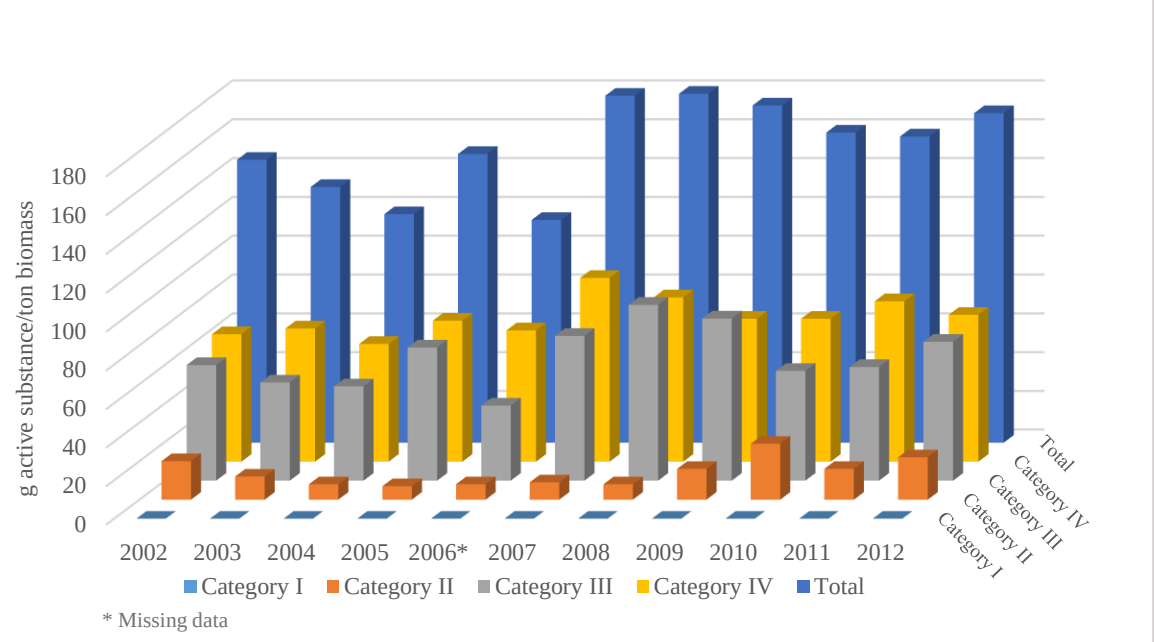

Figure 1: Annual antibiotic use in British Columbia categorized by importance of the active substance in human medicine (data from: "Use of Over-the-Counter Antibiotics in BC Livestock and Poultry, 2002 – 2012"[128])

4.2. CURRENT LEGAL SITUATION IN CANADA

In Canada, medicated feed is regulated as well on the federal as on the provincial level. The federal legislation gives the framework, which cannot be attenuated, but only be tightened by provincial laws.

Therefore, in the following, the federal legislative framework will be described in detail, and afterwards provincial specifics will be addressed.

4.2.1. FEDERAL LEGISLATION

In Canadian federal law, medicated feed is regulated under the Food and Drugs Act[133] and the Food and Drug Regulations[134] as well as the Feeds Act[135] and the Feeds Regulations[136]. The Feeds Act[135] and Regulations[136] only regulate livestock feed; feed and feed ingredients manufactured in Canada for companion animals are not regulated specifically[135–137].
In addition to the legislation mentioned above, animal food, especially its importation into Canada, is regulated under the Health of Animals Act[138] and the Health of Animals Regulations[139] in order to prevent introduction of animal diseases into Canada. The Health of Animals Act[138] states in Article 64 that regulations are to be made by the Governor of the Council to regulate the "construction, operation and maintenance of […] animal food factories" and "importation, exportation, preparation, manufacturing, preserving, packaging, labelling, storing, distribution, sale, conditions of sale and advertising for sale of products of […] animal food factories". Those corresponding regulations are laid down in the Health of Animals Regulations[139]. Details on for instance record keeping requirements are given in Section 171 of the Health of Animals Regulations[139] along with recall procedures in Section 170.1 or on animal food containing prohibited food materials. Since medicated feed contains animal food as a basis, the regulations laid down in the Health of Animals Act and Regulations[138,139] apply as well.
The Feeds Act and Regulations[135,136] regulate amongst other things the registration or approval procedures of feeds for livestock, the manufacturing, sale, importation or exportation of any feed that presents a risk of harm to human or animal health or the environment, prescribing standards for feed manufacturing and feed safety, packaging, labelling and analysing feed.

4.2.1.1. DEFINITIONS

4.2.1.1.1. DRUG

Pursuant to the Food and Drugs Act[133], the term 'drug' includes "any substance or mixture of substances manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, (b) restoring, correcting or modifying organic functions in human beings or animals, or (c) disinfection in premises in which food is manufactured, prepared or kept"; each drug is assigned to one or more so called "Schedules", pursuant to the Food and Drug Regulations[134], and the Controlled Drugs and Substances Act[140], which set out the status of the drug, i.e. for instance whether it is classified as prescription drug, over-the-counter-drug, narcotic etc.[141].

4.2.1.1.2. MEDICATING INGREDIENTS AND MEDICATED FEED

Pursuant to the Feeds Regulations[136], medicated feed is defined as "a mixed feed that contains a medicating ingredient"[136]. A medicating ingredient is "a substance that is

intended for use in the prevention or treatment of disease in livestock, or a substance, other than feed, that is intended to affect the structure or any function of the body of the livestock and that has assigned to it a drug identification number (DIN) pursuant to the Food and Drugs Act"[133,136]. Livestock is defined in the Feeds Act[135] as "horses, cattle, sheep, goats, swine, foxes, fish, mink, rabbits and poultry and […] such other creatures as may be designated by regulation as livestock for the purposes of this Act".

Medicated feed can either be produced based on a formula belonging to the manufacturer and used for sale to every interested purchaser ("medicated feed"), according to a formula, where the feed is manufactured pursuant to a written order signed by the purchaser, which states kind and amount of each single ingredient feed to be used by the manufacturer ("medicated feed customer formula") or based on a formula formulated and manufactured by a seller in order to meet the requirements of a specific purchaser and that is not intended for resale ("medicated feed consultant formula")[136,142]. Additionally, there is the option of "veterinary prescription feed". A "veterinary prescription" is defined in the Feeds Regulations[136] as "an order prescribing a medicated feed made in writing by a veterinarian licensed to practise in the province in which the feed is to be fed to livestock", and the medicated feed manufactured in accord with this prescription is therefore defined as "veterinary prescription feed". There are some differences regarding the regulatory framework of medicated feed and veterinary prescription feed, which are set out in the following.

4.2.1.2. LICENSING OF MEDICATING INGREDIENTS

The competent authority responsible for the licensing of the drugs used in medicated feed is "Health Canada", while the Canadian Food Inspection Agency (CFIA) is responsible for ensuring livestock feed manufactured, sold or imported into Canada to be safe, effective and labelled correctly[135,143]; the main responsibilities regarding inspections and control of medicated feed lie with the CFIA as well[129], along with the registration of feeds and feed ingredients, the development of feed-related policies and the management of publications such as the Compendium of Medicating Ingredient Brochures (CMIB)[129].

The feed used as a basis for producing medicated feed or veterinary prescription feed is manufactured under the regulations of the Feeds Act[135] and Feeds Regulations[136] and under the Health of Animals Act[138] and Regulations[139]. Table 4 of Schedule I of the Feeds Regulations[136] lays down minimum and maximum contents for several nutrients; as long as a livestock feed's guaranteed nutrient levels comply with the ranges set out in this table, the feed is exempt from registration[136]. Feeds manufactured for exportation are widely exempt from the requirements set out in the Feeds Regulations[131,136]. All other feeds need to be registered besides "any brand of medicating ingredient premix listed in the Compendium of Medicating Ingredient Brochures"[136] (CMIB) and veterinary prescription feed as long as the prerequisites associated with veterinary prescription feed are met[136]. Medicated feed to be used in new drug clinical testing (pursuant to Section C.08.005 of the

Food and Drug Regulations[134]) is exempt as well from the Feeds Act[135] and Feeds Regulations[136].

The medicating ingredients have to be authorised in Canada in accordance with the Food and Drug Regulations[134]. For new drugs the manufacturer has to file a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission or an abbreviated extraordinary use new drug submission pursuant to Sections C.08.002, C.08.002.01 or C.08.002.1[134]; only if under Section C.08.004 or C.08.004.01 of the Food and Drug Regulations[134] a notice of compliance to the manufacturer of the new drug in respect of the submission has been issued, the drug receives a drug identification number (DIN). If the drug intended for use as a medicating ingredient is not a new drug, the manufacturer of the drug or a person authorised on their behalf, or, in case of an imported drug, the importer has to apply for a DIN in accord with Section C.01.014.1[134], where the required information in order to receive a DIN are set out in detail.

4.2.1.3. GOOD MANUFACTURING PRACTICE

There are no mandatory Good Manufacturing Practice Guidelines (or similar guidance) in place in Canada regarding the manufacturing of feeds in general or of medicated feeds in particular. The CFIA references the "Code of Practice on Good Animal Feeding"[144], conformance to which is not mandatory neither for the industry nor for the government; it contains, along with guidance on good animal feeding practices at farm level, guidance on good manufacturing practices regarding animal feed and feed ingredients for food producing animals[145]. The CFIA states in a "Discussion Paper on Modernizing Canada's livestock feed regulations"[145] that the Feeds Regulations[136] currently in place do not comprise all aspects addressed in the Code of Practice on Good Animal Feeding[144]; therefore, adherence to the Good Manufacturing Practices set out in the Code of Practice on Good Animal Feeding[144] currently cannot be enforced against feed manufacturers.

Regarding the manufacturing of the drug component of medicated feed, on the other hand, there are Good Manufacturing Practices[146] in place, established by the Drug Good Manufacturing Practices Unit of the Health Products and Food Branch Inspectorate of Health Canada. Since the guidelines[146] do not constitute a part of the Food and Drugs Act[133] or its associated Regulations[134] and are only intended to facilitate compliance with the applicable legislation, the Food and Drugs Act[133] and Regulations[134] supersede the guidelines in case of inconsistencies[146]. Nevertheless, compliance with the guidelines is mandatory unless appropriate scientific justification for a deviating approach can be given[146].

4.2.1.4. REGISTRATION OF MEDICATED FEED MANUFACTURERS

Feed business operators (except rendering facilities which require a permit to manufacture rendered animal by-products) do not need a license, registration or authorisation in order to

place feed on the market[137]. It only depends on the product manufactured whether an individual authorisation or registration for the product is required[137]. Importers of feed do not need a specific license as well, but are required to adhere to all Canadian Acts and Regulations pertaining to their product[137].

4.2.1.5. RESPONSIBILITIES OF MEDICATED FEED MANUFACTURERS

In accordance with the Feeds Regulations[136] and the Food and Drug Regulations[134], medicating ingredients can be added to animal feed either as active substance in a "drug premix" or "dilute drug premix" (a drug premix that is "diluted" by mixing it with feed to a level that at least 10 kg of the resulting mixture is required to medicate one ton of complete feed; therefore, this term is more or less equivalent to the term "intermediate product" used in the European Union) pursuant to Division 1 AC.01A.001.(1) of the Food and Drug Regulations[134] or as part of a so-called "micro-premix"[136]; mixed feed, i.e. a feed containing two or more single ingredient feeds, as well as mineral feed can contain medicating ingredients[136].

The Compendium of Medicating Ingredient Brochures (CMIB)[147] lists the medicating ingredients (the vast majority being antimicrobials, followed by coccidiostats and deworming agents) which are permitted to be incorporated into livestock feed without the prescription of a veterinarian as long as the requirements indicated in the respective Medicating Ingredient Brochure (MIB) are met[128,147]. The MIB specifies the species of livestock, the medication level and feeding directions as well as the purpose for which each medicating ingredient may be used legally. Additionally, the brands approved for use in Canada are listed, together with drugs compatible with the medicating ingredient and the type of animal feed to be used to add the drug to. All the medicating ingredients listed in the CMIB[147] have a drug identification number (DIN), which is unique for each product produced by each company[134,137], and are approved for use by Health Canada[148], whose Veterinary Drugs Directorate "evaluates and monitors the safety, quality and effectiveness, sets standards, and promotes the prudent use of veterinary drugs administered to food-producing and companion animals"[149]. If any of the specifications made in the MIBs are not met, e.g. the dosage specified is to be exceeded, a veterinarian's prescription is mandatory in order to manufacture the respective medicated feed[128,147].

So as to comply with the Feeds Regulations[136] all medicated livestock feed imported, manufactured or sold in Canada must adhere to the standards set out in the CMIB[147] unless the feed is a veterinary prescription feed (a feed manufactured pursuant to a veterinary prescription)[148]. Conformably to the "Regulatory Guidance on prudent use of veterinary drugs in livestock feeds (RG-7)"[148], feed manufacturers have to ensure that any medicating ingredient used in the preparation of medicated feed complies with the CMIB[147] or the veterinarian's prescription, whichever applicable. Additionally, they must ensure that any medicating ingredient used in the manufacturing of a medicated feed, including medicating ingredients supplied by a compounded product, originates from a drug that is approved for sale by Health Canada, for instance bears a DIN[148].

Medicated livestock feeds must be labelled as per the requirements of the Feeds Regulations[136]. The slightly varying labelling requirements for the different types of medicated feeds and veterinary prescription feed are shown in Table 3.

Table 3: Comparison of some of the labelling requirements for the different types of medicated feeds and veterinary prescription feed according to Regulatory Guidance RG-1 Chapter 4.1 Labelling of Livestock Feeds[142]

Labelling Requirement	**Medicated Feed**	**Medicated Feed Costumer Formula**	**Medicated Feed Consultant Formula**	**Veterinary Prescription Feed**
Brand name	Optional	Optional	Optional	Optional
Feed name	✓	✓	✓	✓, must include name and amount of medicating ingredient
Form of Feed (if other than mash)	✓	✓	✓	✓
Type of livestock the feed is intended for	✓	✓	✓	✓
Name and level of medicating ingredient	Per Medicating Ingredient Brochure (MIB)	Per MIB	Per MIB	Per Veterinary Prescription
(Approved) Claim	Per MIB	Per MIB	Per MIB	Per Veterinary Prescription, if any
Additional information	Registrant's Name and Address (if registered) **or** Name and Address of Manufacturer or Person who caused it to be manufactured (if not registered) and Registration	Name of the Supplier of the Formula and Name and Address of the Supplier of the Feed	Name and Address of Purchaser of Feed; Name and Address of the Manufacturer or Person who caused it to be manufactured	Name of Person for whom the Feed was manufactured; Name of Veterinarian who issued Prescription; Name and Address of Manufacturer

Labelling Requirement	Medicated Feed	Medicated Feed Costumer Formula	Medicated Feed Consultant Formula	Veterinary Prescription Feed
	number of feed (if required)			
Statement "This feed contains added selenium at xx mg/kg)" *	If selenium is added	–	If selenium is added	If selenium is added
Guaranteed analysis	✓	–	✓	✓
Required guarantees per table 3 of Schedule I of the Feeds Regulations[136] for the specified feed type	✓	–	✓	✓
Complete list of ingredients (if required for feed type) or statement, that list may be obtained from manufacturer or registrant	✓	–	✓	✓
Directions for Use	Per MIB for medication level/claim	Per MIB for medication level/claim	Per MIB for medication level/claim	including duration of use as per veterinary prescription
Warnings	Per MIB for medication level/claim	Per MIB for medication level/claim	Per MIB for medication level/claim	Per Veterinary Prescription
Cautions	Per MIB for medication level/claim	Per MIB for medication level/claim	Per MIB for medication level/claim	Per Veterinary Prescription

Labelling Requirement	Medicated Feed	Medicated Feed Costumer Formula	Medicated Feed Consultant Formula	Veterinary Prescription Feed
Notes	If required by MIB for medication level/claim	If required by MIB for medication level/claim	If required by MIB for medication level/claim	–
BSE statement if feed contains "prohibited material" **	If applicable	If applicable	If applicable	If applicable
Net Weight (kg)	✓	✓	✓	✓

* Selenium Caution(s) if selenium is added: "Directions for use must be carefully followed" (all species) and "Do not use in association with another feed containing supplemental selenium" (ruminants only)
** "Feeding this product to cattle, sheep, deer or other ruminants is illegal and is subject to fines or other punishment under the Health of Animals Act."

The general labelling requirements for medicated feed comprise the name and address of the registrant (if the manufacturer is registered; otherwise the name and address of the manufacturer or the person who caused the medicated feed to be manufactured[142]), the registration number of the feed, if required (registration of a feed is only required in cases of manufacture outside of Canada, mineral or converter feeds, micro-premixes, forage additives and other specialty feeds, milk replacers, fox feeds, single ingredient feeds listed in Part 2 of Schedule IV or V of the Feeds Regulations[136] or if the nutrient guarantee levels labelled do not meet the ranges indicated in Table 4 of Schedule I of the Feeds Regulations[136])[142], the name and, if applicable, brand of the feed, the net amount, the guaranteed analysis in respect of the feed, the amount of added selenium, if applicable, directions (on the label or an insert within the package) for safe and effective use for users without special knowledge regarding purpose and use of the feed, and, depending on the type of feed (referred to in Table 3 of Schedule I of the Feeds Regulations[136]) used as a basis for the medicated feed, either the name of each ingredient or the statement that a list of the ingredients can be obtained from the manufacturer, the particular form of the feed, if it is not a mash, and an identification number in case of a micro-premix or a whole milk replacer for livestock[136]. In direct association with the feed name the name and actual amount of the medicating ingredient used for preparation of the medicated feed in accordance with the CIMB[147] have to be indicated as well as the claim(s) applicable to the medicating ingredient, the level of the medicating ingredient present in the feed and the type of livestock for which the feed is intended[136]. Any other information, notes, directions for use or warning and caution statements indicated in the CIMB or necessary to convey useful information for the user of the feed must be presented under or next to the heading, if applicable, with the words "Warning" or "Mise en garde" or "Caution" or "Précaution", respectively, in bold print and every caution or warning statement clearly separated from

any other such statement or other information on the label[136]. In case selenium is added, there have to be special selenium cautions on the labels stating "Directions for use must be carefully followed" (all species) and "Do not use in association with another feed containing supplemental selenium" (ruminants only)[142]. In case the feed contains "prohibited material", the following statement regarding transmissible spongiform encephalopathies must be labelled: "Feeding this product to cattle, sheep, deer or other ruminants is illegal and is subject to fines or other punishment under the Health of Animals Act."[142].

When a manufacturer produces medicated feed with different medicating ingredients or medicated feed along with non-medicated feed, there is the risk of carry-over of drug residues from the produced medicated feed to the feed next in line, when the same production equipment is used and no physical cleaning of the equipment occurs between manufacturing of different feed types. This could harm species that are sensitive to the drug residues they consume (e.g. ionophores in horses[150]), conduce to antimicrobial resistance and cause drug residues in food products[116]. In order to reduce the risk associated with cross-contamination of feeds by drug residues the CFIA has developed guidelines "to permit the production of medicated and non-medicated feeds in cross-utilized equipment, where feeds containing medications are followed only by feeds intended to contain those same medications, or by feeds where residual levels of the carry-over medications present an acceptable risk"[116]. Feed manufacturers producing medicated feed must follow these guidelines in order "to be considered in regulatory compliance"[151]. The CFIA holds the opinion that flexibility in production sequencing is to be tolerated if the impact on animal and human health is as minimal as possible, since they claim this strategy to be "internationally acceptable as it is generally recognized that thorough cleaning of feed manufacturing and distribution equipment following every batch of medicated feed is impractical"[152]. Nevertheless, it is not accepted by the CFIA to add feed containing unintended medication (for instance residues from the previous production process) to other feed for food-producing animals, even if that feed contains the same active substance[152].
Consequently, the CFIA deems those sequencing guidelines a practical approach, since, to their opinion, the use of dedicated equipment or physical equipment cleaning is not always practical and therefore the risk associated with drug carry-over is considered acceptable "in cases where there is no negative impact on animal or human health"[116], i.e. when the feed next in line after producing a medicated feed is used for animals specified in the "Medication Sequencing Guideline for Management of Drug Carryover"[116]. For the most recent updates of this guideline a specific "Drug Ranking Model" taking into account several parameters such as oral availability of a therapeutically active agent and its terminal half-life in order to estimate accumulation in edible tissues of livestock as well as information from feeding trials on transfer factors of drugs to milk or eggs was developed and used as a basis for establishing a sequencing order[116,151]. If the sequence of feed production is acceptable pursuant to the Medication Sequencing Guideline[116], no specific cleanout procedures have to be carried out. Only if the correct sequencing order in accordance with the guidelines cannot be achieved, the equipment used for the manufacturing has to be cleaned either by flushing or by other physical cleanout

procedures[116]. The document "Medication Residues Validation Testing Procedures for Equipment Cleanout Procedures"[153] provides information on how to validate equipment cleanout procedures in order to meet company standards and applicable regulations. The validation procedures are focussed on the final processing step(s), since it is considered from a risk perspective that the desired feed safety outcome is associated with the final feed product[153]. For medicated feeds there are clear specifications for the desired feed safety outcome set out in Section 14 (b) of the Feeds Regulations[136], which state that only medicating ingredients of a brand, at a level or for a species or purpose as set out in the corresponding CMIB are allowed to be contained in a medicated feed unless it is veterinary prescription feed, where the prescribing veterinarian can set out deviations from the CMIB deliberately. If appropriate feed sequencing in accordance with the Medication Sequencing Guideline[116] is not an option, validation of the specific cleanout procedures is mandatory[154]; there is no universally accepted validation method since manufacturing practices and equipment used vary widely and scientific information regarding appropriate cleanout is scarce[154]. The effectiveness of the cleanout procedures needs only be validated once as long as no significant changes are made to the equipment cleaning procedures (e.g. regarding the type or amount of flush material used) or to the manufacturing equipment[153]. The written equipment cleanout validation testing procedures must contain the drug carry-over management strategy, which may not only consist of production sequencing standards[153]. For validation purposes, a scenario typical for production procedures with a higher risk within the facility should be used, such as use of a drug with a specified withdrawal period, drugs with known issues regarding toxicity or drug handling characteristics or situations where feeds with various drug concentrations are produced (e.g. medicated complete feeds manufactured directly after medicated premixes containing much higher concentrations of the respective drug)[153]. Information is given regarding how the testing procedures are to be carried out and which drugs cannot be used in validation testing due to interference issues in the analytic tests[153].

The "Measurement of Feed Carryover Level"-Guidance Document[155] determines the methodology how the feed manufacturers have to "consistently and accurately measure feed carryover level", i.e. the contamination of a feed with another material or feed that originates from previous use of the same equipment. The measurements have to be carried out at least every ten years as well as after every major repair or change of manufacturing equipment. Written documentation and records have to be kept regarding the procedures for determination of carry-over, the verification records of the carry-over tests and the equipment maintenance records[155].

The Feeds Regulations[136] require the feed manufacturer to be able to demonstrate their ability to produce homogenous feed (a feature especially important in the production of medicated feed in order to not over- or under-medicate the animals to be treated). According to the CFIA's Guidance Document "Developing Scale and Metering Device Calibration and Verification Procedures"[156], this obligation can be fulfilled by either testing the weighing equipment for accuracy in accordance with the requirements set out in the

corresponding Guidance Document[156] or by analysing "a statistically valid number of feed samples […] to confirm label guarantees are met"[156]. The applicable in-service limits of error for the scales and metering devices used in the production of (medicated) feed are set out in the Divisions VI and XI of Part V of the Weights and Measures Regulations[157].

The CFIA's Guidance Document Repository[158] sets out some key points regarding the tasks feed manufacturers have to fulfil to in order to pass inspections unobjectedly. For instance they have to provide written procedures regarding mixer performance testing; these testing procedures which have to be carried out every one to three years depending on the risk profile of the facility and within 90 days after changes to the mixing equipment (e.g. a new or replacement mixer) are described in the Guideline Document "Developing Mixer Performance Testing Procedures"[159].

Pursuant to Section 170.1 of the Health of Animals Regulations[139], every person responsible for import, manufacturing, packaging, labelling, storing, distribution or (advertising for) sale of livestock feed has to establish and implement effective recall procedures for the livestock feed[160]. Those recall procedures have to be laid down in written form and records including mixing formula and mixing sheet, distribution records and invoices as well as recall records are to be kept[160].

4.2.1.6. VETERINARY PRESCRIPTION FEEDS

If the medicated feed is manufactured according to a veterinary prescription, the prescription is supposed to contain the information required by the Food and Drug Regulations[134]. The veterinarian has to ensure that the drug prescription for food-producing animals will not lead to harmful or violative residues in food and additionally conforms to other regulatory requirements in accordance with the Feeds Regulations[136] and the Food and Drug Regulations[134]. Veterinary prescription feed is permitted only for therapeutic use[134]. It is possible to use the same prescription over a longer period of time (e.g. one year) and for successive batches of feed, which was pointed out during an audit[161] carried out in Canada by the Food and Veterinary Office of the European Commission in 2011, since Section 5(g)(ii) of the Feeds Regulations[136] only lays down that the amount of medicated feed manufactured may not exceed the amount consumed by the animals prescribed to consume the feed during the prescription period, but does not elaborate on a maximum prescription period.

A medicated feed is exempt from complying with the standards set out in the CMIB[147] only if the medicated feed has been manufactured pursuant to a veterinary prescription and if, amongst other criteria, the source of the medicating ingredient prescribed and used in the medicated feed is in compliance with the Feeds Regulations[136] and with the conditions set out in Section C.08.012 of the Food and Drug Regulations[134]. There it is indicated that "a person may sell a medicated feed, pursuant to a written prescription of a veterinary practitioner, if all drugs used in the medicated feed as medicating ingredients have been approved for sale by the competent authority Health Canada, i.e., each drug has either a

valid DIN or has been permitted for sale through an Investigational New Drug (IND), an Emergency Drug Release (EDR), or an Experimental Studies Certificate (ESC)[134,148]. Veterinary prescription feed may only be sold, if the animals intended for treatment are under the direct care of the veterinary practitioner who signed the prescription and the medicated feed is for treatment only[134,148].

Veterinary prescription feeds manufactured do not need to be registered as long as they are authorised for sale in conformity with the above mentioned Section C.08.012 of the Food and Drug Regulations[134] and "the amount of feed manufactured does not exceed the amount that would be normally consumed by the number of animals prescribed to receive the feed during the prescribed period of medication, […] the veterinary prescription pursuant to which the feed is manufactured is signed by the veterinarian who issued it and the prescription contains […] information" on the issue date of the prescription, name and address of the person for whom the feed is manufactured and by whom it is intended to be used, name and inclusion level of the prescribed medicating ingredient, the type and amount of feed to be manufactured, the number, kind, class and age or weight of the livestock intended to be fed the feed[134,136]. Furthermore, "special manufacturing instructions including necessary mill clean-up warnings, if any, feeding instructions or directions for use of the feed including the period of medication during which the feed is to be fed to the livestock, and warning statements and caution statements, where applicable" have to be contained in the prescription, along with a statement signed by the person who is supposed to use the veterinary prescription feed[136] (which is usually the livestock farmer). This assertion indicates that the person is aware of all feeding instructions, directions for use, caution and warning statements pertaining to the use of the medicated feed; the affirmation is not needed in cases where the prescription is directly issued to the manufacturer by the veterinarian and the veterinarian is "satisfied that the person for whom the prescription was issued was adequately aware of the information set out on the prescription"[136]. When all these prerequisites are met and the feed manufacturer is in the possession of the prescription prior to delivering the – correctly labelled – feed, the veterinary prescription feed does not need to be registered[136].
The manufacturer is obliged to keep a copy of the veterinary prescription during the production of that feed (except in case of emergency, where the prescription together with a written and signed explanation of the nature of the emergency[162] must only be in the manufacturer's hands prior to delivering the feed) and shall retain it together with the mixing formula used and a list of each date of manufacture of that feed for the period of one year from the last date of manufacture of the respective prescription feed[136].

The labelling requirements pursuant to the Feeds Regulations[136] for veterinary prescription feeds are compared to those for other medicated feeds in Table 3. Declaration of a lot-number (be it of the feed or the drug within) on the label is not required[134].

4.2.1.7. ON-FARM MIXING

The Feeds Act and Regulations do not have special provisions for on-farm mixing; therefore, on-farm manufacturing of medicated feed is regulated the same way as commercial feed mills and on-farm mixing of medicated feed is also part of the National Feed Inspection Program[145,163].

4.2.1.8. RESPONSIBILITIES OF THE LIVESTOCK FARMER

In general, neither Health Canada nor the CFIA are responsible for on-farm controls regarding acquisition, storage and use of veterinary medicinal products (including medicated feed); therefore, livestock farms are only obliged to keep treatment records or similar proof of usage of veterinary medicinal products, if they are enrolled in one of the (non-obligatory) certification programmes such as the "ractopamine-free pork certification program" (developed by the Canadian pork industry) or the "equine lot program" by the CFIA[161]. Livestock farmers may be inspected as part of a post-sale compliance monitoring within the frame of the National Feed Inspection Program[163].

There are some provinces (e.g. Ontario) that have developed a voluntary programme for livestock farmers called "Advantage Good Agricultural Practices" that helps farmers set out a manual containing all the procedures and records needed to ensure food safety as a "whole farm approach"[164] which is also applicable regarding the manufacturing and use of medicated feed on-farm.

4.2.1.9. INSPECTIONS

The CFIA carries out inspections in accordance with its Compliance and Enforcement Operational Policy[165] which lays down the principles guiding the CFIA's feed inspectors. They assess compliance with regulatory requirements and usually seek a cooperative approach with the regulated party[166]. The CFIA's National Chemical Residues Monitoring Program Report[167] showed that in 2012/2013 approximately 97.5% of the food samples of animal origin tested for veterinary drug residues were compliant; the majority of non-compliant samples resulted from commodity-drug combinations without set maximum residue limits. On the other hand, other programmes such as the CFIA's Medicating Ingredients Guarantee Verification Program, showed that in the years 1995/1996 and 2006/2007 42% of medicated feed samples from on-farm mills and 22% from commercial mills contained medicating ingredients exceeding the amounts guaranteed on the label[168]. The Drug Residue Contamination Inspection Program, which monitored unintentional drug residues in non-medicated feed during the years 1991/1992 and 2006/2007, revealed residues in approximately 20% of samples tested from commercial and on-farm feed mills[168]. This shows the need for thorough inspection of feed mills, be it on-farm or commercial.

The main approach of CFIA's feed inspectors when verifying compliance with the regulatory framework in commercial feed mills is the "Compliance Verification System[166]". The tasks (e.g. on-site observations, interviews, and reviews of procedures and records in order to assess compliance with the regulatory requirements) carried out by the CFIA's inspectors are consolidated in the document "Compliance Verification System Feed Mill Verification Task Procedures"[169]. Every task procedure sets out the frequency it must be performed in by the inspectors, furthermore the activities to be conducted to assess regulatory compliance and indications on non-compliant objective evidence regarding the respective task[169]. In case of non-compliance the inspectors request the feed mill operator to commit to a corrective action plan to fix the problem and to prevent reoccurrence and they also verify the correct implementation of the plan; if the plan is unsuccessful or the manufacturer unable or unwilling to correct the problem, stronger enforcement options in accord with the Compliance and Enforcement Operational Policy[165] are put into action[166]. Currently, there are 21 tasks specified in the Compliance Verification System for Feed Mills[169]. On-farm feed manufacturers and livestock farmers are inspected pursuant to the National Feed Inspection Program[163] which includes an on-farm feed inspection component as a form of post-sale compliance monitoring. The CFIA inspectors confirm during their on-farm visits that livestock feeds contain only approved ingredients in accordance with Schedules IV and V of the Feeds Regulations[136], furthermore, if applicable, contain only approved medications at the correct levels, for the intended purpose and for the intended species or class of livestock as well as no harmful levels of chemical and biological contaminants, including drug residues[170]. Although for some species such as fish more antimicrobials are approved for use in Canada, the CMIB does not list all of them[171]. Since the national sampling program targets the drugs listed in the CMIB, several drugs used in medicated fish feed are not sampled at all by the CFIA in spite of their representing a majority of all drugs prescribed and administered via fish feeds (for example in the Atlantic Area of Canada 65% of the drugs used even are unapproved, such as Emamectin Benzoate or "off-label" drugs such as Ivermectin)[171].

4.2.1.10. IMPORT AND EXPORT

In pursuance of the Feeds Regulations[136], medicated feed imported into Canada has to abide by all standards set out in the CMIB, unless the feed is a veterinary prescription feed, in which case it has to comply with the veterinary prescription[148,172]. Regarding the importation of veterinary drugs, it is possible to import veterinary drugs for "personal" use with hardly any regulatory oversight ("own-use-importation"); the importation of active pharmaceutical ingredients is not very strictly controlled either[172]; details on the requirements for those ways of importation of veterinary drugs are given by Health Canada in a Guidance Document on the Import Requirements for Health Products under the Food and Drugs Act and its Regulations[173].

In accordance with Section 3(a) of the Feeds Regulations[136], medicated feeds produced for export purposes are exempt from the regulations for medicated feed for domestic use.

4.2.2. PROVINCIAL LEGISLATION

Provincial legislation is superseded by federal regulation. Every province has its own control body and provincial laws may only be more stringent, but not more lenient, than federal regulation[174].
Regarding the medicated feed regulatory framework, it can mainly be affected by provincial laws governing the veterinary profession or by acts or regulations pertaining to drug prescription such as pharmacy and drug acts and regulations.
If no specific provincial laws are set out, solely the federal law applies which means that all veterinary drugs not listed in the Food and Drug Regulations[134] are regarded as non-prescription drugs[175] and can therefore be purchased by every person without the need for a veterinary prescription or a valid veterinarian-client-patient relationship (VCPR).

4.2.2.1. ALBERTA

The Authorized Medicine Sales Regulation[176] which is enacted by the Animal Health Act[177] regulates who, aside from pharmacists (governed through the Pharmacy and Drug Act[178] and Regulation[179]) and veterinarians (regulated by the Veterinary Profession Act[180] and Veterinary Profession General Regulation[181]), may acquire a license to sell authorised veterinary drugs pursuant to the regulation. Medicated feed in general is exempt from this regulation as long as it is either in accordance with the CMIB[147] set out by the CFIA or manufactured pursuant to a veterinary prescription[182] and in accordance with the Feeds Act[135]. Still, non-prescription medication such as many antimicrobials may be purchased by livestock farmers from licensed persons authorised pursuant to the Authorized Medicine Sales Regulation[182] and used in their livestock animals via for instance feed[183]. The Drug Schedules of Alberta are similar to the national model, especially with regard to Schedule I and II drugs, i.e. drugs that need prescription or are to be sold in a pharmacy; only Schedule III drugs are currently listed to a lesser extent in Alberta than on the federal level[184].

4.2.2.2. BRITISH COLUMBIA

British Columbia's Drug Schedules Regulation[185], enacted by the Pharmacy Operations and Drug Scheduling Act[186], lists drugs (including antimicrobials) that may be sold in British Columbia for use in animals without requiring a veterinarian's prescription[128]. The province adopted the National Drug Scheduling System[187] in 1998, but still the drug scheduling decisions have to be approved by the College of Pharmacists of British Columbia[188], which causes a waiting period between the national and provincial implementation[184].

The British Columbia Veterinary Drugs Act[189] and the British Columbia Veterinary Drug and Medicated Feed Regulation[190] lay down the issuing of diverse licences regarding the sale of veterinary drugs and medicated feed. These regulations do not affect the sale of veterinary drugs by pharmacists or registered veterinarians[191].

A limited medicated feed licence comprises the right to sell, but not manufacture, medicated feed in accord with the Veterinary Drug and Feed Regulation[190].

A medicated feed licence, which is subject not only to the Veterinary Drug and Feed Regulation[190], but also to the Feeds Act[135] and Regulations[136], authorises the licence holder to manufacture and sell medicated feeds which contain veterinary drugs listed in the most recent edition of the CMIB and which comply with the other prerequisites set out in the respective MIB[190]. Furthermore, the licensee is entitled to manufacture veterinary prescription feeds containing veterinary drugs listed in the most recent CMIB, but with strengths exceeding those authorised there[190]. Additionally, the licence holder may manufacture and sell medicated feeds containing "veterinary drugs listed or described in Part II, Schedule F of the Food and Drug Regulations[134]". Since Schedule F of the Food and Drug Regulations[134] has been repealed in 2013[192], but the latest amendment (January 19, 2015) of the Veterinary Drug and Feed Regulation[190] still refers to that Section, it can only be assumed that this regulation shall still be applied by analogy.

Neither for the limited medicated feed licence nor for the medicated feed licence there are any prerequisites set out as to which categories of persons are allowed to buy such a licence.

In addition to those licences concerned with medicated feed directly, there are two other types of licences, the veterinary drug licence and the veterinary drug dispenser licence. A veterinary drug licence can be acquired by holders of a limited medicated feed licence or a medicated feed licence, by operators of registered hatcheries, persons living in areas where professional veterinary or pharmaceutical advice is not available or by persons deemed appropriate by the Minister of Agriculture, upon advice of the Advisory Committee on Veterinary Drugs[190].

A veterinary drug licence allows for selling injectable biologicals for disease prevention or treatment (exceptions are set out in the regulation), antibiotics and sulphonamides for livestock animals (again, Schedule F of the Food and Drug Regulations[134] is referenced, which has been repealed in 2013) including drug preparations listed in the current edition of the CMIB; furthermore, specific vitamin and mineral preparations, growth promotants, anti-cannibalism compounds for poultry, disinfectants, and some other drug preparations are listed and can be sold by veterinary drug licensees without a veterinary prescription[190].

The homepage of the Ministry of Agriculture of the Province of British Columbia, confusingly, still references Schedule A Table 1 and 2 of the Veterinary Drug and Medicated Feed Regulation[190], which has been repealed in 2009; these tables list all the drugs permitted to be incorporated in medicated feed and to be sold by veterinary drug licence holders. The reason why schedules already repealed are still referenced in current British Columbian legislation could not be fathomed.

All holders of one of the licences mentioned above are required to record all purchases of medicated feed that have been imported for sale from another province or another country, or all drug and/or biological purchases as received in the Veterinary Drug Purchase Register[190,193]. The purchase records include the date of purchase, name of supplier, quantity purchased, the generic name, trade name and name of the manufacturer of the drug[128]. The original copy of the Veterinary Drug Purchase Register must be forwarded to the Chief (Provincial) Veterinarian annually[190,193].

The veterinary drug dispenser licence is only issued after the person applying for it has passed an examination about properties, correct use and abuse of veterinary drugs and information on related topics[193]. It is normally valid for five years and has to be renewed by re-examination after the five-year-period or earlier at the request of the chief (provincial) veterinarian[193]. Every medicated feed licensee and veterinary drug licensee is obliged to have a licensed veterinary drug dispenser on the premises during working hours of the business and the chief (provincial) veterinarian is to be notified of any changes such as ceasing to have a veterinary drug dispenser or having a different or additional veterinary drug dispenser on the premises[190].

4.2.2.3. MANITOBA

Manitoba relies completely on federal legislation regarding the regulatory framework of medicated feed[174]. Drug scheduling is based solely on the National Drug Scheduling System[184,187].

4.2.2.4. MARITIME PROVINCES

The maritime provinces New Brunswick, Nova Scotia and Prince Edward Island do not have further province-specific legislation regarding medicated feed aside from acts governing veterinarians[174]. All three of them have adopted the National Drug Scheduling System[187] ("scheduling by reference"); changes become immediately effective in these provinces[184].

4.2.2.5. NEWFOUNDLAND AND LABRADOR

Newfoundland and Labrador have adopted the National Drug Scheduling System[187], though all scheduling decisions have to be approved first by the Newfoundland and Labrador Pharmacy Board[194], thereby causing a delay of approximately three months in the national scheduling decisions' becoming effective[184]. The Animal Health Regulations[195], enacted by the Animal Health and Protection Act[196], set out in Section 10 the conditions for the sale of antibiotics for animal use, thereby stating that antibiotics used as a medicating ingredient in accord with the Feeds Act[135] are exempt from the sales restrictions laid down in this Section.

4.2.2.6. NORTHWEST TERRITORIES

The Northwest Territories do not have any legislation more stringent and specific for medicated feed on the provincial level, aside from the Veterinary Profession Act[197] governing veterinarians working in the province. Drug scheduling is carried out by reference to the National Drug Scheduling System[184,187].

4.2.2.7. NUNAVUT

Regarding the drug schedules, Nunavut has adopted the National Drug Scheduling System[187] with scheduling changes becoming immediately effective[184]. This has been laid down in the Consolidation of the Drug Schedules Regulations[198], which is enacted by the Pharmacy Act[199]; the veterinary profession is regulated under the Veterinary Profession Act[200].

4.2.2.8. ONTARIO

In the province of Ontario the sale of veterinary drugs is regulated through the Animal Health Act[201] which sets out amongst other things the licensing for the sale of over-the-counter drugs by non-veterinarians. Pursuant to the Drug and Pharmacies Regulation Act[202] Section 155.(02), drugs that are listed in Schedule I of the Drug and Pharmacies Regulation General[203] may be sold by retail as long as they are sold in a container labelled by the manufacturer as for veterinary or agricultural use or sold in a form unsuitable for human use. Schedule I drugs in accord with the Drug and Pharmacies Regulation General[204] are drugs listed in Schedule I of the manual published by the National Association of Pharmacy Regulatory Authorities entitled "Canada's National Drug Scheduling System"[187] in its most recent edition, furthermore drugs listed for veterinary non-prescription use (former schedule F of the Food and Drug Regulations[134] – in the current version of the Drug and Pharmacies Regulation General[204] of Ontario it is still referred to though it has been repealed in 2013) and the substances listed in the Schedules I – VIII of the federal Controlled Drugs and Substances Act[140]. The veterinary profession is governed through the Veterinarians Act[205] and Veterinarians Regulation General[206].

4.2.2.9. QUÉBEC

The province of Québec has a more restrictive regulatory framework compared to the federal regulations or to other Canadian provinces. Manufacturing, distribution and sale of medicated feed or the respective medicate premixes require a special permit in accordance with Section 55.2 of the Animal Health Protection Act[174,207]. In contrast to other provinces, it is mandatory for a medicated feed manufacturer not only to hold the permit mentioned, but also to obtain and keep a veterinary prescription as a prerequisite to sell medicated feed[174]. The only exception in accord with Section 55.3 of the Animal Health Protection Act[207] is the preparation of medicated feed for a person's own animals without the obligation to hold a permit as long as the animal owner prepares a maximum of one kilogram or one litre of medicated feed[174,207] or the animals or their products are not intended for human consumption or fur production[207].

The sale of veterinary drugs, regardless which type of drug, is restricted to veterinarians and pharmacists; there are no options in the legislation to license lay persons for selling veterinary drugs[174] (unless they are prepared as a medicated feed). Three acts, the Pharmacy Act[208], the Veterinary Surgeons Act[209] and the Animal Health Protection Act[207] pertain to

the sale of veterinary drugs[174]. Veterinary drugs are distinguished between the ones that may only be sold under a veterinary prescription and therefore require a VCPR, whereas others may also be sold in a veterinary office[174]. The Regulation respecting the terms and conditions for the sale of medications[210], which is enacted by the Pharmacy Act[208] and the Veterinary Surgeons Act[209], contains five annexes; the Schedules I to III list drugs for humans, Schedule IV determines which drugs may only be sold under veterinary prescription and Schedule V lists those which must be sold in a veterinary office[174,210].

In consequence of the more stringent provincial legislation in place in Québec, the National Drug Scheduling System[187] is not adopted by the province of Québec, nor appear there to be plans to adopt it in the near future[184].

4.2.2.10. SASKATCHEWAN

The province of Saskatchewan does not have special provincial legislation regarding medicated feed, but relies solely on the regulations imposed federally[174]. The National Drug Scheduling System[187] has been adopted in 1998, but currently the implementation of scheduling changes still needs approval by the Saskatchewan College of Pharmacy Professionals[211], though legal changes to adopt the model of "scheduling by reference" are currently taking place[184].

4.2.2.11. YUKON

Very recently, in April 2015, the Yukon government has adopted a new Pharmacy and Drug Act[212], which has not come into force yet. This act permits the sale of non-prescription veterinary drugs (and therefore also medicated feed in accordance with the Food and Drugs Act[133] and Feeds Act[135]) by any person as long as they comply with the pertaining acts[212]. Pursuant to the currently in force Yukon Pharmacists Act[213] and the Drug Regulation[214], the National Drug Schedules System[187] was adopted in 2010; therefore drugs are scheduled by reference and, consequently, changes are immediately effective[184]. In accord with the Pharmacists Act[215] and the Drug Regulation[214] drugs unscheduled in the National Drug Schedules System[187] may be sold by any person.

4.3. FUTURE LEGAL SITUATION IN CANADA

The last complete renewal of the Feeds Regulations[136] occurred in 1983, and of the Food and Drug Regulations[134] in 2005. Since then only amendments to the existing regulations have been made, but no major changes. The CFIA as well as representatives of the Canadian feed industry agree in the opinion that a modernisation of the existing legislation regarding not only feed, but also medicated feed is necessary[216,217].
In the 1990s the CFIA had already consulted extensively with representatives of the Canadian feed industry and livestock producer organisations and they had developed a

proposed set of Medicated Feed Regulations, which intended to introduce process controls for the manufacturing of feeds containing medicating ingredients[217]. In 2008, a regulatory initiative and extensive consultation on a proposal to introduce new controls respecting the manufacture of medicated feeds was elaborated[145], but not yet integrated in the current legislation.

In 2011, the CFIA initiated a systematic, multi-year review of the regulatory frameworks for food safety, animal health and plant health with the intention to identify overlaps and redundancies, increase the ability to respond faster to industry changes, to address possibly existing weaknesses, gaps and inconsistencies and to provide flexibility and clarity to the regulated parties[217,218]. The current product-based and pre-market-approval-oriented regulatory feed framework, which relies on a mixed approach of prescriptive, systems-based and outcome-based regulation, is supposed to be replaced by a modernised, more risk- and outcome-based approach[217], which was identified by the CFIA to be a short-term (i.e.one to three years) priority[145,218] and is supposed to attain the most effective and efficient balance between fair and competitive trade in the market and to minimize the regulatory burden while safeguarding feeds and the food production continuum[145]. The CFIA started the development with a stakeholder survey and stakeholder workshops in order to have all parties concerned participate in the process of developing a new regulatory framework[218]. A main basis and starting point for the discussion with the stakeholders was the United Nation's and World Health Organization's Code of Practice on Good Animal Feeding[144], which also contains some guidance on good manufacturing practice, as well for on-farm as commercial feed and ingredient production[217]. The survey indicated, amongst other things, support for higher levels of control or oversight for medicated feeds compared to non-medicated feeds[217]. The stakeholders also agreed that issues regarding medicated feeds, including antimicrobial resistance, residues in food, and alternatives to antimicrobials will have a high future impact which, at least to some extent, can be controlled and therefore is of high importance in the development of a new regulatory feed framework[218]. The working group of the stakeholder workshops concerned with medicated feed identified some risks in the current legislation which should be abolished within a new regulatory framework in a joint effort of the government and the industry: they complained about the inability to access new, useful drug products such as alternatives to antimicrobials, the (to their opinion) irrelevant and impractical near-zero residue testing, an improper mixing of medicated feeds produced at farm level and the resulting over- and under-medication of feeds[218]. One risk the elimination of which lies within the responsibility of the government was identified to be the lack of Canadian oversight of active pharmaceutical ingredients and own-use importation of drugs[218]. Furthermore, aside from risks regarding medicated feeds, some risks in other more general areas to be addressed in the new regulatory framework such as feed labelling and feed ingredients, process and product controls, efficacy of for instance "novel" ingredients or ingredient claims, enforcement and harmonisation of the legislation were identified[218].

Main parts of the proposal are constituted of so called "preventive control plans (PCP)", with seven major elements[217]:

- product and process control
- sanitation, biosecurity, and pest control
- hygiene, biosecurity, and employee training
- equipment design and maintenance
- physical structure and maintenance
- receiving, transportation, and storage
- recalls, complaints, and record keeping

In order to supervise those elements the PCP for feeds produced and distributed in Canada are supposed to implement monitoring procedures to determine whether a control measure is effective, verification procedures to show whether the control measures are operating as intended and planned corrective actions in case validated controls are ineffective at controlling a hazard or the regulatory requirements are not met[217]. Furthermore, the person responsible for the implementation of the monitoring, verification and corrective action activities has to be identified along with training requirements and individual competencies and the frequency of delivering those activities and the person responsible[217]. Frequency and kind of record keeping as well as retention time of records have to be determined[217]. Livestock producers who produce livestock feeds on-farm and are not generally exempted from the new regulations (livestock farmers producing feeds only for their own animals and not using medicating ingredients in their feeds are subject to exemption) are only supposed to have minimised forms of a PCP and therefore also a minimised regulatory burden, dependent on the individual risk the products manufactured on their farms pose[217]. Importers will be required to have at least the first and last element of the PCPs in place, i.e. process and product controls and traceability, recall and complaint procedures or all seven elements, risk-based and depending on further activities such as e.g. re-packaging, whereas exporters will have to meet the respective foreign regulatory requirements[217].

The CFIA regards the PCP as a more comprehensive approach than the more commonly used term HACCP (Hazard Analysis and Critical Control Points), which is currently used in Canada as well in the Food Safety Enhancement Program[219,220] as in the Quality Management Program[221] for fish and seafood[217]. The CFIA states that the intent of a HACCP is solely focused on food safety risks, whereas a PCP needs to address (within the scope of the regulatory framework) hazards to animal or plant health and the environment as well[217]. The proposal of the CFIA postulates several performance criteria for the seven elements of a PCP laid down in the annex to the proposal[217] which could act as a guidance for the regulated parties regarding which aspects to address in preparing their PCP.

The Animal Nutrition Association of Canada, which is the national trade association of the livestock and poultry feed industry and whose members allegedly represent 90 percent of commercial feed manufactured in Canada[222], has postulated in its 2010 policy paper "The Case for Modernization of the Canadian Feeds Regulations"[216] to register facilities based on their risk-safety-profile rather than focus on registration of feeds not meeting nutrient levels pre-set in the Feeds Regulations[136]. To their opinion, the registration could be based on the CFIA's already existing four-level risk ranking system for facilities, which is based

on the deemed level of animal health risk and the degree of medication risks in the feeds produced[216]. Currently, this risk ranking system is used in the CFIA's Compliance Verification System[166] in order to identify the necessary inspection frequency of a facility. Nevertheless, this approach for a mandatory registration of facilities in a tiered approach depending on the individual risk of the feeds produced and feed ingredients used or type of livestock the feeds are intended for, is currently not incorporated in the CFIA's proposal[217].

The Agricultural Growth Act[223] which has been tabled in the Canadian parliament by the Minister of Agriculture and Agri-Food in 2013 contained the amendment of several federal agricultural statutes, including the Feeds Act[135,217]. The amendment pertaining the Feeds Act[135], which came into force on the 27th of February 2015, authorises the CFIA to make regulations respecting quality management and quality control programmes, safety programmes, PCPs or similar programmes and therefore enables the CFIA to not only mitigate public health risks, but to also address hazards to animal or plant health or the environment specifically[217]. Therefore, it can be expected that the regulatory feeds framework will proceed from the form of a mere proposal to an amendment of the existing legislation or maybe even to a new, auxiliary statute in addition to the existing regulatory framework. But still, there are no major changes to the current approach regarding medicated feeds to be found in the proposal, since no effort seems to be made to put medicated feeds in general under the control of veterinarians by making them prescription-only and the closure of "loopholes" such as the own-use importation of drugs for use in e.g. the livestock farmer's own animals and importation of active ingredients is currently not addressed specifically in the proposal. Furthermore, there are some drugs with a MIB (such as e.g. virginiamycin or ractopamine for growth promotion) and therefore permitted to be incorporated into medicated feeds and sold over-the-counter; those drugs are, according to the Final Report[161] of an audit to evaluate the monitoring of residues and the controls on VMPs carried out by the Food and Veterinary Office of DG SANCO, banned in other regions such as the European Union and are not available there, even under prescription.

5. DISCUSSION

As the European Union, the United States of America, and Canada do not have the same approaches regarding their regulation of medicated feeds, not every difference can be compared. Especially the fact that the EU's current legislation allows for very different interpretations in the member states and that medicated feed in Canada is handled slightly differently in the provinces and not regulated entirely on the federal level makes comparing rather complex. Therefore, the comparison will focus mainly on differences on the federal level, taking into account member states' or provincial level only where it seems necessary or appropriate.

MARKETING AUTHORISATION

Regarding the necessity to have the veterinary medicinal product (or drug, respectively) authorised before it may be incorporated into medicated feed, there is not much difference between the EU, the USA and Canada. They all postulate a marketing authorisation in accord with the national or community-wide legislation, respectively, for the veterinary medicinal product/drug used, but neither of them requires the medicated feed as a finished product to have a marketing authorisation of its own.

GOOD MANUFACTURING PRACTICE

In all, the United States of America have the strictest approach, since the cGMP rules are mandatory with more detailed standards for feed manufacturers who require a MFML than for those without one, whereas Canada's rules are the laxest. In Canada, the Code of Practice on Good Animal Feeding[144] as a model for GMP rules is only referenced, but not mandatory and can therefore not be enforced. The EU Directive 90/167/EEC[11] demands that manufacturers abide by the Good Manufacturing Practice Rules the respective member state has in place. In consequence, no GMP rules have to be complied with, if the member state does not have those in force, which is the case with a few of the EU member states. Hence, the GMP rules' requirements the medicated feed manufacturers have to adhere to in the EU vary considerably from none effective to the same extent of detailed regulations veterinary medicinal product manufacturers have to abide by.

In the author's opinion, mandatory GMP rules do not only help to improve quality standards of the medicated feed manufactured, but as well to increase predictability for the feed manufacturers regarding compliance to the regulatory framework by giving clear advice as to which standards to adhere to. Therefore, the USA's approach appears to be favourable.

APPROVAL OF MANUFACTURING FACILITIES

The EU has set out in Council Directive 90/167/EEC[11] that only manufacturers approved previous to starting production of medicated feed are permitted to do so and gives details on which aspects have to be covered by the pre-approval inspection. The USA have a different approach in so far as they differentiate between drugs used for the medicated feed

which oblige the manufacturer to apply for a MFML and others that do not. The MFML application form obligates the manufacturers to make several commitments regarding the correct manufacture, labelling and record keeping, but no pre-approval inspection by the competent authority is required. Canada neither licenses nor approves feed business operators, independently of what type of feed, including medicated feed, is produced. Only certain types of feed need to be registered, but medicated feeds produced in accordance with the CMIB or a veterinary prescription do not number among those.

Therefore, the EU has the strictest regulations and Canada the most lenient, whereas the United States' legislation is somewhere in between. Since the increase in antimicrobial resistance is a perceived concern, it appears recommendable to identify potential issues impeding correct and safe production of medicated in advance, which favours the EU's strategy.

VETERINARY PRESCRIPTION

In the EU medicated feed may only be sold upon a prescription[11], either by a veterinarian only (as in Germany[44]), a pharmacist, or, as for instance in the United Kingdom[37], by "suitably qualified persons", depending on the veterinary medicinal product's status; there are no exceptions to that rule. In the United States, under the current regulatory framework, the majority of medicated feeds contain over-the-counter drugs that do not need veterinary oversight in any respect. A few drugs that are considered to need veterinary oversight are classified as Veterinary Feed Directive Drugs[98]. The resulting VFD feeds require a valid VCPR and a VFD by a licensed veterinarian before they may be issued to an animal holder. By the end of 2016 all drug sponsors are supposed to have changed the status of antimicrobials used in medicated feeds that are considered of high importance to human medicine from OTC to VFD drugs. In consequence, those VFD feeds may only be used for therapeutic indications, not for production purposes.

In Canada, all medicated feeds that are produced in accordance with the CMIB[147] are available over-the-counter for animal owners. Only if a deviation from the contents of the CMIB is intended, e.g. the authorised concentration of medicating ingredient is supposed to be exceeded, a veterinary prescription is needed[134]. In those cases, a valid VCPR is required and the veterinary prescription feed may only be used for therapeutic indications.

Currently, the United States of America and Canada appear to have similarly lenient approaches as to how easily medicated feeds can be accessed by animal owners without veterinary prescription or oversight, whereas the EU is very strict regarding the aspect that each and every medicated feed sold must have been prescribed by a veterinarian. Still, in some European countries such as the United Kingdom, this prerequisite is handled slightly differently: some veterinary medicinal products and therefore some medicated feeds can be prescribed by not only veterinarians and pharmacists, but also by so-called suitably qualified persons who must have proven their knowledge on the subject by an examination. By the end of 2016, the United States will have an approach a bit more similar to the one

of the European Union in the way that many antimicrobials incorporated into medicated feed will only be available as VFD feed; still, some medicated feeds containing antimicrobials will be available over-the-counter and be allowed to be used for production purposes.

As most medicated feeds contain antimicrobials (of varying importance to human health) it is crucial, according to the author's judgment, to have professional oversight over not only the indication for treatment, but as well correct dosage and treatment duration of medicated feed. Therefore, mandatory veterinary prescription for medicated feeds containing antimicrobials appears utterly necessary. The approach the European Union has taken applied in the strictest sense, i.e. veterinary-only prescription, without permitting exceptions such as "suitably qualified persons" etc., seems highly recommendable.

USE OF ANTIMICROBIALS FOR GROWTH PROMOTION

Antimicrobials have been used in sub-therapeutic dosages for growth promotion purposes since their respective potential was discovered in the late 1940s[224]. Depending on the husbandry conditions, antimicrobials at low doses were found to be able to increase growth rate and/or feed conversion efficiency as well as improve egg production in laying hens or increase milk yield in dairy cows[224]. The mechanism of action of the growth promoting potential of antimicrobials is not clearly understood until today[225,226]. Nevertheless, it could be shown that the growth promoting properties of low-dose antimicrobials are most effective under suboptimal management conditions, since improved nutrition or hygiene management and reduced intensity of husbandry conditions reduced or eliminated the growth promoting effects[174,227–229]. Additionally, the use of antimicrobial growth promoters has been shown to contribute to the development of antimicrobial resistance[224,225,229,230]. Similar to the use of antimicrobials as growth promotants, antibiotics are used in prophylactic ways, i.e. as preventative treatment of healthy animals that are stressed or in other ways potentially susceptible to disease[228]. Metaphylactic use, on the other hand, means treatment of clinically healthy animals belonging to the same herd or flock as animals showing clinical signs. The intention of this approach is to treat infections before those animals become clinically ill and to try to shorten the treatment period for all animals[228]. All the application areas mentioned use antimicrobials in clinically healthy animals, an aspect that makes their use in this context (especially for growth promotion and prophylactic purposes) at least questionable according to the author's view considering the efforts needed to minimise antimicrobial usage in all areas of application in order to try to reduce the potential for emergence of antimicrobial resistance.

In the European Union the use of antibiotics for production purposes such as growth promotion has been banned completely in 2006[67]. The hurdles for having claims for preventative use of an antimicrobial approved have been set high by the European Medicines Agency and the need for prevention must be justified individually for every single target species and indication in order to ensure compliance with prudent use

principles[231]. Even a claim for metaphylactic use must be thoroughly discussed and can only be approved in conjunction with a treatment claim[231].

In the United States of America, the planned status change of many antimicrobials will probably at least reduce the amount of antimicrobials used for growth promotion purposes. Nevertheless, since those claims will not be banned completely for all antimicrobials, though, this approach as well might only shift the usage of those antimicrobials needing a VFD in the future towards those still available over-the-counter. This might reduce the selection pressure for antimicrobial resistance for the VFD drugs, but there will still be antimicrobials left used at sub-therapeutic dosage that might contribute to overall bacterial antimicrobial resistance. Extralabel use of antimicrobials via feed is not permitted, not even for veterinarians, therefore prophylactic or metaphylactic use of VFD drugs is only possible if a valid claim exists[232].

In Canada, the approach regarding the usage of antimicrobials for production purposes is not intended to be changed in the near future. Therefore, no improvement of the potential problems associated with antimicrobial use for growth promotion can be perceived.

With regard to the world-wide increasing threat for human as well as animal health by antimicrobial resistance, the European Union's approach to totally ban growth promotion usage of antimicrobials and at least scrutinise potential prophylaxis or metaphylaxis claims for antimicrobials appears, in the author's opinion, to be the most consequent approach to try to reduce the contribution of deliberately sup-therapeutic and overall antimicrobial treatment to the emergence of antimicrobial resistance. The USA's strategy appears to be at least less stringent, while Canada currently does not even make a half-hearted attempt to curb antimicrobial usage for production purposes. This hesitancy is probably due to "socio-economic arguments (e.g. costs and convenience)" as was stated by the "Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health" (established by Health Canada) in a report on the use of antimicrobials[174].

ON-FARM MIXING

On-farm mixing is allowed pursuant to all three legislative frameworks, though it has been abolished in some EU member states such as Germany. If on-farm mixing is permitted, the on-farm mixers are subject to the same approval, registration and inspection procedures as commercial feed mills in the EU as well as in the United States of America and Canada.

INSPECTIONS

Directive 90/167/EEC[11] obliges the member states to ensure compliance with the rules by carrying out sampling checks at all stages of production and marketing and by inspecting not only the feed mills, but also (especially) farms and slaughterhouses to make sure conditions of use of medicated feeds and withdrawal periods are abided by. Both Germany and the United Kingdom whose implementations of the directive[11] were examined more closely in this thesis have chosen a risk-based approach regarding the inspection frequency

with all facilities having to undergo official inspection regularly, but in varying intervals depending on their risk profile.

In the United States, licensed feed mills are inspected once every two years by the FDA and additionally in case of specific incidences such as for instance adulterated feed, though a more risk-based approach regarding the inspection frequency is stipulated by the FDA Safety & Innovation Act[111]. Non-licensed feed mills are not inspected at all by the FDA, but they might be subject to inspections by state officials, dependent on state legislation.

Canada inspects feed mills as well as on-farm mixers as part of various National Inspection Programmes such as the National Feed Inspection Program[163] or the Medicating Ingredient Guarantee Verification Program[168]. However, since medicated feed samples are only examined for medicating ingredients listed in the CMIB[147], it appears to be not very likely that undesired drug residues of drugs not listed are found in the first place – still, for instance in aquaculture, those non-listed drugs or drugs used off-label represent the majority of drugs prescribed and administered via fish feed[171]. Therefore, it does not seem likely considering these circumstances that violations of the current regulations will be detected via sampling of medicated feed.

In comparison, the EU has the strictest approach in demanding risk-based inspections of all medicated feed manufacturers, whereas the USA only inspect licensed feed mills regularly, while non-licensed mills which are considered to pose less of a risk are only inspected if state laws stipulate this. Canada's approach appears similar to the one in the EU at first sight, but taking into account that only approved drugs are considered when sampling feeds or animal products for residues, this shows a more or less large gap in the likelihood of detecting violations.

As mentioned above, it appears necessary, in the author's opinion, to ensure the correct and safe production of medicated feed in accordance with the set standards. This renders regular inspections (though in a risk-based frequency) which are compulsory for all facilities producing medicated feed, necessary, thus favouring the approach implemented by the European Union.

IMPORT

The EU Council Directive 90/167/EEC[11] stipulates that member states do not impede the intra-union trade of medicated feed. Safeguard measures and veterinary controls may be put in place, but may not prohibit trade within the community with medicated pre-mixes and medicated feed. Imports from third countries have to fulfil at least the requirements laid down in Directive 90/167/EEC[11] – Germany and the United Kingdom have both resorted to prohibiting third country importation.

The United States of America permit importation of medicated feeds or of the drugs used for the production of such only, if the drugs have an approved NADA, an abbreviated or

conditional NADA, or an investigational new animal drug exemption, otherwise the products are considered adulterated and therefore violating US law.

In Canada, medicated feed can be imported as long as it is compliant with all standards set in the CMIB or is conformable with a veterinary prescription. In addition, it is possible to import veterinary drugs for own use with comparatively little regulatory oversight[173].

In all, the three approaches are quite similar as to that they require the imported veterinary medicinal products or medicated feed to comply with the standards set in the country of destination. Nevertheless, Canada could be considered to have the most lenient approach, since the "loophole" of own-use-importation[173] and other such ways allow for importation of drugs without much regulatory oversight. As opposed to that, many EU member states have chosen a very strict path in prohibiting third country importation completely.

In the author's view, it might be sufficient regarding safety aspects to permit third country importation as long as the specific domestic standards for medicated feed of the importing country or region can verifiably be met and "loopholes" as in the Canadian legislation are reliably excluded. Whether it is economically reasonable to permit third country importation of medicated feed or not is a separate question that is not part of this thesis and shall therefore not be addressed at this point.

FUTURE LEGAL SITUATION

With regard to the future situation, the EU is going to take an approach which is somewhere in the middle between the current situation in the member states with the strictest and the laxest interpretation of Directive 90/167/EEC[11]. The resulting regulation proposal is additionally taking aspects into account which had not been addressed at all by the current legislation, such as medicated feed for pets (the necessity and reasonableness of which is currently discussed controversially[58,233–235]). The United States of America are going to tighten their medicated feed legislation somewhat by increasing the number of drugs requiring a VFD. With Canada, there seems to be no fundamental change planned with regard to how the access to medicated feed is regulated, even with respect to antimicrobials and in spite of the current discussions about antimicrobial resistance; only the self-monitoring obligations for the medicated feed manufacturers will increase remarkably compared to the current regulations.

In the author's opinion, it appears sensible to harmonise the standards in the European Union. This will facilitate market access for sponsors, which improves the realisation of economies of scale and consequently reduces production and treatment costs of medicated feed. Furthermore, feed safety will be enhanced in member states with currently lower standards. Treatment correctness might increase in all member states as not only mixing homogeneity is ameliorated in countries with currently more lenient legislation, but less accurate treatment options such as "top-dressing" might be repressed in high-standard countries in favour of (high-quality) medicated feed, if medicated feed is more readily available at reasonable costs due to economy of scale for the manufacturers. It would have

been desirable that the United States of America and especially Canada had found a more ambitious way to renew their medicated feed legislation and to address the current concerns regarding the spreading of antimicrobial resistance by further tightening their regulatory framework.

6. CONCLUSION

As a result, it can be stated that, in its entirety, even the current state of legislation in the European Union with its quite large variations between member states appears to be the strictest regarding the requirements for the involved parties if compared to the legal framework in the United States of America and Canada. Although the regulatory framework might become slightly more lenient in some EU member states and more stringent in others if the regulation proposal in its current state enters into force without major revision, it still will have higher requirements than those that are planned to come into force in the United States of America by end of 2016. On the other hand, the changes planned for the Canadian legislation in the near future will continue to constitute a much less stringent regulatory framework than the European Union's proposal and will nonetheless be more lenient than what is contrived for the USA.

As pointed out, the public and political awareness regarding antimicrobial resistance of bacteria has been increasing in the last years[236] and the use of antimicrobials (especially those deemed of high medical importance for human use) in the treatment of animals is presently under scrutiny for being regarded by many parties as one of many factors potentially contributing to the increase of antimicrobial resistance around the world[236–244]. It remains to be seen whether the adjustments to the current legislation as planned in the United States of America and Canada, but also those proposed for the European Union will be sufficient in the future in order to strive against those issues and be able to guarantee human as well as animal health.

7. SUMMARY

In animal husbandries housing large numbers of animals, the use of medicated feed is a common treatment option in many countries. Medicated feed consists of a compound feed as a carrier and one (or more) veterinary medicinal product(s). The resulting ready-to-use feed can be offered to large groups of animals to be treated simultaneously.

The European Union regulates this type of medication in Council Directive 90/167/EEC[11] which came into force in 1990. The directive had to be implemented into national law in every EU member state. Since the directive was never substantially amended and the national implementations were highly divergent, the EU recently decided to replace the directive by a regulation that will then be immediately binding in all member states at once. The proposal for this new regulation is currently on its way.

The present thesis aims at comparing the regulatory framework in the EU with the regulatory approach in other countries, i.e. in the United States of America and Canada, and at uncovering differences as well as similarities.

In general, the three regions or countries developed rather different ways to deal with the regulatory topic "medicated feed". While in the EU every member state found its own interpretation, the USA regulated medicated feed on federal basis, whereas in Canada there is federal law that can be complemented by provincial legislation. These facts make a detailed comparison rather complex.

Overall, the EU appears to have the strictest legislation including mandatory approval and regular risk-based inspections of manufacturing sites, compulsory veterinary prescription of medicated feed, and a complete ban of antimicrobial usage for growth promotion purposes. The Canadian legislation, on the other hand, appears to be the most lenient, with neither pre-production approval of medicated feed manufacturers nor regular inspections aside from those carried out within the frame of some national inspection programmes which do not mandatorily include all medicated feed manufacturers. Most medicated feeds are available over-the-counter as long as they comply with some pre-set requirements; the use of medicated feed for growth promotion is common and not planned to be banned anytime in the near future. The USA's current medicated feed regulation is somewhere in between the Canadian and the EU's approach in so far as they have a rather strict course of action regarding the implementation of Good Manufacturing Practices and the approval and inspection of (certain types of) medicated feed manufacturers, but the veterinary oversight over medicated feed is lacking, which is planned to be changed by the beginning of 2017.

By repealing Directive 90/167/EEC[11] and passing a new regulation similar to the current proposal the EU will tighten its regulatory framework in most member states (though it will be mitigated in some of them) and retain its position as region with the strictest medicated feed legislation amongst those compared within this thesis, an approach that appears to be

highly important regarding the potential threat of antimicrobial resistance which could be fostered by a lax legislation for medicated feed containing antimicrobials.

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DECLARATION

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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