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Ministerie van Landbouw, Natuur en Voedselkwaliteit

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To the Minister of Agriculture, Nature and Food Quality and to the Inspector General of the NVWA

Copy to the Minister for Medical Care and Sport

Advisory Report by the Director of the Office for Risk Assessment and Research on

the implementation of Regulations (EU) 2019/4 and (EU) 2019/6 in relation to antibiotic resistance

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Our reference
TRCVWA/2021/2721

Date
1 June 2021

Background

Regulations (EU) 2019/4 on the manufacture, placing on the market and use of medicated animal feed and (EU) 2019/6 on veterinary medicinal products will come into effect on 28 January 2022. These regulations include provisions specifically pertaining to antimicrobial agents, such as antibiotics. The regulations fall under the NVWA's enforcement mandate, and proper use of antibiotics has long been an issue requiring attention.

When it comes to antibiotic resistance, the various EU member states are in very different situations. The two aforementioned regulations will give national authorities some room to shape their own policies with regard to the use of antibiotics. Therefore, country-specific application of the regulations may be necessary to ensure good veterinary care while minimising the development and spread of antimicrobial resistance. Recital 4 of Regulation (EU) 2019/4 and Recital 8 of Regulation (EU) 2019/6 state that the aim is to ensure the best possible protection of human health from antibiotic resistance caused by the use of antibiotics in animals, while taking into account the consequences for livestock farms.

Both the Dutch government and the Dutch veterinary industry have recognised the risks inherent in increasing antibiotic resistance and have taken measures to limit the use of antibiotics in livestock farming to the maximum extent possible. Compared to the reference year 2009, the use of antibiotics in the Netherlands has decreased by 68% in broilers, 58% in pigs, 47% in dairy cattle and 44% in calves reared for veal in 2018 (Heederik et al., 2019). In 2019, further reductions of the 2018 percentages were realised: 2.2% in broilers, 4.9% in dairy cattle, 8.2% in pigs and 11.3% in calves reared for veal. All in all, the use of antibiotics has been reduced by almost 70% since 2009 (Heederik, 2020). The measures by which this reduction was achieved were based on the principles of "prudent use". These principles did not have the force of law and therefore had to be enforced through an indirect construction. This situation has now changed, because Regulations (EU) 2019/4 and 2019/6 were adopted in early 2019 and will apply

from 28 January 2022. The regulations cover veterinary medicinal products in general, but antibiotics, referred to as "antimicrobials" in the regulations, are an important component. The regulations translate the existing consensus on the prudent use of antibiotics in livestock farming into legislation that has been harmonised across the EU.

Regulations (EU) 2019/4 and 2019/6, together with Regulation (EU) 2019/5, form part of a set of three regulations that are clearly interrelated. Regulation (EU) 2019/4 deals with the manufacture, placing on the market and the use of medicated feed. Medicated animal feed is not used in the Netherlands at the time of writing, but because its use is legally allowed, the present advisory report will touch on this particular regulation. The provisions of the regulation may result in the NVWA having to enforce certain rules. The second regulation, (EU) 2019/5, governs procedures for the authorisation and monitoring of medicinal products for human use and forms the legal basis for the evaluation of medicinal products by the European Medicines Agency (EMA). This regulation does not relate to the Netherlands Food and Consumer Product Safety Authority (NVWA) duties and will not be discussed further in this advisory report. The third regulation, (EU) 2019/6, lays down rules for the manufacture, marketing authorisation, import, export, distribution, control and use of veterinary medicinal products. The regulation contains many detailed rules on the administration and use of antibiotics in animals reared for meat production. Enforcing all these regulations will be quite the challenge for the NVWA. This advisory report therefore focuses on the use of antibiotics in farm animals in accordance with Regulations 2019/4 and, more particularly, 2019/6.

Purpose
The purpose of this advisory report, which was drawn up at the behest of the Office for Risk Assessment & Research (BuRO), is to draw up a proposal for the practical definition by the NVWA of the tasks arising from the regulations, in such a way that the development and spread of antibiotic resistance will be prevented to the maximum extent possible, without compromising animal health and animal well-being in the process.

Strategy
Since 2002, antibiotic resistance in the veterinary industry and found in food has been monitored and reported on in the MARAN reports by Wageningen Bioveterinary Research and its predecessors. The NVWA has funded research on antimicrobial resistance carried out by the National Institute for Public Health and the Environment (RIVM) and the University of Amsterdam for many years now. The present advisory report was informed by insights into the emergence, development and spread of antimicrobial resistance gained from various fields of research, as well as by insights obtained from academic literature. These insights informed the potential measures formulated to control antimicrobial resistance, in particular, but they also came into play in the drafting of the section on current practices in livestock farming. In order to get an impression of the practical aspects of the problem, the writer joined inspections of a broiler farm, pig farm and veal farm.

The report discusses the treatment protocols and modes of administration in considerable detail, because a blanket and untargeted reduction in the use of antibiotics in livestock animals may have a negative impact on animal health and

animal welfare. Therefore, it is likely that changing the treatment methods will provide us with the best ways to obtain the desired therapeutic results while minimising the development of antibiotic resistance. The implications of the provisions of Regulations (EU) 2019/4 and 2019/6 for the NVWA's enforcement of rules regarding improvements to farm management that will help us control antibiotic resistance are examined from the combined perspective of public health, animal health and animal welfare. The report outlines the small number of methods available to us to prevent the transmission of antibiotic resistance from the agriculture sector to human health. The report then goes on to discuss obligations with regard to monitoring antimicrobial resistance and the use of antibiotics, as well as the labelling requirements and warnings stipulated in the regulations. Those recommendations that require policy-making assessments are addressed to the Ministry of Agriculture, Nature and Food Quality, whereas those recommendations that bear more relevance to the implementation and enforcement of rules are addressed to the Inspector General of the NVWA. In the appendix, those considerations and provisions of the regulations that pertain to antibiotic resistance are quoted. The citations come with annotations that explain in brief how the various provisions are relevant to and may have implications for the ministries drawing up the relevant policies, the NVWA and livestock farms.

Earlier drafts of this advisory report were submitted for consultation to inspectors who have experience of this subject in daily practice, and to experts both affiliated with and not affiliated with the NVWA's BuRO.

Findings and conclusions

- The main risk for the development of antimicrobial resistance is bacterial exposure to non-lethal concentrations of antibiotics. This is most likely to happen to farm animals when antibiotics are administered in drinking water or feed.
- As far as the prevention of antimicrobial resistance is concerned, the best way to treat a sick animal is to give it the highest dose that the animal can tolerate for the shortest amount of time in which the infection can be cleared.
- Once the new regulations come into effect, EU member states will be required to submit to the European Commission data on the sale and use of antibiotics in animal husbandry, on top of antibiotic resistance prevention data. In the Netherlands, this data is collected annually by the SDa, with the help of the various commercial parties.
- The manufacturers' current instructions for use do not always allow for the desired adjustments to the dosage protocol.
- It is absolutely vital to public health that veterinary use be prevented of antibiotics that are reserved for use in humans.
- By using systems that record antibiotic sales and administration volumes and benchmark values, we will be able to identify those livestock farms (e.g. veal farms) that administer more antibiotics than other such farms, as well as veterinarians who are more wont to prescribe antibiotics than their colleagues.
- In order to minimise the development of antimicrobial resistance, antibiotics for veterinary use must be supplied in exactly the right quantities, or alternatively, a watertight system must be designed for the disposal and destruction of left-over antibiotics.

- For flock treatments, direct administration of antibiotics to individual animals (e.g. by means of a repeater syringe) is preferable to the administration of antibiotics in drinking water or feed, unless it can be guaranteed that each animal receives the correct dose.
- The discharge of low concentrations of antibiotics in the form of left-over medicated feed or drinking water with residues in it, or through carry-over, must be prevented. Likewise, the spreading of manure containing antibiotics and the improper disposal of milk containing antibiotics are undesirable.
- We may be able to come up with measures to reduce the degree of antibiotic resistance selected by veterinary use of antibiotics that affects human health, but research is needed to determine whether such measures are cost-effective.
- Regulations (EU) 2019/4 and 2019/6 prohibit the use of antibiotics to counteract the effects of poor hygiene, inadequate animal husbandry, lack of care or poor farm management. These vaguely worded standards require further definition to help us determine whether a farmer is guilty of such practices.
- Microbiological criteria for the quality of animal feed may be a useful tool in preventing unnecessary exposure of farm animals to pathogenic micro-organisms.
- The provisions of Regulations (EU) 2019/4 and 2019/6 do not touch on control measures in the event of the emergence of forms of antibiotic resistance in farm animals that are undesirable from a human health point of view.

Recommendations

To the Ministry of Agriculture, Nature and Food Quality

- In consultation with manufacturers and suppliers of antibiotics and also with the Veterinary Antibiotic Policy Working Group established by the Royal Dutch Society for Veterinary Medicine (KNMvD), draw up guidelines designed to ensure that the instructions for use and formularies for the administration of antibiotics are in line with the latest scientific insights.
- Give the NVWA a way to authorise well-argued derogations from formularies and the guidelines issued by manufacturers.
- Continue to identify veterinarians who prescribe more antibiotics than is usual for their practice through the monitoring required under the Regulation, and consider on a case-by-case basis whether action is required.
- Require suppliers of antibiotics to deliver them in the prescribed quantities, or design and implement a watertight system for the disposal and destruction of left-over antibiotics.
- Take action, where necessary and in addition to the provisions of Regulations (EU) 2019/4 and 2019/6, to combat forms of antibiotic resistance in farm animals that are undesirable from a human health point of view.

Office for Risk Assessment & Research

Date
1 June 2021

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To the Inspector-General of the NVWA

- Oversee the implementation of flock treatment plans and flock health plans, paying special attention to farm hygiene and farm management in general.
- Monitor livestock farms that use more antibiotics over the years than other, similar farms, and monitor veterinarians who prescribe more antibiotics than colleagues who have similar practices.
- Consult policy-makers so as to require people in the livestock industry to administer antibiotics directly to animals by means of a syringe, rather than in their drinking water or feed, where possible.
- Draft enforceable standards for terms used in the regulations, such as "poor hygiene", "inadequate animal husbandry", "lack of care" and "poor farm management".
- Encourage the industry to use flock treatment plans and flock health plans so as to ensure that its methods are in line with Regulations (EU) 2019/4 and 2019/6.
- In consultation with the Ministries of Agriculture, Nature and Food Quality and Health, Welfare and Sport, draft an intervention policy for incidents in which forms of resistance are found that are rare but do pose a risk to public health.

In addition to the above recommendations, BuRO will investigate ways in which the spread of antibiotics via manure or milk from livestock farms can be minimised. Furthermore, in addition to the chain-of-responsibility assessment for animal feed, BuRO seeks to determine whether the setting of microbiological criteria for the quality of animal feed may help us minimise livestock animals' exposure to pathogenic micro-organisms, thereby reducing the need for treatment with antibiotics.

Yours faithfully,

Prof. A. Opperhuizen
Director of the Office for Risk Assessment and Research

SUBSTANTIATION

Antimicrobial resistance

The steadily increasing bacterial resistance to antimicrobial agents, commonly referred to as "antibiotics", is a widely recognised global public health problem, as it means that infectious diseases can no longer be controlled optimally (Andersson & Hughes, 2014; Chatterjee et al., 2018; Naylor et al., 2018). The administration of antibiotics results in antibiotic resistance when bacteria survive exposure to the antibiotics and adapt. They then become antibiotic-resistant to a greater or lesser extent. Bacteria that are resistant survive exposure to antibiotics and can therefore grow while sensitive cells die. This is how selection for resistance occurs. As with humans, the use of antibiotics to treat farm animals results in selection for resistance. Some of the resistance selected in the livestock industry finds its way into human pathogens (Ter Kuile et al., 2016; Mughini-Gras et al., 2019). In other words, bacteria that have become resistant through the use of antibiotics in the livestock industry may eventually transmit that resistance to human pathogens.

The treatment of infectious diseases is more expensive when a pathogen is resistant to the drug of first choice. Bacteria can be resistant to several or even nearly all antibiotics, prompting doctors to resort to methods which often come with more severe side effects, as well as other drawbacks, such as higher prices (Huebner et al., 2019). This means that, on the one hand, the patient will experience more severe symptoms and the therapy will be more expensive, while on the other hand, animal health and animal welfare may be compromised. A 2015 estimate suggests that antibiotic resistance across the EU costs an additional €1.5 billion in human healthcare expenditure, and also results in an estimated 33,000 avoidable deaths (EU, 2017; Cassini et al., 2019; Freitas et al., 2020). Doomsday scenarios have been drawn up in which, for example, 10 million people a year will die worldwide in the year 2050 from infections with antibiotic-resistant pathogens (IACG, 2019). However, an analysis of the development of the level of resistance in the Netherlands, as reported over the past years in the NethMap and MARAN reports, does not support such scenarios (Heederik, 2020; Veldman et al., 2020). In veterinary medicine, the percentage of antibiotic-resistant bacterial isolates is declining, and in the human healthcare, the percentage is more or less stable. In humans, avoidable deaths from infections with bacteria that cannot be treated due to antibiotic resistance are not reported, but there has been a slight increase in the use of drugs of last resort, which are only used if there really is no other way to treat a patient. The favourable trends in the veterinary medicine industry have resulted from significant improvements in the use of antibiotics in farm animals since 2007. This being the case, it will remain necessary for us to use antibiotics in a way that cures infections while only developing minimal antibiotic resistance.

All these factors combined make the treatment of a patient with an antibiotic-resistant pathogen more expensive than the treatment of a patient with an antibiotic-sensitive variant of the same type of infection. If the estimated number of 33,000 mortalities and €1.5 billion in additional healthcare costs were distributed proportionally across the EU, it would result in estimated additional costs of €50 million for the Netherlands, as well as an estimated additional 1,200 mortalities. Data that would allow us to make a better-informed estimate is not available and there is no consensus on the correct way to perform such estimates,

anyway (Dunachie et al., 2020). The only well-supported estimate of the cost to the livestock industry if no antimicrobial agents were available any longer due to antibiotic resistance or for some other reason is an American estimate of $60 per dairy cow per annum (Lhermie et al., 2018b;2018a). Extrapolating from this amount, we can estimate that the additional costs for the entire livestock industry in the Netherlands would run in the hundreds of millions of euros. The additional costs the veterinary medicine industry incurs at the present level of antibiotic resistance are unknown, but are believed to be a mere fraction of that amount. For the purpose of risk assessment, the risk to humans from veterinary use of antibiotics is defined as the additional morbidity and increased costs incurred by the human healthcare industry due to the use of antimicrobials in farm animals. This definition effectively forces us to adopt a "One Health" approach, whereby human healthcare and veterinary medicine are considered inseparable (Queenan et al., 2016). As a result, the Netherlands' antibiotic resistance prevention policy has been based on this "One Health" concept since 2015. For its part, the EU uses a similar approach. The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report (ECDC et al., 2017) was drafted from a One Health angle, as were the Dutch NethMap and MARAN reports on antibiotic use and resistance (Veldman et al., 2019).

Worldwide, between 50 and 80 per cent of all antibiotics are used for veterinary purposes (Cully, 2014). This has resulted in a high level of antibiotic resistance in agricultural micro-organisms and has indirectly resulted in a higher level of resistance in human pathogens. In a comparative study of antibiotic resistance levels measured in the United States, Denmark and Spain, it was found that bacteria in human faeces were most resistant to antibiotics authorised for veterinary use in the country where the donor of the faeces sample resided (Forslund et al., 2013). This observation is one of many indications that veterinary use of antibiotics selects for resistance in human pathogens. For a long time it was not possible to quantify the extent to which selection in the veterinary medicine industry contributes to the overall degree of antibiotic resistance in humans. Recently, it has been estimated on the basis of solid arguments that veterinary use of antibiotics has contributed approximately 20% to 25% to Extended Spectrum Beta-Lactamase (ESBL) resistance in hospital pathogens (Mughini-Gras et al., 2019). Most penicillin-type antibiotics are no longer effective against this type of bacteria.

Emergence, development and spread of resistance

Bacteria can become resistant to antibiotics in two ways:

1) De novo by exposure to non-lethal concentrations, after which the bacteria first adapt in terms of gene expression, while at a later stage, mutations occur in the DNA, leading to a high level of resistance.
2) Through the transfer of so-called resistance genes from bacterium to bacterium. These resistance genes are often situated on plasmids, i.e. circular pieces of DNA that replicate independently from the chromosome.

In both cases, selection for resistance occurs when bacteria are exposed to non-lethal amounts of antibiotics. At high concentrations, sensitive cells are killed before they can become resistant in either of the two ways outlined above (Handel et al., 2015).

Antibiotics are divided into so-called bactericidal agents, which kill bacteria, and bacteriostatic agents, which halt their growth. De novo resistance occurs when bacteria are exposed to concentrations of antibiotics that are not high enough to kill them in the case of bactericidal antibiotics, or to halt growth completely in the case of bacteriostatic agents. It appears that when bacteria survive exposure to antibiotics, they build up resistance to bactericidal agents faster than to bacteriostatic agents (van der Horst et al., 2011; Handel et al., 2014; Hoeksema et al., 2018). To survive exposure, bacteria must by definition have been in contact with concentrations lower than the minimum inhibitory concentration (MIC). Within less than an hour, the first changes in the expression of various genes occur, and after a few hours, the regulation of 100 to 200 genes is altered (Handel et al., 2013; Handel et al., 2014). The genes in question tend to be involved in the metabolism. The MIC increases by a factor of between 4 and 16, so that resistance can already be said to exist. After a few days at increasing but non-lethal concentrations, mutations occur that will lead to much greater resistance, at 100 to 10,000 times the original MIC (Handel et al., 2014; Hoeksema et al., 2019). This is more practically relevant than one might think at first, as even during a normal course of antibiotics the MIC of a pathogen can grow so high that the pathogen becomes antibiotic-resistant for clinical purposes (Feng et al., 2016). This form of de novo acquisition of resistance can occur wherever bacteria are exposed to non-lethal concentrations of antibiotics for whatever reason. We have no data on the degree to which this process plays a role in the emergence of antibiotic residence in farm animals, but it seems very likely that this process does play a part.

We do have numbers on how so-called resistance plasmids are involved in the spread of antibiotic resistance (Davies & Davies, 2010; Partridge et al., 2018). Plasmids are circular pieces of DNA that are not part of the chromosome, can replicate independently and are exchanged between bacteria. Many plasmids described in scientific literature contain genes that code for resistance to antibiotics. Several resistance genes have been identified for almost every type of antibiotic (Aminov, 2009). They can be transmitted via resistance plasmids. They spread most easily between related types of bacteria, but they do not necessarily have to be related (Partridge et al., 2018). The presence of antibiotics in the environment seems to slow down rather than promote transmission (Schuurmans et al., 2014; Handel et al., 2015). Plasmids containing resistance genes can be transferred under many conditions, as long as the recipient cell is viable. Two steps are necessary for a successful transfer: 1) The plasmid must be transferred from the donor cell to the acceptor cell and stay alive there. 2) The resistance genes on the plasmid must be expressed and selection for that particular type of resistance must occur so that the newly resistant cell can survive and grow, whereas the same bacteria without a plasmid cannot. After the transfer, the resistance gene must be able to be expressed to give it a selective advantage (Stepanenko & Heng, 2017). When that happens, the cell is more likely to survive when exposed to antibiotics so that selection takes place. Concentrations of antibiotics that do not kill the susceptible recipient cell, but do select for resistance, pose the greatest risk for transfer of resistance plasmids. These are by definition concentrations lower than the MIC of the recipient cell.

It follows from the above that concentrations lower than the MIC constitute an important risk both for de novo resistance and for the transfer of resistance plasmids (Ter Kuile et al., 2016; Llewelyn et al., 2017). Bacterial exposure in livestock farms to such concentrations is an inevitable consequence of all modes of antibiotic administration other than injections. When antibiotics are administered in drinking water, not all animals will receive the same dose, and moreover, antibiotics can precipitate in the pipes and then dissolve again. When antibiotics are administered in medicated feed, carry-over (cross-contamination) may occur, and top-dressing will result in uneven distribution. Antibiotic resistance starts building at very low concentrations. In the case of quinolones and fluoroquinolones it starts at less than 1% of the MIC (Gullberg et al., 2011). Most other antibiotics have a higher threshold, but selection for resistance commences at around 10% of the MIC (Andersson & Hughes, 2014; Hughes, 2014).

In summary, we must conclude here that concentrations of antibiotics below the so-called minimum inhibitory concentration (MIC), which is the lowest concentration that completely halts the growth of the bacteria, pose a grave risk for the development and spread of antimicrobial resistance (Ter Kuile et al., 2016; Llewelyn et al., 2017). Bacteria can be exposed to non-lethal concentrations of antibiotics through carry-over, under-dosing, spillage, uneven distribution of the antibiotic in top-dressed feed, to name but a few examples.

Targets and possible measures that may help us reduce the impact of antibiotic use in animal husbandry

When proposing measures to reduce the effects of antibiotic use in animal husbandry, a policy trade-off will have to be made between the benefits to public health on the one hand and animal health, animal welfare and the costs incurred by farmers on the other. It makes little sense to implement expensive measures in animal husbandry if we will not reap sufficient rewards in the form of improved human health. On the other hand, antimicrobial resistance also represents a cost for the livestock industry (Lhermie et al., 2018a). Animals stay sick longer, farmers may lose more animals and therapy will be more expensive. Therefore, the livestock industry itself also holds a stake in preventing the development and spread of antibiotic resistance. The financial value of this stake cannot be calculated with the data currently available. If all antibiotics were to become completely useless due to antimicrobial resistance, the cost to the Dutch livestock industry could amount to hundreds of millions of euros per annum.

As for the treatment of infections in humans, doctors have been required to minimise the amount of antibiotics they prescribe for many years now (Adriaenssens et al., 2011). The aim of the treatment protocols is to control the infection as well as possible without causing unnecessary antibiotic resistance or other unwanted side effects (Schuts et al., 2016). In the past, per-animal antibiotic administration rates in the Dutch livestock industry ranked among the highest in the EU. This resulted in a curious situation, whereby the efforts to use fewer antibiotics in human health care may have been cancelled out by the resistance transferred by livestock. The situation has improved significantly since the overall volume of antibiotics prescribed by veterinarians across the industry was reduced drastically after 2007. Further non-targeted reductions may compromise animal health and animal well-being. Therefore, now that we have reduced our overall antibiotic use, specific measures, such as sophisticated dosage

methods that prevent bacterial exposure to low concentrations of antibiotics, will be most effective in achieving therapeutic goals while minimising resistance.

The reduction by almost 70% in antibiotic use by the Dutch livestock industry in the ten years between 2009 and 2019 (Heederik, 2020; Veldman et al., 2020) has had a measurable impact on the degree of antibiotic resistance in the microbiota of farm animals. For the indicator organism *E. coli* collected from different sources, the percentage of resistant cells had declined by more than 50% by 2018, compared to the highest values measured in the years 2007-2011. Perhaps even more importantly, we have also witnessed a simultaneous decrease in resistance of *Salmonella* isolated in human beings. *Salmonella* infections are generally caused by contaminated food (Pires et al., 2014) and the treatment protocols for infections in humans did not change in the period under discussion. This suggests that this decrease in resistance levels is at least partly due to the reduction in veterinary antibiotic use.

As previously stated, the extent to which exposure to sub-lethal concentrations of antibiotics leads to the emergence and spread of resistance depends on the duration and frequency of that exposure (Andersson & Hughes, 2014). Reduced antibiotic use by lowering the dose causes more, rather than less, resistance because the pathogen is exposed to non-lethal concentrations. This means that, in addition to reducing the total number of times antibiotics are administered, improving the way in which the antibiotics are administered may also reduce the emergence of antimicrobial resistance. According to the latest insights, the best possible treatment is the highest infection-clearing dose that the patient, be they human or animal, can tolerate, for the shortest period of time (Ter Kuile et al., 2016; Llewelyn et al., 2017). In an earlier advisory report, BuRO recommended that, under the right circumstances, it should be possible to deviate from general instructions for use regarding the duration of the treatment and that a course of antibiotics should be able to be terminated earlier if the infection has been cleared. Legally, this is not possible in the present situation because patient information leaflets stipulate otherwise. It would be a good thing if the patient information leaflets could be revised in this regard, or if doctors or veterinarians were given the opportunity to deviate from the standard protocol. In addition to optimal treatment protocols, it is vital that livestock farmers avoid micro-organism exposure to low concentrations of antibiotics through carry-over, discharge, the spread of manure containing traces of antibiotics, etc.

It cannot be ruled out that at some point, veterinary use of antibiotics will reach a point where a further reduction will be contrary to the principles of animal welfare and animal health (Ferri et al., 2017). If, in order to minimise the use of antibiotics, infections are not treated in time, animals will suffer needlessly and their health will be impaired. This being the case, the development and selection of resistance and its transfer to humans must be reduced in a carefully considered manner. If infections are left untreated, or if the antibiotics are under-dosed, there will be a risk that the infections will spread. The Council on Animal Affairs has stated that a further reduction of the total volume of antibiotics administered to farm animals will then no longer be able to be achieved by treating fewer infections with antibiotics without compromising animal health and animal welfare (Stegeman & Schakenraad, 2016). The same report suggests three possible methods that may allow us to counteract the development and selection of resistance: 1) the prevention of infections through farm management measures

such as improved hygiene, 2) protection through vaccination, and 3) improved treatment protocols that clear the infection but are less selective for resistance. The purpose of such measures must always be to reduce the risk of bacterial exposure to sub-lethal concentrations of antibiotics.

Current use of antibiotics in poultry, pigs and calves reared for veal
Since 1 March 2014, antibiotics have had UDD status (to be administered only by veterinarians) and farmers are only allowed to stock and administer them themselves under certain conditions. Antibiotics must be included in the farm's flock health and flock treatment plan, which is a separate document drawn up by the farmer and the veterinarian in which common diseases and conditions are described, as well as the veterinary medicinal products to be used to treat them. Veterinarians must prescribe antibiotics and other prescription drugs separately from the farm's flock health and flock treatment plan. This requires a diagnosis. However, farmers may start to treat the animals themselves in the event that they develop symptoms described in the farm's flock treatment plan(https://www.rvo.nl/onderwerpen/agrarisch-ondernemen/dieren-houden/dierenwelzijn/antibiotica-gebruiken-de-veehouderij/voorwaarden-voor-zelf-toedienen). This plan is tailored to the farm's particular situation and includes a prescribed treatment for each relevant condition. Farmers have the right to keep antibiotics on their premises if their farm's flock treatment plan provides for such. Working with flock treatment plans seems a good way to put Recital 5 of Regulation (EU) 2019/6 into practice and protect public health without adding much in the way of red tape.

The Royal Dutch Society for Veterinary Medicine (KNMvD) has a Veterinary Antibiotic Use Policy Working Group (WVAB) whose tasks include drafting guidelines and so-called formularies (KNMvD, 2015). A formulary is a prescription based on the latest scientific insights on the use of antibiotics in livestock, which is drawn up to ensure that animals receive proper treatment while at the same time preventing the emergence of antibiotic resistance. Veterinarians use formularies to indicate the drugs of first, second and third choice for the treatment of particular infections. Drugs of first choice are effective and do not pose a great risk for the development of resistance. They can therefore be included in flock treatment plans. Drugs of second choice must only be used if there is a clear necessity to do so and can only be included in flock treatment plans in exceptional cases. Drugs of third choice are critical to human health care and must only be used for individual animals in cases where a microbiological examination with antibiotic sensitivity testing has demonstrated that there are no alternatives. Prudent use guidelines and formularies do not have an independent legal status, but the industry is required by law to comply with them. Veterinarians continue to be responsible for compliance with laws and regulations concerning the use of antibiotics. In daily practice, situations will occasionally arise in which a veterinarian wishes to exercise his or her medical judgement and prescribe a type of treatment that contravenes the formularies or instructions for use. This is not allowed under current laws and regulations.

The WHO has drawn up a list of highest priority critically important antimicrobials for human medicine (Collignon et al., 2016). The antibiotics on this list must not be used in farm animals, except on highly exceptional conditions. Every few years, the list is updated to reflect the current situation regarding human infection control. The most recent update was published in 2016. A similar, more detailed

list has recently been published by the EEA (EMA, 2019). The current list reserves quinolones, third-generation-and-up cephalosporins, macrolides, ketolides, glycopeptides and polymyxins for human use, thus banning their use in veterinary medicine. Conversely, some drugs belonging to these categories are explicitly reserved for veterinary use. At present, drugs intended for human use are used in animals only as drugs of third choice, in cases where antibiotic resistance testing has shown that they are the only drugs that will still be effective. In the Netherlands, the quantity of such drugs used for veterinary purposes is very low. It constitutes less than 0.5% of the overall amount used for all animal species, except for turkeys (3% in 2018) (Heederik et al., 2019). The EU reserves the right to deviate from the WHO's list – a decision based on balancing the pros and cons outlined in the lists published by the WHO, EMA and OIE. Deviations from the WHO's list will generally be at the detail level. Given the impact not following these rules may have on human health, strict enforcement is required. Article 37(3) of Regulation (EU) 2019/6 states that antibiotics reserved for the treatment of infections in humans must not be used in animals. At the time of writing, EMA was drafting recommendations that will inform implementing decisions.

The authorisation of, and therefore specifications for, veterinary medicinal products will be harmonised for the entire EU under the new regulations. To this end, arguments for indications, dosages and the duration of courses of antibiotics will be presented afresh. As part of this project, we should possibly revise treatment protocols, as well, according to the principle of a short course of a heavy-duty antibiotic so as to further minimise the development of antibiotic resistance (Llewelyn et al., 2017). The question to be answered is how to ensure that this theoretically ideal treatment (i.e. administering the highest dose the animal can tolerate for the briefest amount of time needed to cure the infection) is enshrined in law and covers as many situations as possible. The course of infections can vary greatly from one case to the next, and in large flocks, in particular, an infection will spread over time (Stacey et al., 2007). It is up to veterinarians to determine the most effective type of treatment, taking into account the prevention of antibiotic resistance (NVWA, 2019a). The latter is also in the best interest of the industry, since infections with antibiotic-resistant animal pathogens are more difficult to treat than antibiotic-susceptible variants. Therefore, we may have to allow veterinarians to deviate from existing protocols in certain situations, provided that they have clear and well-argued reasons to do so. The situations in which veterinarians are allowed to deviate from the protocols must be formulated in a way that does not allow for abuse – for example, because the deviation is more convenient in terms of waiting periods.

The antibiotics will be prescribed by veterinarians, who will also supply them to livestock farms. As the trade in veterinary medicinal products such as antibiotics constitutes a source of income for veterinarians, they have a conflict of interest, strictly speaking. Recital 47 of Regulation (EU) 2019/6 states that veterinarians must ensure that they are not in a situation of conflict of interest when prescribing medicinal products, and that they are not influenced by economic incentives when prescribing medicinal products. Regardless of whether veterinarians actually allow their issuance of prescriptions to be influenced by such improper considerations, prescription monitoring is a good way to identify veterinarians whose prescriptions do not conform to accepted standards. The monitoring of antibiotic use is mandatory under Article 57 of Regulation (EU) 2019/6 and can be used to identify veterinarians who prescribe more antibiotics than usual. They can then be asked

why they administer so many antibiotics, and if they cannot satisfactorily answer this question, action can be taken, or the veterinarians concerned can be subjected to disciplinary proceedings.

Mode of administration
Broilers and laying hens must always have any antibiotics they may need administered in the form of flock treatments, i.e. the group administration of medicinal products to animals that form an epidemiological unit. Poultry are given antibiotics in their drinking water as necessary. For this purpose, a dosage system is connected to the pipes supplying them with their drinking water. Sick chickens drink less than healthy animals and therefore consume lower doses of antibiotics, despite the fact that they actually need more. As a result, either sick animals are under-dosed or healthy animals receive an over-dose, or both to some extent. The main problem with providing antibiotics dissolved in drinking water is that antibiotics precipitate in the pipes that supply the animals with their water. They will later re-dissolve, meaning that the animals' drinking water will still contain low concentrations of antibiotics even after the end of their therapy. This is highly undesirable as far as the development of antibiotic resistance is concerned. The EMA is preparing a recommendation on the administration of antibiotics in drinking water or by top-dressing, i.e. spreading antibiotics over the animals' feed. As an additional problem, when inspectors collect samples of the drinking water, there will be traces of antibiotics in it, and it may be very hard to determine whether these are the result of a treatment illegally administered or of a properly conducted treatment that was administered longer ago. The problem of initial precipitation in drinking water pipes and the subsequent re-dissolution of this precipitate could, in principle, be solved by flushing the pipes thoroughly after each treatment. This procedure requires time and attention on the part of the farmer. The NVWA must ensure that this procedure is carried out correctly.

Pigs must be given antibiotics in herd treatments with a repeater syringe, or in their drinking water or feed. In many respects, administration with a repeater syringe is the best way to minimise the development of antibiotic resistance, because the dose is precise, no residues are left outside the animal and the microbiota of the gut are less exposed to antibiotics than they would be if the antibiotics were administered in feed or drinking water. If drugs are administered to pigs in water, the same problem will occur that we have seen with chickens. Due to technical issues such as cross-contamination, mixed feed manufacturers no longer produce feed medicated with antibiotics. Therefore, farmers now administer antibiotics in feed by means of top-dressing (i.e. putting the medicine on top of the food). Unless the medicine is mixed with the feed very thoroughly, it will be distributed unevenly across the feed (Alleweldt, 2010). As a result, one animal may consume far more antibiotics than another. Recital 14 of Regulation (EU) 2019/4 states that homogeneous dispersion of the medicinal product is crucial for the manufacture of a safe medicated animal feed. A homogeneous dispersion of the medicinal product cannot be guaranteed when a farmer top-dresses the feed. As an added problem, sick animals eat and drink less than healthy ones. Therefore, the very animals that need the antibiotics the most will consume the least. This mode of administration is therefore less suitable for the treatment of herds of pigs, and treatment of individual animals with a repeater syringe is infinitely preferable. This method is already widely used and has proven to be quite practicable.

Veal farms are known to be a major user of antibiotics, unlike the dairy cow industry, where problematic use of antibiotics is limited to dry cows (Heederik et al., 2019). Milk produced by cows treated with antibiotics cannot be sold on the market, so antibiotics are only used when necessary. With calves, too, it should be quite possible to administer antibiotics to individual animals, and there is little reason not to require this mode of administration. Calves reared for veal are transferred to Dutch veal farms from a variety of countries and may transfer pathogens from the old environment to the new one (Marcato et al., 2018). Furthermore, the immune systems of young calves are not yet sufficiently developed to cope with infections on their own (Siddiqui et al., 2012).

Veal farms usually operate on an all-in all-out system, whereby the stables are kept vacant for cleaning and maintenance for a few days after all the calves have been taken to the slaughterhouse, and then a new batch of calves arrives. This method has the advantage of there being no risk of young calves being infected by older animals. However, the young calves do not all arrive at exactly the same time; generally they arrive over a period of a few days to as much as two weeks. Upon arrival, they often require the administration of an antibiotic. Therefore, until the introduction of the aforementioned veterinarian-only regulations, so-called "starter packs" containing antibiotics effective against the most common diseases used to be prepared and delivered in advance. Under the veterinarian-only regulations that are currently in force, the calves must be examined by a veterinarian before said veterinarian can supply any antibiotics. Despite this regulation, antibiotic use rates have remained relatively high in young calves reared for veal. The high antibiotic use rates in young calves may well be the inevitable result of existing practices whereby immunologically immature calves from a wide variety of locations are placed together in a barn, thus allowing pathogens to spread rapidly (Marcato et al., 2018).

Dosage size and antibiotic residues

A practical problem that arises with all production animals is the fact that the packages in which the antibiotics are sold by the manufacturer often do not correspond to the prescribed quantities. As a result, some unused antibiotics end up left over on the farm. Recital 32 of Regulation (EU) 2019/4 states that a system for the collection or disposal of unused veterinary medicinal products should be in place in order to manage the risk to human and animal health and to the environment. EU member states must ensure that their disposal systems are fit to achieve their intended purpose. As things stand, it is difficult, in practical terms, to dispose of the left-over medicine in a responsible and verifiable manner. Returning left-over antibiotics for use elsewhere is impossible because of the danger of cross-contamination, and having them destroyed responsibly is technically difficult and extremely hard to monitor. Leaving the left-over antibiotics on the farm for later use also has a few drawbacks, in that veterinarians must then keep records of how many antibiotics are held at each farm and are thereafter more or less forced to prescribe the same drug again in the event of a subsequent infection.

The best way to tackle this problem is to always sell the exact dosages prescribed by veterinarians or to design a watertight system for the disposal of left-over antibiotics. This would involve getting manufacturers to commit to making antibiotics available in smaller packages or to issue precise doses when the antibiotics are dispensed. Article 105(6) of Regulation (EU) 2019/6 states that:

The quantity of the medicinal products prescribed shall be limited to the amount required for the treatment or therapy concerned. Perhaps this provision can be used to force manufacturers to deliver the exact quantities of antibiotics required, by asking pharmaceutical companies to sell antibiotics in smaller packages as well.

In addition to general measures to reduce the use of antibiotics, specific measures to prevent antibiotic resistance caused by the use of antibiotics in farm animals may have to be implemented. As mentioned above, exposure to low concentrations of antibiotics is a clear risk factor for the development of antibiotic resistance. This means that the discharge of antibiotics via spilt medicated drinking water, left-over medicated feed or manure containing excreted antibiotics must be prevented to the maximum extent possible. There are quite a few measures that may be able to be implemented, but there is no quantitative data on the costs and benefits of any of these measures. As these cases involve exposure to low concentrations, there is a significant risk that antibiotic resistance may develop. A study on the costs and effectiveness of the various possible measures will therefore be necessary.

Measures designed to reduce the need for antibiotics

The recitals of Regulation (EU) 2019/4 state that "*treatments with medicinal products, in particular with antimicrobials, should never replace good husbandry, biosecurity and management practices".* Article 107(12) of Regulation (EU) 2019/6 conveys the same sentiment in slightly different words: *"Antimicrobial medicinal products shall not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care, or to compensate for poor farm management."* This article provides the NVWA with new legal tools to enforce regulations calling for proper farm hygiene and other practices designed to reduce antibiotic resistance. The wording of the standards is very much open for interpretation. How is poor hygiene defined? When is animal husbandry inadequate? We will have to do more than deal only with the extreme cases that clearly fall into this category. For consistent and predictable enforcement of the regulations, the vaguely worded standards will have to be defined in greater detail, so that it will be clear to livestock farmers, veterinarians and monitoring entities what standards they have to live up to.

When it comes to antibiotic resistance, poor hygiene refers to exposure to a large number of micro-organisms, including pathogens (Collignon & McEwen, 2019). On the one hand, farms that strive to achieve the desired level of hygiene incur costs. On the other hand, proper hygiene promotes the health of the farm's animals, thus increasing yields and reducing the costs of animal health care. The question, therefore, is what requirements can be set for hygiene and how to maintain these standards. The NVWA's inspectors have excellent knowledge of and insight into the situation of livestock farms. Therefore, it would make sense to talk to these inspectors and formulate criteria for the various types of livestock farms based on their recommendations. The Ministry of Agriculture, Nature and Food Quality can then use these recommendations when dotting the i's and crossing the t's of the hitherto vaguely formulated standards.

Polluted air and poor ventilation may cause the lungs to be exposed to pathogenic microbes, thus putting them at risk of respiratory infections (Roland et al., 2016).

Respiratory tract infections are a common reason for the use of antimicrobials in all production animals kept in stables. Clean air and good ventilation are achieved when animals do not contract avoidable respiratory tract infections due to poor air quality. Frequent check-ups of automatic ventilation systems in stables can improve air quality and thus be beneficial to the animals' health (Schnyder et al., 2019). It is possible, in principle, to establish criteria for microbiological air quality in stables. Such criteria must be derived from a clear relation to animal health, based on real-life observations.

Dirt in stables also causes infections, and infections reduce animal growth (Strauch, 1991) and animal well-being (Van der Meer, 2017). Poor barn hygiene is a cause of mastitis in dairy cows (Visser et al., 2015). Good hygiene is therefore a condition in which few or no avoidable infections are caused by manure and other dirt and filth in the animals' environment. Regular disposal of manure and other organic material in which pathogenic bacteria can multiply is hard work. Calculations will have to be made to identify those cleaning and disinfection procedures where the benefits for animal health, animal welfare and public health outweigh the costs. When new stables are constructed, in addition to animal welfare considerations, stables should be designed in a way that prevents the accumulation of manure, dirt and dust: no ledges, no exposed beams and no other surfaces where dust can settle, and vertical surfaces that are smooth and washable and therefore easy to keep clean. As for floor surfaces, a compromise must be made between slip prevention and easy cleaning.

"Inadequate animal husbandry" is an even vaguer definition, since it encompasses several aspects of farm management. Low-quality feed containing micro-organisms that are pathogenic to a farm's animals constitutes a clear risk factor (Davies et al., 2004). It is known that *Salmonella* often enters the farm in animal feed, contaminates the animals and then re-contaminates them through manure (Wilhelm et al., 2012), while the presence of *Campylobacter* is more likely to be caused by poor hygiene (Nather et al., 2009). There are no microbiological criteria or other laws and regulations in force that govern the presence of *Salmonella* in animal feed. We may wish to investigate whether such standards could reduce the risk of exposure, treatment with antibiotics and the spread of antibiotic resistance. One of the recommendations made in BuRO's animal feed chain advisory report of 2019 (NVWA, 2019b) is to specifically monitor for the presence of pathogenic micro-organisms in animal feed. This could be an important first step towards better control of pathogens in animal feed.

Lack of care or poor farm management are more severe shortcomings than poor hygiene or inadequate animal husbandry. Lack of care directly affects animal welfare and animal health and the NVWA already enforces regulations governing these aspects. Poor farm management is a general term that clearly goes beyond inadequate animal husbandry but does include the latter. When a farm is found to be poorly managed, the NVWA is forced to intervene in the business for several reasons. Potential use of antibiotics down the track is only one of the things taken into consideration when this situation arises, and it is certainly not the most important concern.

What kind of farm management measures and hygiene-related measures in particular can and should be required? The answer to this question cannot be derived directly from the relevant article of the Regulation. The NVWA will have to

formulate reasonable, clear and enforceable guidelines in consultation with the Ministry of Agriculture, Nature and Food Quality's policy department and possibly in consultation with the industry and veterinarians. Existing practice already provides guidance in this regard. Veterinarians are already required to include measures to reduce the use of antibiotics in their farms' flock health plans. The nature of these measures depends largely on the conditions at the farm, but many of the aforementioned considerations also come into play. We may wish to clearly define this responsibility on the veterinarian's part and also to specify that compliance with the instructions on the farmer's part is not optional, but rather an obligation.

The question as to what kind of measures and investments can be imposed is especially relevant with respect to so-called frequent antibiotic users and frequent prescribers. Frequent antibiotic users are livestock farmers who, over a period of several years, use a significantly greater quantity of antibiotics than other, similar farms. This may be due to poor hygiene, poor ventilation or low-quality feed, or it may be due to a combination of the aforementioned factors, as well as other factors. Revisions to farms' flock health plans and rigorous compliance with said plans may improve the situation. In turn, improved hygiene, high-quality animal feed and other parameters will reduce the need for antibiotics.

Prevention of transfer to humans
After developing and being selected in farm animals, antibiotic-resistant bacteria can be transferred to humans in several ways that have not yet been fully identified (Mughini-Gras et al., 2019). Potential transmission routes include direct contact between animals and humans, exposure to food of animal origin, or exposure to contaminated soil, air or water, including manure (Huijbers et al., 2015). Transmission through food may seem the most likely route, but it is certainly not the only route. Initially, studies on the impact of surface water suggested that surface water might be involved in the transport of antibiotic-resistant pathogens to human populations, but further studies have debunked this theory (Pallares-Vega et al., 2019). Soil bacteria are rarely fully sensitive to all agents included in the most commonly used test panels. In one study, more than 80% of the 412 strains tested were resistant to more than 16 of the 23 antibiotics used in the study (Walsh & Duffy, 2013). It therefore seems likely that the environment also plays a role in the exchange of resistance genes between humans and livestock. However, it seems quite unlikely that effective measures can be taken to prevent or even slightly reduce this exchange. Another reason why it will be difficult to prevent such exchanges is the fact that resistance is often transmitted through plasmids and other mechanisms, such as bacteriophages, rather than through intact bacteria (Davies & Davies, 2010).

At the request of the NVWA, the National Institute for Public Health and the Environment (RIVM) looked into the transmission of ESBL *E. coli* from broiler chicken farms to the immediate environment (Blaak et al., 2015). This study showed that bacteria travel through the air and are also spread by flies. In addition, in the days after a broiler chicken farm was cleaned in between separate batches of chickens, a clear increase in the quantity of viable ESBL *E. coli* was measured in the surrounding surface water resources. The water used in the cleaning process flowed off the site and ended up in nearby surface water resources. This suggests that surface water plays a part in the spread of micro-organisms from farms to the inhabited environment. To quantify this effect, a

follow-up study was carried out in which the quantities of ESBL *E. coli* in samples obtained from several carefully selected places were measured. The monitoring points were selected for several exclusion criteria, so that the remaining points were not affected to any serious degree by human activities such as wastewater treatment plants (WWTP), and so that a comparison could be drawn between monitoring points with significant farm activity in the vicinity of the upper course and monitoring points with very little agricultural activity in the vicinity of the upper course (Pallares-Vega et al., 2019). A thorough analysis only demonstrated a barely significant correlation between laying hen farms and ESBL *E. coli* in the surface water. Otherwise, the presence of livestock near the upper course had no lasting effect on the number of antibiotic-resistant bacteria in the water. Only freshly applied manure followed by rain resulted in a peak load. Apart from that, there was no correlation between the application of manure to cropland and the presence of ESBL *E. coli* in the surface water. Surface water was found to be much more severely impacted by WWTPs in samples collected at other monitoring points, as part of a different programme.

The concentration of antibiotics in milk from cows treated for mastitis is low, but probably not negligible. Therefore, this milk must be disposed of properly. The EFSA recommendation entitled "Risk for the Development of Antimicrobial Resistance (AMR) due to Feeding of Calves with Milk Containing Residues of Antibiotics" presents several options for the processing of this milk (Ricci et al., 2017), e.g. fermentation, temporary increase of the pH to 10.0 or electrochemical oxidation. Further research will have to show which measures will be able to be implemented effectively.

Theoretically, it seems possible that countermeasures may be devised that will reduce the transmission of resistance genes from livestock to humans (Ter Kuile et al., 2016). Nevertheless, judging from the aforementioned observations, it seems unlikely that, without further research, effective measures will be able to be devised that will prevent transmission of antibiotic-resistant bacteria once selection for resistance has taken place on the farm. A method that prevents the development and selection of resistance will probably prove to be more effective. Possible exceptions could be the collection and treatment of water used in cleaning broiler chicken coops after a flock of chicks has been transferred and the proper disposal of milk containing antibiotics. However, with today's knowledge, it is difficult to determine how beneficial this would be, and without a clear strategy and proof that this strategy is effective, it seems unfair to impose such requirements on farmers. Therefore, we should commission a study on measures we may wish to implement on the farm level to prevent the development and spread of antibiotic resistance.

Monitoring of antibiotic resistance and antibiotic use

All EU member states have been required since 2014 to participate in the EU's programme for monitoring antimicrobial resistance in isolates from farm animals and food of animal origin, under Implementing Decision 2013/652/EU. This Decision specifies in detail which types of resistance data are to be submitted annually to the Commission, but antibiotic usage data is not included in this programme. This omission was rectified by Article 57(2) of Regulation (EU) 2019/6, under which member states are required to collect such sales and use volume data and submit it to the Commission. In the Netherlands, this data is collected by the Netherlands Veterinary Medicines Institute (SDa), which reports

on it annually. FIDIN (Manufacturers and Importers of Veterinary Medicinal Products in the Netherlands) has submitted sales volume data to the SDa over the years and makes it available to others as part of the annual MARAN reports, to which the NVWA contributes antibiotic resistance data. The SDa collects antibiotic use data (submitted by the various types of industry) in the form of prescriptions for antibiotics issued to livestock farmers by veterinarians. The full wording of Article 57 suggests that the Commission will present an implementing decision on the reporting of antibiotic use data, as well.

Article 57(1) states that the EU member states shall evaluate individual farms' use of antibiotics by collating data on sales volumes and use of antibiotics in animals. In addition, member states are required to report to the EMA data on sales volumes and antibiotic use per animal species and per type of antimicrobial medicinal product. The EMA then analyses this data, in cooperation with the member states, and issues an annual report on it. Article 57(3) gives the Commission the power to impose quality requirements on the data submitted. The SDa already collects this data on behalf of the Dutch government. The data received by the SDa is submitted by the various industries that pass on the volume of antibiotics dispensed to livestock farms. The SDa is already in informal talks with EMA staff on this. Therefore, we expect this data to meet the EU's quality requirements.

In 2018, the quantity of antibiotics sold by the FIDIN exceeded the quantity of antibiotics covered by the reported prescriptions by about 10%. In 2019, the difference only amounted to 2.3%. This difference may be due to a failure to report some of the prescribed antibiotics, or alternatively, it may very well relate to some unused antibiotics left over from a treatment, or a supply that has yet to be used. Perhaps, as with prescription guidelines for individual veterinarians, any semblance of a conflict of interest should be avoided here, too, meaning it would be better to send the prescriptions to the SDa automatically.

Livestock farmers can use the benchmark values to compare their own use of antibiotics with similar farms'. The SDa revised the benchmark values issued to veterinarians in 2019. The objective is for companies and veterinarians to take action when an action value set by experts is exceeded. Such benchmark values would also allow the authorities to identify veterinarians whose prescription policies may be in need of a revision. In Denmark, too, the quantities of antibiotics prescribed by veterinarians are compared on an annual basis, and there too experience shows that this monitoring reduces the total quantity of antibiotics prescribed (Dupont et al., 2017).

What is not covered by the regulations

The regulations govern the production authorisation, trade in and administration of veterinary medicinal products. One aspect of the problems inherent in antimicrobial resistance is not covered by these regulations: control of certain types of resistance in the agriculture industry that have been proclaimed a risk. This is not about the common resistance to antibiotics commonly used in animal husbandry, but about less common types of resistance to drugs essential in human health care, such as colistin resistance or carbapenemase-producing micro-organisms found occasionally on the odd farm. Resistance to medicinal products that have not been authorised for use in farm animals can still be selected if the relevant genes are on a plasmid with multiple types of resistance

genes. One example we saw in the past is the emergence of livestock-associated MRSA that was selected by tetracycline resistance. The implementation of case-specific measures is only useful in cases like that. The Regulations do not contain any provisions on measures to be taken in the event of such incidents. The NVWA and the Ministries of Health, Welfare and Sport and Agriculture, Nature and Food Quality must decide in advance how to deal with incidents or crises involving antibiotic-resistant microbes in the agriculture industry. The most obvious strategy would seem to be a case-specific set of specific measures, to be selected after the performance of an urgent risk assessment.

Conclusions

The costs incurred by the Dutch human healthcare industry due to antibiotic resistance originally selected by the use of antibiotics in livestock animals are estimated to amount to approximately €12 million per annum. In addition, antibiotic resistance also causes the veterinary medicine industry to incur higher costs, which might exceed €200 million for the Netherlands if antibiotics were to become completely useless due to general antimicrobial resistance. Better modes of administration may be able to prevent development of antimicrobial resistance. In particular, exposure to low concentrations of antibiotics should be avoided. Without new vaccines and without changes to the way farms are managed, a significant reduction in the quantity of antibiotics administered because the number of conditions treated is reduced may pose a threat to animal welfare and animal health. Reducing dosages so as to use less antibiotics will have a negative rather than a positive effect on the development and spread of antibiotic resistance.

Regulations (EU) 2019/4 and 2019/6 provide us with a good legal basis on which we can enforce the proper use of antibiotics in veterinary medicine. Many of the provisions of the Regulations can be enforced without any need for further explanation. However, other, less clearly defined standards set out in the Regulations will need further definition. In the appendix to this document, more information is provided on the NVWA-enforcement-related aspects of those articles in Regulations (EU) 2019/4 and 2019/6 that relate to the use of antibiotics in livestock. This document will touch on both duties and powers.

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Appendix

This appendix consists of extracts from Regulations (EU) 2019/4 and 2019/6 and their recitals. The passages in question were selected for their relevance to antibiotic use and the control of antibiotic resistance, and in some cases, certain parts of the text have been omitted (indicated with square brackets as follows: [...]) to improve readability. Each article comes with a brief comment on the enforcement-related implications for the NVWA and, where relevant, the room the NVWA is given in drawing up its own policies, both in terms of preventing the development of antimicrobial resistance and selection of resistance.

(EU) 2019/4

Recitals:

(3) The pursuit of a high level of protection of human health is one of the fundamental objectives of Union food law [...] In addition, the protection of animal health constitutes one of the general objectives of Union food law.

(4) Prevention of disease is better than cure. Medicinal treatments, especially with antimicrobials, should never replace good husbandry, bio-security and management practices.

(6) Medicated feed is one of the routes for the oral administration of veterinary medicinal products. [...] Other routes for oral administration, such as mixing of water for drinking with a veterinary medicinal product or manual mixing of a veterinary medicinal product into feed, should not fall within the scope of this Regulation. [...]

(14) Homogeneous dispersion of the veterinary medicinal product into the feed is also crucial for the manufacture of a safe and efficient medicated feed. Therefore, the possibility to establish criteria, such as target values, for the homogeneity of the medicated feed should be provided for.

(18) Labelling of medicated feed should comply with the general principles laid down in Regulation (EC) No 767/2009 and should be subject to specific labelling requirements in order to provide the user with the information necessary to correctly administer the medicated feed. [...]

(22) It is important to take into consideration the international dimension of the development of antimicrobial resistance. Furthermore [...], steps restricting the use of medicated feed containing antimicrobials in order to prevent a disease should be considered worldwide for animals and products of animal origin exported from third countries to the Union.

(27) Prophylaxis or use of medicated feed to enhance the performance of animals should not be allowed [...] The use of medicated feed containing antimicrobials for metaphylaxis should only be allowed when the risk of spread of an infection or of an infectious disease is high.

(30) The "One Health" concept [...] recognises that human health, animal health and ecosystems are interconnected and it is therefore essential for both animal and human health to ensure prudent use of antimicrobial medicinal products in food-producing animals.

(31) On 17 June 2016, the Council adopted conclusions on the next steps under a One Health approach to combat antimicrobial resistance. On 13 September 2018, the European Parliament adopted a resolution on a European One Health Action Plan against Antimicrobial Resistance.

(32) A system for the collection or discard of unused or expired intermediate products and medicated feed should be in place, including through existing systems and when managed by feed business operators, in order to control any risk that such products might raise with regard to the protection of animal or human health or the environment. The decision as to who is responsible for such a collection or discard system should remain a national competence. Member states should take measures to ensure that appropriate consultations with relevant stakeholders are carried out to ensure the fitness for purpose of such systems.

Regulation

Article 7(3), Cross-contamination (carry-over)
The Commission shall establish specific maximum levels of cross-contamination for active substances in non-target feed and methods of analysis for active substances in feed.
NVWA: little or no policy-making discretion; to be enforced in accordance with the provisions of the Regulation.

Article 11(4) *Medicated feed containing antimicrobial veterinary medicinal products shall not be distributed for promotional purposes as samples or in any other presentation.*
NVWA: little or no policy-making discretion; to be enforced in accordance with the provisions of the Regulation.

Article 16(5)
A member state may allow a veterinary prescription for medicated feed to be issued by a veterinarian or another professional person qualified to do so. Such prescriptions shall exclude prescription of medicated feed containing antimicrobial veterinary medicinal products or any other veterinary medicinal products where a diagnosis by a veterinarian is necessary and shall be valid only in that member state.
NVWA: This provision is hardly relevant to daily practice in the Netherlands, because in the Netherlands the power to prescribe veterinary medicinal products has always been exclusive to veterinarians.

Article 16(8) *In the case of medicated feed containing antimicrobial veterinary medicinal products, the prescription shall be valid from the date of its issuance for a maximum period of five days.*
NVWA: little or no policy-making discretion; to be enforced in accordance with the provisions of the Regulation. When working with an animal treatment plan, care should be taken to ensure that the prescription is not more than 5 days old.

Article 16(9) *The veterinarian issuing the veterinary prescription for medicated feed shall verify that that medication is justified for the target animals on veterinary grounds. [...] In particular, the veterinarian shall not prescribe medicated feed with more than one veterinary medicinal product containing antimicrobials.*
NVWA: The obligation outlined in the first sentence can be used to call to account veterinarians who prescribe antibiotics unnecessarily or incorrectly. The principles of responsible use can be the guiding principle here. The second sentence prohibits the simultaneous mixing of two antibiotics into the feed, unless an authorised veterinary medicinal product contains two or more antibiotics.

Article 17(3) *Medicated feed containing antimicrobial veterinary medicinal products shall be used in accordance with Article 107 of Regulation (EU) 2019/6, except as regards paragraph 3 thereof, and shall not be used for prophylaxis.*
NVWA: Prophylaxis is only allowed in exceptional situations and then only in individual animals. It makes a certain amount of sense that prophylaxis must not be administered in medicated feed, as other modes of administration are more effective and do not cause complications such as carry-over and left-over unconsumed medicated feed.

Annex IV, Tolerances *Where the composition of a medicated feed or an intermediate product is found to deviate from the amount of an antimicrobial active substance indicated on the label, a tolerance of 10% shall apply.*
NVWA: little or no policy-making discretion; to be enforced in accordance with the provisions of the Regulation.

(EU) 2019/6

Recitals

(5) This Regulation aims to reduce the administrative burden, enhance the internal market and increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection.

(8) [...] Animal diseases transmissible to humans can also have a significant impact on public health. Therefore sufficient and effective veterinary medicinal products should be available in the Union in order to ensure high standards of public and animal health, and for the development of the agriculture and aquaculture sectors.

(10) This Regulation should not apply to veterinary medicinal products which have not undergone an industrial process such as, for example, non-processed blood.

(14) To ensure the proper administration and appropriate dosing of certain veterinary medicinal products which are to be administered to animals orally in feed or drinking water, especially in the case of treatment of groups of animals, such administration should be properly described in the product information. [...]

(25) There may be, however, situations where no suitable authorised veterinary medicinal product is available. In those situations, by way of exception, veterinarians should be allowed to prescribe other medicinal products to the animals under their responsibility in conformity with strict rules and only in the interest of animal health or animal welfare. [...] particular care should therefore be taken when administering antimicrobials.

(41) Antimicrobial resistance to medicinal products for human use and veterinary medicinal products is a growing health problem in the Union and worldwide. Due to the complexity of the problem, its cross-border dimension and the high economic burden, its impact goes beyond its severe consequences for human and animal health and has become a global public health concern that affects the whole of society and requires urgent and coordinated intersectoral action in accordance with the "One Health" approach. Such action includes strengthening of the prudent use of antimicrobials, avoiding their routine prophylactic and metaphylactic use, actions to restrict the use in animals of antimicrobials that are of critical importance for preventing or treating life-threatening infections in humans and encouraging and incentivising the development of new antimicrobials. It also needs to be ensured that appropriate warnings and guidance are included on the labels of veterinary antimicrobials. Use that is not covered by the terms of the marketing authorisation of certain new or critically important antimicrobials for humans should be restricted in the veterinary sector. The rules for advertising veterinary antimicrobials should be tightened, and the authorisation requirements should sufficiently address the risks and benefits of antimicrobial veterinary medicinal products.

(45) In order to strengthen member states' national policies on the prudent use of antimicrobials [...] member states should be allowed [...], following scientific recommendations, to define restrictive conditions for their use. [...]

(46) In order to preserve as long as possible the efficacy of certain antimicrobials in the treatment of infections in humans, it may be necessary to reserve those antimicrobials for humans only. [...]

(47) [...] Veterinarians have a key role in ensuring prudent use of antimicrobials and consequently they should prescribe the antimicrobial medicinal products based on their knowledge of antimicrobial resistance, their epidemiological and clinical knowledge and their understanding of the risk factors for the individual animal or group of animals. In addition, the veterinarians should respect their professional code of conduct. Veterinarians should ensure that they are not in a situation of conflict of interest when prescribing medicinal products, while recognising their legitimate activity of retail in accordance with national law. In particular, veterinarians should not to be influenced, directly or indirectly, by economic incentives when prescribing those medicinal products. Furthermore, the supply of veterinary medicinal products by veterinarians should be restricted to the amount required for treatment of the animals under their care.

(48) [...] ..... In addition, member states should be allowed to take further restrictive measures to implement national policy on the prudent use of antimicrobials, provided that those measures do not unduly restrict the functioning of the internal market.

(49) It is important to consider the international dimension of the development of antimicrobial resistance when assessing the benefit-risk balance of certain veterinary antimicrobials in the Union. [...]

(50) There is still a lack of sufficiently detailed and comparable data at Union level to determine the trends and identify possible risk factors that could lead to the development of measures to limit the risk from antimicrobial resistance and to monitor the effect of measures already introduced. It is therefore important to continue the collection of such data and further develop it in line with a stepwise approach. [...]

(64) It is necessary to exercise control over the entire chain of distribution of veterinary medicinal products, from manufacture or import into the Union through supply to the end-user. [...]

(78) Collection systems for the disposal of waste veterinary medicinal products should continue to be in place in the member states in order to control any risk that such products might raise with regard to the protection of human and animal health or the environment.

Regulation

Article 8(2) Where the application concerns an antimicrobial veterinary medicinal product, the following shall be submitted in addition to the information, technical documentation and summary listed in paragraph 1:
(a) documentation on the direct or indirect risks to public or animal health or to the environment of use of the antimicrobial veterinary medicinal product in animals; (b) information about risk mitigation measures to limit antimicrobial resistance development related to the use of the veterinary medicinal product.
NVWA: The NVWA is not involved in the authorisation of veterinary medicinal products.

Article 34(1) *The competent authority or the Commission [...] shall classify the following veterinary medicinal products as subject to veterinary prescription: (c) antimicrobial veterinary medicinal products;*
NVWA: Reaffirms that antibiotics should only be used when prescribed by a veterinarian. To be enforced in accordance with the Regulation.

Article 35(1) *The summary of the product characteristics [...] shall contain [...] the following information: (xii) special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance;*
NVWA: The NVWA is not involved in this.

Article 37*(3) A marketing authorisation for an antimicrobial veterinary medicinal product shall be refused if the antimicrobial is reserved for treatment of certain infections in humans as provided for in paragraph 5. (4) The Commission shall adopt delegated acts in accordance with Article 147 in order to supplement this Regulation by establishing the criteria for the designation of the antimicrobials which are to be reserved for treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials. (5) The Commission shall, by means*

of implementing acts, designate antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 145(2).
NVWA: The foregoing refers to the list of antibiotics reserved exclusively for use in humans. This list has been laid down in EU implementing decisions. At the time of writing, the list included quinolones, third-generation-and-up cephalosporins, macrolides, ketolides, glycopeptides and polymyxins. These products have been banned for use in animals. Strict adherence to this rule is crucial to ensure that no resistance develops to essential means of human infection control.

Article 57 *Collection of data on antimicrobial medicinal products used in animals*
(1) Member states shall collect relevant and comparable data on the volume of sales and on the use of antimicrobial medicinal products used in animals, to enable in particular the direct or indirect evaluation of the use of such products in food-producing animals at farm level.
(2) Member states shall send collated data on the volume of sales and the use per animal species and per type of antimicrobial medicinal products used in animals to the Agency. The Agency shall cooperate with member states and with other Union agencies to analyse those data and shall publish an annual report. The Agency shall take into account those data when adopting any relevant guidelines and recommendations.
NVWA: This article forms the legal basis for the collection of antibiotic use data. This data is collected for the Netherlands and submitted to EMA by the SDa. NVWA is not involved in this.

Article 105 Veterinary prescription (1) *A veterinary prescription for an antimicrobial medicinal product for metaphylaxis shall only be issued after a diagnosis of the infectious disease by a veterinarian.*
NVWA: This rule should be enforced, but it will be hard to produce evidence. In principle, one sick animal constitutes sufficient ground to use metaphylaxis. (2) *The veterinarian shall be able to provide justification for a veterinary prescription of antimicrobial medicinal products, in particular for metaphylaxis and for prophylaxis.*
NVWA: to be enforced in accordance with the Regulation. This provision could be interpreted to mean that when a veterinarian is able to properly justify a deviation from the rules on antibiotic use, said deviation may be authorised. (5*) A veterinary prescription shall contain at least the following elements: (k) any warnings necessary to ensure the proper use including, where relevant, to ensure prudent use of antimicrobials;*
NVWA: Enforce the presence of such warnings.
(6) *The quantity of the medicinal products prescribed shall be limited to the amount required for the treatment or therapy concerned. As regards antimicrobial medicinal products for metaphylaxis or prophylaxis, they shall be prescribed only for a limited duration to cover the period of risk.*
NVWA: This provision forms the legal basis for ensuring that farms dispose of their old supplies of antibiotics, etc. Perhaps this provision may also be used to require manufacturers to sell antibiotics in the exact right quantities. (10) *A veterinary prescription for antimicrobial medicinal products shall be valid for five days from the date of its issue.*

NVWA: To be enforced in accordance with the Regulation. The issuance of prescriptions in conjunction with flock treatment plans must be carefully aligned with this provision.

Article 107 Use of antimicrobial medicinal products (1) *Antimicrobial medicinal products shall not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care or to compensate for poor farm management.*
NVWA: This is one of the key provisions of the Regulations. It allows the NVWA to intervene in farms that use more antibiotics than better managed farms due to poor management. No benchmarks have been defined, so guidelines will have to be drawn up to provide greater clarity.
(2) *Antimicrobial medicinal products shall not be used in animals for the purpose of promoting growth nor to increase yield.*
NVWA: This is the existing ban on the use of antibiotics to promote growth. To be enforced in accordance with the provision. It may be hard to provide evidence, but low doses are particularly suspect.
(3) *Antimicrobial medicinal products shall not be used for prophylaxis other than in exceptional cases, for the administration to an individual animal or a restricted number of animals when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe. In such cases, the use of antibiotic medicinal products for prophylaxis shall be limited to the administration to an individual animal only, under the conditions laid down in the first subparagraph.*
NVWA: prophylaxis is not allowed, unless certain conditions are met. In actual practice, prophylaxis will be administered in certain situations – for example, prior to surgery. These conditions can be interpreted in several different ways, but it is clear that flock prophylaxis treatments are not allowed.
(4) *Antimicrobial medicinal products shall be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no other appropriate alternatives are available. Member states may provide guidance regarding such other appropriate alternatives and shall actively support the development and application of guidelines which promote the understanding of risk factors associated with metaphylaxis and include criteria for its initiation.*
NVWA: The key phrase here is the conditional clause "where no other appropriate alternatives are available". How does a prescribing veterinarian decide that there are no appropriate alternatives? The NVWA can be proactive in this matter by drawing up a list of alternatives and criteria for when to allow their use. (5) *Medicinal products which contain the designated antimicrobials referred to in Article 37(5) shall not be used in accordance with Articles 112, 113 and 114.*
NVWA: Pursuant to this article, antibiotics that are reserved for exclusive use in humans cannot be used as indicated in the Off-Label Use of Veterinary Medicinal Products Flowchart (the so-called "Cascade Flowchart"). To be enforced in accordance with the Regulation. (6) *The Commission may, by means of implementing acts, and taking into consideration scientific advice of the Agency, establish a list of antimicrobials which: (a) shall not be used in accordance with Articles 112, 113 and 114; or (b) shall only be used in accordance with Articles 112, 113 and 114 subject to certain conditions.*
NVWA: Under this provision, the Commission is allowed to authorise the use of certain antibiotics as indicated in the Off-Label Use of Veterinary Medicinal Products Flowchart (the so-called "Cascade Flowchart"). We must determine

whether such a list is necessary for veterinarians practising in the Netherlands. If this is the case, the matter should be brought before the Commission. (7) *A member state may further restrict or prohibit the use of certain antimicrobials in animals on its territory if the administration of such antimicrobials to animals is contrary to the implementation of a national policy on prudent use of antimicrobials.*
(8) Measures adopted by the member states on the basis of paragraph 7 shall be proportionate and justified. (9) The member state shall inform the Commission of any measure it has adopted on the basis of paragraph 7.
NVWA: Subparagraphs 7, 8 and 9 allow the Netherlands to pursue its own policy on banning certain antibiotics which, for example, are of particular importance to the Dutch healthcare system but are not included in the list of antibiotics reserved for exclusive use in humans. This policy must be easy to account for, and the outcomes must be submitted to the Commission by the Ministry.

Article 118 Animals or products of animal origin imported into the Union (1) *Article 107(2) shall apply, mutatis mutandis, to operators in third countries and those operators shall not use the designated antimicrobials referred to in Article 37(5), insofar as relevant in respect of animals or products of animal origin exported from such third countries to the Union.*
NVWA: The first subparagraph of this article says two things: Animals reared with growth-promoting factors and products thereof cannot be imported into the EU, and animals and products of animal origin imported into the EU must not have been treated with antibiotics reserved for human use only. Both provisions aim to prevent unnecessary and unwelcome forms of antimicrobial resistance from being imported in the form of animals or products of animal origin. In enforcing this provision, it will be hard to present good evidence of rule-breaking, because it is not possible to conclude from antibiotic resistance findings alone that certain antibiotics have been used. However, a particular pattern of resistance may constitute a ground for suspicion.

Article 139 Committee for Veterinary Medicinal Products (1) *A Committee for Veterinary Medicinal Products ("the Committee") is hereby set up within the Agency. Article 141 Tasks of the Committee (i) provide scientific advice on the use of antimicrobials and antiparasitics in animals in order to minimise the occurrence of resistance in the Union, and update that advice when needed;*
NVWA: The NVWA has no obligations or authority in this regard, but it is important to note that combatting antimicrobial resistance is a specific task of the Committee.

Article 152 Existing veterinary medicinal products, marketing authorisations and registrations
(1) *Marketing authorisations of veterinary medicinal products and registrations of homeopathic veterinary medicinal products granted in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 before 28 January 2022 shall be deemed to have been issued in accordance with this Regulation, and are, as such, subject to the relevant provisions of this Regulation. The first subparagraph of this paragraph shall not apply to marketing authorisations for antimicrobial veterinary medicinal products containing antimicrobials which have been reserved for treatment in humans in accordance with implementing acts referred to in Article 37(5).*

NVWA: Unlike other veterinary medicinal products, antibiotics that have been reserved for exclusive use in humans cannot be traded under the old authorisation, granted before 28 January 2022. To be enforced in accordance with the Regulation.