Overview of the Dutch (Veterinary) Medicines Sector. One Health Approach?

PEER REVIEWED

In order to keep the world's population healthy and treat it for diseases, the world needs (veterinary) medicines. There are some similarities between the veterinary and human medicines sectors, but unfortunately these are hard to find. This holds true for the Netherlands. This article is meant to provide an overview specifically of the Dutch situation. There is a focus on economic parameters (labour force, turnover and expenditure), legislation procedures, the distribution situation and some social developments (worrying about antibiotic resistance; increasing specialisation).

The size of the Dutch human pharmaceutical market (4.3 billion euros in 2013[1]) is about the same as the size of the European veterinary pharmaceutical market. The Dutch 2013 veterinary medicines turnover was approximately €250,000,000[2], of which the livestock farming industry accounts for around 70%. By way of comparison, in the European market (4.5 billion euros in 2012[3]) about 50% of the veterinary medicines were used in the livestock farming industry. Still, the Dutch turnover is only 6% of the total EU veterinary medicines turnover. The Dutch human healthcare sector is one of the biggest sectors in the Netherlands when it comes to employment. Over 1.1 million people work in the sector out of a total 11 million (potential labour force)[4]. The total expenses are 45 billion euros, of which 4.3 billion are for medicines[1]. The Netherlands is amongst the European countries with the highest expenditure as a percentage of GDP (643 billion in 2013[5]). The most expensive healthcare is long-term care[6]; around 15% of the Dutch are over 65. Also, it is expected that these elderly people more often will live on their own[7]. This demographic development has a significant influence on the healthcare industry. The Dutch healthcare system is publicly organised, whereas the farming industry is private in nature. Therefore the use of veterinary medicines is, amongst other factors, related to a professionally organised livestock farming industry. This branch produces food, milk and eggs meant for consumption, and a large proportion of this is goods for export. In April 2012[8], the agricultural census stated 2.3 million cows of over one year old (of which 1.48 million were dairy cows). 1.4 million cows and 14.3 million pigs were slaughtered for the industry in that year; there were almost 400,000 goats and the sheep flock consisted of over one million. The poultry production industry counts approximately 29.6 million chickens and has a gross production of 810,000 tons. Smaller in size but nevertheless important is the group of companion animals, although the amount of companion animals has been decreasing for a few years, likely due to the economic crisis and the ongoing urbanisation. Nevertheless, 59% of families in the Netherlands have at least one companion animal, and the number of families with a companion animal is increasing. Companion animals are most likely to be cats (2.9 million), dogs (1.5 million), (song)birds (2 million) or aquarium fish (6.6 million). The Dutch spend 2.12 billion per year on the acquisition and care of these animals. The companion animal sector provides 18,000 fte's (education, research, trade, services) and is worth around 3 billion euros per year[9].

Legislation

Registration of veterinary medicines has been harmonised based on European Regulation. This means that the same policies concerning the assessment needed to receive marketing authorisation apply to all EU member states. As is the case with veterinary medicines, medicines for human use also need marketing authorisation before they can be released onto the market. The competent authority is the Medicines Evaluation Board (College Beoordeling Geneesmiddelen, CBG). The CBG assesses whether or not the advantages of a medicine outweigh the disadvantages by closely examining the efficacy, risks and quality of the medicine[10]. In the Netherlands the Veterinary Department (Bureau Diergeneesmiddelen, BD), part of the CBG, coordinates the marketing authorisation for veterinary medicines[11]. The BD uses the test results and research from external institutes such as the National Institute for Public Health and the Environment (RIVM) and the Central Veterinary Institute (CVI). Particular to the assessment of veterinary medicines in comparison to medicines for humans is the additional ecotox assessment.

Distribution

In general it is safe to say that a (veterinary or human) medicine is prescription-only when a physician or veterinarian is needed for a diagnosis. There are four situations in which a prescription is necessary:

- When there might be a direct or indirect danger when the medicine is used without medical supervision, e.g. antibiotics;
- When, due to using the medicine differently from stated in the SPC or due to using the medicine for food-producing animals, there might be a direct or indirect danger to one's health;
- When a medicine is so new the efficacy or possible side-effects have to be investigated. As a rule of thumb, a medicine should have been used for at least five years as POM;
- When parenteral application is involved.

Most medicines for human use are only to be delivered by a pharmacist after prescription from a physician or other authorised healthcare professional. Some medicines, however, are for sale at local druggists or pharmacies[12]. This way there are two types of medicines: POM and non-POM. The criteria for POM are stated in article 71 from 2001/83/EC. This POM/non-POM distinction also applies to veterinary medicines. For veterinary medicines the Netherlands has created a combined policy consisting of both the European regulated prescription policies and the national distribution regulation, the so-called 'canalisation policy', which regulates whether

or not a veterinarian's prescription is needed for distribution of the veterinary medicine, who may deliver the medicine (veterinarian or pharmacist (human)), or the possibility of selling the medicine by a licensed merchandiser. The four types of canalisation are UDD (only to be delivered and administered by a vet), UDA (only to be delivered by a vet or a pharmacist (on prescription)), URA (only to be delivered by a vet, pharmacist or licensed merchant (on prescription), VRIJ (may be traded without prescription). At this moment pharmacists play no significant role in the Netherlands in the distribution of veterinary medicines. Furthermore, the healthcare inspectorate (IGZ) supervises the entire medicine distribution chain. In order to ensure the quality of medicines, manufacturers and wholesalers need to comply to strict regulation for good distribution practices. This is different from the veterinary market. The IGZ, in cooperation with BD, also carries out GMP inspections at manufacturers of veterinary medicines.

Antimicrobial Resistance

In the Netherlands, antimicrobial resistance is relatively low. There are many countries in which resistance is a bigger problem. One factor explaining this is the fact that in the Netherlands antibiotics are only available after prescription. Also, healthcare organisations are on the alert. There has been considerable attention paid to the use of antibiotics in the livestock farming industry. The first reports to make a comparison between EU member states showed a relatively high use of antibiotics in the Netherlands. This is contrary to the human healthcare sector, where the Netherlands are amongst the lowest-ranked countries. This comparison led to a lot of political attention on the use of antibiotics, which in turn led to regulations to decrease their use, which in 2014 resulted in a 60% decrease compared to 2009[13]. Now, the Netherlands are among the average users in Europe [14], which is, given the intensity of the industry, quite an achievement.

Human patients with antimicrobial resistance are treated separately and professionals follow strict hygiene measures. By doing so, professionals and organisations avoid new contaminations[15]. The Dutch Working Party on Antibiotic Policy (SWAB) formulates national legislation for the use of antibiotics. These are meant for adult patients and are used as a foundation for composing local and regional antibiotic formularies. The SWAB is also involved in surveillance of the use of antibiotics and the resistance in various micro-organisms. Over the past decade antibiotic use has increased by 15%, from 9.86 to 11.34 DDD/1000/day[16]. The increase we've seen between 2002 and 2009 seems to have been stabilising within Dutch hospitals since 2010[17]. There are few cases with MDR or superbugs in the Netherlands. Infections with these types of bacteria are hard to treat, because these bacteria are also increasingly resistant to last-resort antibiotics. Based on data from 2007 it is estimated that seven people die each year from MRSA, and MRSA leads to 300 extra days in hospital, costing around €78,000 in total. *E. coli*, resistant to third-generation cephalosporin, causes 37 deaths per year and 1600 days, costing around €378,000[18].

The need for reduction in the use of antibiotics in animals is related to possible public health risks. One consequence of increasing bacterial resistance is the impossibility of treating certain patients with antibiotics. The latest scientific insights reveal a rather small contribution to antimicrobial resistance from the livestock farming industry[19]; nevertheless it is necessary to restrict the use as much as possible, and also to control the resistance within animals and livestock. Therefore the use of fluoroquinolones and third- and fourth-generation cephalosporin has been restricted over the last years. As a result, Cefotaxime resistance in *E. coli* in poultry dropped from 20% in 2007 to 5.8% in 2012. In 2012, 37% of the *E. coli* in livestock animals was resistant to amoxicillin and 4.9% to ciprofloxacine[20].

As a consequence of the increasing attention paid to antibiotic resistance on the one hand, and the veterinarian's authorisation to distribute and deliver veterinary medicines on the other, there has been a great deal of attention on the interpretation of good veterinary practice. The veterinary professional organisation (the KNMvD) has implemented good veterinary practice by means of guidelines and formularies (also concerning antibiotics). The veterinary disciplinary tribune supervises the veterinarians. The public debate on the widespread use of antibiotics in the livestock farming industry has resulted in a large number of veterinarians appearing before the tribune. The Dutch approach to restricting the use of antibiotics has drawn a lot of attention from the European community due to the fact it was based on the sector's self-regulation. The government determined reduction targets but left the concrete interpretation to the sectors. Consequently there was considerable foundation among those working in the livestock farming industry and progress has been made efficiently and quickly. The approach is known in Europe as The Dutch Approach.

Specialisation

As a consequence of market forces, healthcare organisations are forced to specialise. Specialisation makes organisations more visible for healthcare seekers and health insurance companies[21]. The government stimulates this, aiming at improved quality and lower healthcare expenditure. There are three types of specialisation: specialisation based on efficiency, specialisation based on focus, and domain specialisation. When specialising based on efficiency, the keywords are standardisation and protocolisation. Specialisation based on focus leads to high-end care which distinguishes the organisation from other providers. Domain specialisation means covering a specific domain, such as cardiology[21]. In 2011, out of each thousand men, 168 were referred to a specialist; for women, this was 229 out of 1000[22]. The care for companion animals is getting more and more specialised and veterinarians are forced to differentiate during their training. It is common practice for veterinarians to focus on one species only, and the number of European registered specialists (EBVS[23]) is increasing rapidly in the Netherlands. Nowadays there are 28 veterinary clinics with specialists[24]. Also there are 23 equine specialists working in veterinary clinics[24].

The significant increase in demand for specialised care requires the availability of (veterinary) medicines to develop likewise, that is, the supply of (veterinary) medicines should specialise as well. The veterinary medicines industry is trying to cope with this demand. Given the fact that there is a similar demand in the field of human healthcare, the veterinary medicines industry might benefit from that knowledge and expertise. An existing dilemma, which is not specific to the Netherlands, is the limited availability of medicines for the equine sector. Veterinarians seem to be obliged to use medicines not officially authorised for equine use (off-label). Human healthcare sometimes faces the same problem, for example in specialised hospitals.

One Health Challenge

Based on the information and policies, we can draw a remarkable conclusion. Although there are common grounds in legislation and authorisation institutions, there is little, if any, cooperation between the veterinary and human fields. Some institutions involved, such as the CBG, are responsible for both 'sides', but maintain separate processes in fulfilling their roles. The crosslinks seem to be missing between the sector and even within institutions, resulting in unused potential.

Collaboration between human and veterinary healthcare professionals can be beneficial in controlling resistance more effectively. A striking example is the Dutch cooperation between Nethmap (resistance monitoring, human) and Maran (veterinary)[25]. By publishing the data simultaneously, trends can be analysed and recognised and moreover, there is improved coordination in the fight against antibiotic resistance. A similar cooperation can be found between SWAB and the Veterinary Medicine Authority (SDa)[26]. The private diagnostic laboratories possess a great deal of knowledge about the development of antibiotic resistance of the collected samples. However, due to privacy reasons or corporate interests, these data are not available for further research. Still, these are rare examples of cooperation. The cooperation between specialists and other healthcare professionals is limited and desirable. There is no significant exchange of relevant knowledge, and especially in primary care this would be useful to recognise and analyse infections at an earlier stage. Cooperation between human and veterinary healthcare professionals concerning antibiotic resistance could make a serious contribution to the constraint of the spread of resistant pathogens. There is a lot of knowledge and expertise available in both sectors not being used by one another. Reinventing the wheel should be replaced by symbiotic communication and cooperation.

The development of new medicines would probably also benefit from cooperation. In the past, most veterinary medicines were developed by companies which had already put on the market the active ingredient for human use. These days, pharmaceutical companies increasingly buy new molecules or dossiers for their own market purposes. Both industries, human and veterinary, develop their own molecules and products, instead of building on existing knowledge. This widens the gap between the veterinary division and human division. To be able to use existing knowledge and expertise from pharmaceutical companies operating in different sectors it is imperative to share it. This increases the chances for development of new authorisation for medicines against certain indications. Umbrella associations could play an important role in facilitating this exchange of knowledge and expertise.

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