Health for Animals
global animal medicines association

Illegal Veterinary Medicines

Impact and Effective Control →

2017

Illegal Veterinary Medicines
Impact and Effective Control

HealthforAnimals

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Overview

Illegal veterinary medicines include counterfeit, falsified and unregistered products and unapproved parallel imports. They also include compounded pharmaceuticals and illegal autogenous vaccines when these products are not manufactured or used appropriately and according to regulations. The risks of illegal veterinary medicines are principally issues of safety with secondary effects on business reputation and costs, and on trust in veterinary medicines. The risks of illegal veterinary medicines are not only lack of efficacy and safety for animals given the products, but also risks to human safety through food from animals treated with illegal veterinary medicines, less effective control of zoonotic infections and risks of increasing antimicrobial and antiparasitic resistance.

For the Animal Health industry as a whole, illegal veterinary medicines are a significant and growing problem. In some regions, there are already significant problems with illegal veterinary medicines, for example, illegal compounded pharmaceuticals in the US and Canada, and the full range of illegal veterinary medicines in many developing countries. The continuing rapid growth in online buying and selling of products (e-commerce) and a parallel growth in international trade especially of small packages, has created new opportunities for trade in illegal veterinary medicines. This is affecting all regions including the major markets of the US and the EU, where it is focused on companion animal illegal veterinary medicines purchased from the internet, including illegal internet pharmacies.

This report is a qualitative, rather than quantitative analysis of the problem of illegal veterinary medicines because, as for other clandestine and illicit activities, the scale of illegal veterinary medicines cannot be estimated precisely. A conservative estimate would give a value for annual global losses of US $1-2 billion. For the major Animal Health companies, the risks of illegal veterinary medicines are firstly, damage to business reputation especially arising from safety issues, and secondly, of growth in the market for these products and the associated loss of confidence in authentic medicines by veterinarians, consumers and animal owners.

Overview

Key lessons learned from Crop Protection and Pharmaceutical industries in delivering success against illegal, counterfeit and falsified products

- **Manage reputation** of industry and companies
- **Raise awareness** of all stakeholders
- **Communicate an effective narrative**, emphasise impact on safety
- **Collaborate** with and expand actions of enforcement agencies
- **Use data** to show trends and case studies
- **Don't waste resources** trying to quantify losses
- **Allow 5 - 7 years** for a programme to become fully effective

Recommendations are made to develop an effective strategy for the control of illegal veterinary medicines by Animal Health companies, enforcement agencies, customers and other stakeholders. The recommendations draw on the extensive experiences in the human Pharmaceuticals and Crop Protection industries. Whilst remaining cognisant of the significantly smaller size of the animal health industry, both the Pharmaceuticals and Crop Protection industries suffer from illegal products, and safety is the major consideration for both industries. One successful approach is to leverage smaller budgets against high advocacy. Finally, it is important to recognise that it will take 5 to 7 years and appropriate resources to affect the recommendations and to see the full impact on illegal veterinary medicines.

Main Recommendations

Increase awareness and deliver an effective narrative

- **Develop an effective narrative** for communication to the media, and key partners and stakeholders e.g.
  - Safety of animals, people and society
  - Examples of the consequences of illegal veterinary medicines
  - Animal owners: Avoiding illegal veterinary medicines, and choosing authentic VMs, for example when buying on-line
  - Veterinarians: Liability for compounded products / autogenous vaccines
  - Avoid complicated definitions / subcategories of illegal veterinary medicines
- **Deliver a narrative** and **motivate changed behaviour** by communication to key opinion leaders, veterinarians, animal owners, distribution chains, media, enforcement officers and regulators
- **Active engagement of companies** to deliver commitments to identify illegal veterinary medicines and act against the perpetrators

Strengthen international and national enforcement agency programs

- **Raise priority of action** against illegal veterinary medicines
- **Support initiatives** e.g. to enable customers to identify approved internet pharmacies
- **Encourage prosecution** of offending traders, illegal internet sites, etc.

Improve utilisation of data collection and analysis

- Create an industry-wide **database of incidents** involving illegal veterinary medicines
- **Identify trends** in types of illegal veterinary medicines, regions, channels
- **Communicate results** and case studies through third parties (see narrative)
- **Provide relevant information** for rapid identification of company products to customs and other agencies

Facilitate identification of authenticity

- **Clearly identify regulator-approved outlets** (physical and internet sites for over the counter (OTC) and prescription-only products)
- **Increase adoption of low-cost fraud prevention** (e.g. tamper-evident seals on high vulnerability products and raise awareness of these in veterinarians and owners)
- **Review cost benefit** of security technologies with enforcement agencies (especially customs) for vulnerable products and new products

List of Tables and Graphics

Introduction

The problem of illegal veterinary medicines

Illegal medicines affect both human and veterinary products. They are, first and foremost, a matter of **health and safety**, for both animals and the public. Illegal medicines may cause harm to patients, human or animal, and fail to treat the disease for which they were intended. They do not pass through the usual evaluation of quality, safety and efficacy that is required for authentic, authorised medicines. Illegal medicines pose a threat because of the conditions under which they are often manufactured, in unlicensed, unregulated, uninspected and often unsanitary sites. The "medicines" themselves pose a threat to health and safety because their contents are not regulated, may be contaminated and may contain no or the wrong active pharmaceutical or biological ingredient (API) required to safely deliver the therapeutic / prophylactic benefit for which the medicine was intended or prescribed. Illegal medicines are no longer confined to developing[1] countries but now affect all regions including the US and EU, and affect all the main therapeutic and prophylactic categories [1-6]. Pharmaceutical counterfeiting is a highly profitable, criminal activity that carries a minimal risk to the criminals which is why it has attracted both small-scale criminals and organised crime including drug traffickers, firearm smugglers and even terrorists [1, 7].

Illegal veterinary medicines impact on, and compete with both innovator (originator) and generic veterinary medicines for companion animals (dogs, cats, horses) and production animals (cattle, pigs or swine, poultry, sheep). Authorised veterinary medicines (VMs), both vaccines and pharmaceutical products, are affected by the trade in illegal veterinary medicines which include the growing problem of illegally compounded animal medicinal products [5, 8]. Illegal veterinary medicines are present in both developed and developing countries and have negative effects on human food safety and security, antimicrobial resistance and control of zoonoses, and lead to a loss of confidence in medicines and veterinary care [2, 4, 9, 10].

1 As defined by United Nations 2014

The major provenance region for illegal veterinary medicines is Asia, particularly China and India as sources of both **API and finished products**. However, other regions are also sources including Middle East and Africa. Increasingly, API, primary and secondary packaging, and labels are supplied separately for assembly into finished products in, for example, the EU and the US. This makes detection more difficult for enforcement agencies including customs. Distribution of illegal veterinary medicines may be through either legitimate distribution channels, including officially approved online pharmacies and more traditional distribution channels (wholesalers, pharmacies and veterinarians), or be distributed illicitly to companion animal owners and farmers through illegal internet pharmacies and social media, and in some regions through distributors and even street vendors.

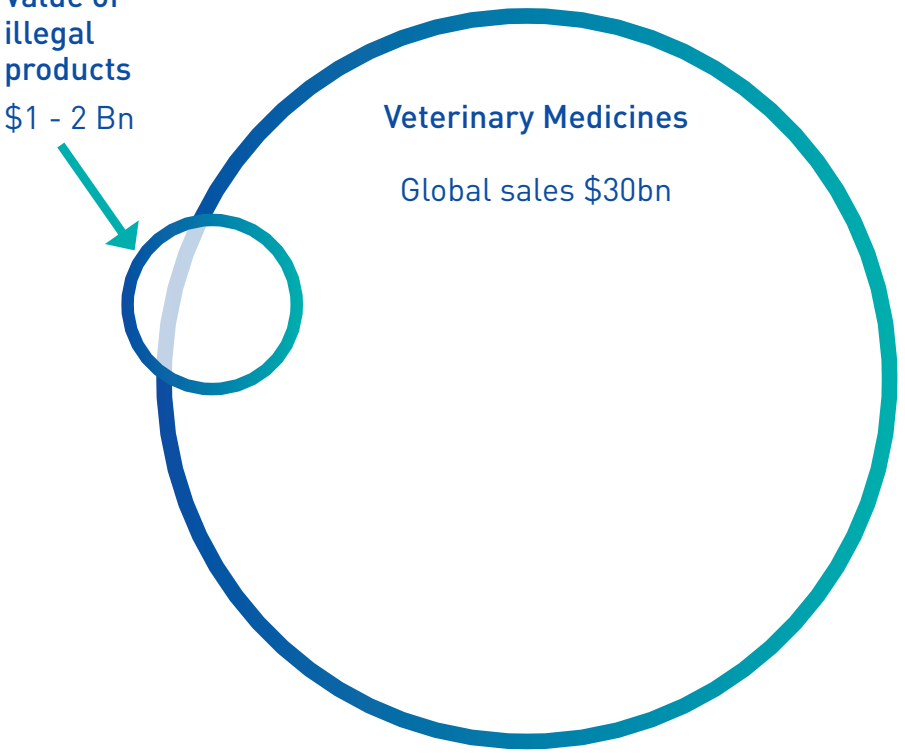
The e-commerce or internet supply of illegal veterinary medicines for companion animals is growing rapidly and is affecting all regions including developed markets such as the EU and the US. The situation with farmers is more variable between countries and regions with few problems regarding illegal veterinary medicines in developed countries (a consequence of effective regulatory testing and supermarket purchasing requirements). However, there is widespread and large use of illegal veterinary medicines in the developing countries of SE Asia, India, Africa and Latin America [11]. The lack of effective VMs especially in developing countries, causes reduced agricultural productivity and aggravates poverty. In all regions, the primary motivation for purchase of illegal veterinary medicines is lower costs often combined with secondary factors principally, lack of awareness by consumers [12].

Estimating the scale of illegal medicines either human or veterinary is, inevitably imprecise because the activity is illicit and clandestine. There are numerous estimates of the size or value of the market for illegal human medicines, and these broadly range from 3 to 10% of the market for authentic approved products.

The veterinary market for approved products is approximately US $30 billion, a significant market for criminals to attack where profitability is high and risks are low but a relatively small market compared with human pharmaceuticals. It's clear from the data gathered in this report that there is a significant and growing problem of illegal veterinary medicines; this affects the major markets in the developed countries as well as the more widely recognised problem in developing countries. It is also reasonable to make a conservative assumption that illegal veterinary medicines are a smaller percentage of the veterinary market compared with the human market, perhaps 3% or US $1 billion of illegal veterinary medicines, annually. This is consistent with OECD – EUIPO data for customs seizures related only to intellectual property right (IPR) counterfeits for all pharmaceutical products (mostly human) which was 2-7% by value [12]. That analysis is very conservative as many IPR-infringing goods are seized domestically. It cannot be excluded that the total value for illegal veterinary medicines may be higher than 3%. For example, a study in Canada estimated that the losses from illegal veterinary medicines were approximately 10% [13] and a figure of 10-15% has been estimated for Brazil (see Appendix 3 and Sections 2.2 and 2.3). Figures for some developing countries in, for example, sub Saharan Africa will be much higher. In addition to direct business costs, there are unquantifiable business risks for the major animal health companies arising from the potential for reputational damage by the presence of illegal veterinary medicines in the wider market.

Value of Illegal Veterinary Medicines
(estimated annual losses)

- Total loss estimated $1 - 2 Bn
- International trade losses $0.75 - 1.5 Bn
- Customs seizures exclude domestic (within country) losses
- Growing losses especially via e-commerce/ Internet and from compounding



The importance of actively countering the existing and growing problem of illegal medicines, specifically human medicines has been increasingly understood over the last 10-15 years by governments, national and international agencies, and businesses.

Identification, interception and prevention of illegal human medicines and illegal veterinary medicines are complicated by the proliferation of products, a wide range of customers, the complexity of pharmaceutical global manufacturing and supply chains, and multiple forms of transport for API, excipients and packaging. Specific obstacles for effective interception of APIs and illegal veterinary medicines include complex and different national and regional regulatory regimes, and the separation or diffusion of chemical (API) and medicines oversight across agriculture, health, environment and other government ministries. Furthermore, there may be inadequate regulation and penalties in some countries.

For international trade, there is additional diffusion of responsibility across numerous agencies and geographic jurisdictions. The ministries and agencies involved are often not well coordinated and may lack investigational or enforcement authority, and sufficient resources to address all issues within their remit. The situation is compounded by lack of awareness of the impacts and market size of illegal medicines in general, and especially so for illegal veterinary medicines. In customs or border control agencies there are particular difficulties in identification of illicitly destined chemicals, and lack of resources for qualified personnel and equipment. Furthermore, the initial identification and verification of illegal veterinary medicines may be predicated on suspicions or information from third parties, most often Animal Health companies, and industry associations, distributors, disgruntled customers or other observers [12].

Defining illegal veterinary medicines

There is a **diversity of opinion on terminology** and definitions of illegitimate pharmaceutical products [1, 14]. This is, in general unhelpful as it creates confusion and complexity with little or no benefit for many of the most important stakeholders including consumers / animal owners, veterinarians and many of the 'first line' enforcement agencies including customs officers.

The WHO has, until very recently used the following definition: Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products. However, in 2017, WHO adopted revised definitions using three, mutually exclusive categories: **Substandard, Unregistered / Unlicensed, Falsified** [15]. Substandard is also referred to as 'out of specification.' Unregistered / unlicensed medical products refer to the country in which they are sold and they may or may not have obtained the relevant authorization from the national/regional regulatory authority of their geographical origin. Where **compounded products and autogenous vaccines** would fit into this classification system is unclear given that they are not subject to full registration requirements and their legal status is situation dependent. They have a valuable and legitimate role but when these products are not manufactured or used appropriately and according to local regulations they may lack efficacy or pose risks to safety. Others have suggested additional categories of products, for example stolen, diverted and product tampering.

The three new, WHO categories deliberately exclude the term **counterfeit** which is often used to define, and associate with the protection of IPR. The EU has also adopted this approach of specifically excluding counterfeits and has adopted the term Falsified Medicines, where "falsified" is used to distinguish the issue from IP violations ("counterfeits"); falsified medicines are a major threat to public health and safety.

The European Medicines Agency (EMA) has adopted the following definitions [2]:

- Falsified medicines are fake medicines that are designed to mimic real medicines.
- Counterfeit medicines are medicines that do not comply with intellectual-property rights or that infringe trademark law.

Of course, **many falsified medicines are also IPR counterfeit medicines**.

However, for OECD, European Union Intellectual Property Office (EUIPO) and the World Customs Organisation (WCO), as well as pharmaceutical companies (human and veterinary), **intellectual property losses are important**. They also represent substantial losses to national economies and reduced tax revenues for governments. Much of the data collected by customs authorities is based on IPR counterfeits and copyright piracy [12]. (Further details regarding terminology is presented below under 'Additional information').

It should be recognised that the term counterfeit is widely used more broadly than in relation to IPR, and in a generic sense, it is used interchangeably with fake or falsified. Furthermore, for many stakeholders including veterinarians and animal owners, customs and enforcement officers, and company field staff, the term 'illegal' is a much clearer term to work with; details of types of illegal product can be clarified subsequently during an investigation. The finer distinctions between the various categories of illegal are not relevant to a decision on whether or not a product is illegal and to initiate appropriate action. This report does not attempt to adjudicate on the preferred terminology for VMs. However, **the term adopted throughout this report is illegal veterinary medicines and this includes falsified, substandard, unregistered / unauthorised, illegal compounded products, illegal autogenous vaccines and IPR counterfeits.**

In this report, the term **e-commerce (electronic commerce)** is used broadly to include the buying and selling of goods and services, or the transmitting of funds or data, over an electronic network, primarily the internet. These business transactions occur either as business-to-business, business-to-consumer, consumer-to-consumer or consumer-to-business.

What are Illegal* Veterinary Medicines?

Illegal Products

Not legally authorised in the country

Illegal supply or use of an authorised veterinary medicine

E.g. Use without a veterinary prescription

Counterfeit or falsified medicines

- Fail to meet specifications of the authorised product
- Reduced or excessive quantities/potency of the active ingredient/antigen
- High concentrations of impurities or contamination
- Different active ingredient/antigen
- False labelling (e.g. invalid claims, wrong expiry date, false batch/lot number

Abuse of extemporaneous preparation regulations e.g. compounding, autogenous vaccines

- Not restricted to use in a specific animal herd or flock
- Compounded drugs and autogenous vaccines do not have verified safety and efficacy
- Manufacturing standards may not be approved

Authorised veterinary medicines are approved by regulators for the treatment and prevention of diseases/disorders, and include vaccines and pharmaceutical drugs

* Illegal products also include products that are stolen or have been tampered with. Counterfeit medicines include products that contravene intellectual property rights (patent, trademark, copyright, design).

Additional Information on terminology

One of the underlying reasons in making counterfeits a separate classification in human medicines is that they are not regarded *per se* as a public health and safety issue but rather as a commercial issue. In addition, for WHO and EU / EMA, the definition of these different terminologies may be important in the context of data collection and to make legal distinctions, for example, between poor quality (substandard) medicines and counterfeits that infringe intellectual property rights (trademarks, designs, patents).

A working definition of "falsified medical products" was approved at the World Health Assembly May 2017 [15]: "Medical products that deliberately/fraudulently misrepresent their identity, composition or source."

Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, or reproduction of an authorized medical product or the manufacture of a medical product that is not an authorized product. Any consideration related to intellectual property rights (IP) does not fall within this definition.

IFPMA has welcomed this approach to use the term "falsified" for the purposes of the work within the Member State mechanism. Reaching this consensus was a major step forward [16]. This definition is in line with IFPMA's position: "...as stated in our Ten Principles, patents have nothing to do with falsified medicines. Falsified medicines are not an IP issue but a public health threat. Purely commercial patent infringement disputes which may arise in the ordinary course of business should not be confused with disputes related to the production of falsified versions of genuine approved medicines. In order to detect a product with a false representation of its identity, some intellectual property tools such as trademark could be used. However, they will not be a determining factor to declare a medicine falsified. Other criteria such as the intention to deceive are key." "As the WHO does not intend to "propose, or affect in any way, national and/or regional legislation either in existence or that may be drafted in the future", the IFPMA and its members will continue to adapt their terminology to their interlocutor."

Risks to Animal and Human Health, Society and Business

Animals, owners and veterinarians

Before authorisation (registration, approval) authentic medicines including VMs have undergone extensive and independent evaluation to confirm the validity of the product label claims for efficacy and safety in the animals for which the product is licenced. In addition, from the beginning of marketing of an authorised VM, **efficacy and safety** information continues to be collected and reviewed through, for example, pharmacovigilance reporting and product reviews by the regulatory authorities. For pharmaceutical drugs, the quality (also referred to as chemistry, manufacturing and control) of a product is confirmed both before approval and during subsequent manufacture. Quality criteria are critically important to ensure that the product specifications remain unchanged both between manufacturing batches and during the shelf-life of the product. These criteria include the specific manufacturing processes and related controls, the source and specification of API and excipient, drug strength, purity (and absence of potentially dangerous impurities), stability (e.g. maintenance of strength and absence of impurities over the product's shelf life), and bioavailability (1, 5, 6, 11, 14, 17].

The effects of **quality criteria** on bioavailability (the systemic exposure of an animal to the drug) have a pivotal effect on efficacy and safety, and may be adversely affected by variations in source / quality of API and formulation excipients, and manufacturing processes. The risks arising from inadequate quality is further exacerbated when compounded products (or extemporaneous formulations) are used as the effects on bioavailability caused by changing formulation excipients, adding flavours and changing from oral to transdermal gels etc. are often completely unknown. Compounded products are typically prepared in pharmacies, and are unregistered products and, in strict terms, are illegal for animals in some jurisdictions including the US [18, 19]. They do provide useful examples of the risks and harm that can occur from use of illegal veterinary medicines in general, as many are produced in completely unregulated premises and without trained staff.

The benefits, harm and risks of veterinary compounded products in the US have been reviewed in general [19] and specifically for small animals [20] and horses [8, 21] and include examples of fatal adverse effects and of clinically significant variations in API content and in bioavailability. It should be noted that the US FDA has indicated within strict guidelines, the acceptance of compounded medicines for individual animals, excluding food animals, and provided that they are not prepared from bulk API and where no alternative licenced product is available. Liability for compounded products is usually that of the prescribing veterinarian and not that of the pharmacy that prepared the product.

For **vaccines**, there are similar quality criteria to those described above for pharmaceutical products. For autogenous vaccines, there is only limited safety data and little or no efficacy data (with variations between regulatory authorities).

All authorised VMs include detailed approval of primary **packaging** (which may be important for product stability), and secondary packaging and **labelling**. These are normally specific to individual countries in which the product is marketed and ensure that the VM is effective against local diseases and meets local safety requirements. However, illegal veterinary medicines may not be appropriately packaged and labelled for individual countries.

Pharmacovigilance. In developed countries and increasingly in less developed countries, there is a requirement to report lack of efficacy and adverse effects of approved VMs. Such reporting of illegal veterinary medicines is much less likely because of their illicit nature and, in the case of compounding there are no pharmacovigilance reporting requirements in many countries including the US.

Adverse effects of illegal veterinary medicines. Illegal veterinary medicines are not approved or registered and their use may result in a variety of problems for the animals being treated and their owners, together with their veterinarian if the medicine was prescribed. Serious clinical illness and even mortality of animals may result from the use of illegal veterinary medicines. Specific adverse effects of an illegal veterinary medicine will depend on the ingredients as the following four scenarios exemplify [17-21]:

1. No active ingredient, no harmful ingredients: The product is not effective and the animals condition may deteriorate. In the case of antimicrobial and antiparasitic products this apparent efficacy failure may result in the unnecessary use of second-line or reserved products and consequently increased risk of resistance development.
2. No active ingredient and one or more harmful ingredients: A wide variety of harmful ingredients have been identified in illegal human medicines including bacterial contamination, boric acid, acetone and ethylene glycol (caused by antifreeze contamination of containers). Bacterial contamination of sterile products is of particular concern. There have been several examples of this in humans leading to fatalities in both developing and developed countries [17]. In animals reports are limited, most likely due to under-reporting, with clinical signs of toxicity often being attributed to the original clinical condition for which treatment was administered rather than to toxicity of the treatment.
3. Wrong drug used in the illegal product: An example of this in human medicine was the substitution of orlistat in counterfeit versions with sibutramine and potentially causing harmful interactions with other medications.
4. Wrong concentration or wrong dose of the drug or antigen: In developing countries this is a recognised hazard with veterinary vaccines. For example, there may be reduced antigen quality and / or dose if the vaccine was not produced to GMP and failed to meet specifications, or if there was a lack of adequate temperature control in the distribution chain, or if the vaccine was diluted excessively. The consequences include increased risk of fatal infections in the animals and failure to control the spread of infection to other animals or herds/ flocks. For vaccines intended to control zoonotic infections (e.g. rabies) an additional, important consequence may be increased risk of infection in humans.

In veterinary pharmaceuticals, two examples involved compounded products [8, 21] as follows:

In 2009, 21 Venezuelan polo ponies, on their way to participate in the US Open Polo Championships, died within hours of receiving a compounded vitamin/mineral injection from a Florida compounding pharmacy. The supplement, made to replicate a European medication contained selenium, magnesium, vitamin B, and potassium had been incorrectly formulated with toxic levels of selenium.

In 2014, 4 horses died and 6 became ill after receiving a compounded oral product containing pyrimethamine and toltrazuril from a veterinary compounding pharmacy in Kentucky. Two lots (one a paste and the other a suspension) were made that were believed to contain extremely high concentrations of pyrimethamine. One of the compounds was tested by the FDA and determined to contain 2380% of the pyrimethamine concentration stated on the label. This drug combination is not approved for any use in the United States and was used to treat horses with equine protozoal myeloencephalitis. FDA-approved drugs (pyrimethamine/sulfadiazine, diclazuril, and ponazuril) were available in the United States and labelled for treatment of the disease but an unapproved product compounded from bulk chemical was administered instead. Remarkably, the veterinary compounding pharmacy in this case filed a third-party complaint against the veterinarian who provided the prescription. Another example caused the death of three race horses treated with a super-potent clenbuterol illegal veterinary medicine [21].

Why do Illegal Veterinary Medicines Matter?
Impacts on Animals, Society and Manufacturers

Animals, Owners & Veterinarians

- ↓ Efficacy
- ↑ Disease
- ↓ Safety
- ↑ Adverse effects
- ↑ Resistance (antimicrobial & antiparasitic)
- ↑ Environmental risk

- ↓ **New drugs**
- ↓ **New vaccines**

Animal Health Companies
(providing authorised medicines)

- ↑ Risk
- ↑ Costs
- ↓ Revenue
- ↓ Brand

- ↓ **R & D Investment**

Society

- ↓ Food safety
- ↑ Risk of antibiotic resistance
- ↓ Agricultural productivity (especially in developing countries where it aggravates poverty)

Lack of new veterinary medicines to treat/prevent disease

People and society

The **health and safety** issues that occur with increasing use of illegal veterinary medicines produce both general and specific issues for people and societies. The failure of some illegal veterinary medicines to deliver the expected therapeutic or prophylactic effect and / or to cause toxic effects is not confined to putting the animals' lives at risk. It may also place the health of the users of the products at risk through contact with the illegal products and the wider human population at risk through consumption of food from animals treated with these products because of chemical residues, and, or through potential effects on the development of increased antimicrobial resistance. When animal vaccines and pharmaceuticals are important to the control of zoonotic infections, then the use of illegal veterinary medicines increases the risk of lack of efficacy and of increased spread of infection to humans from companion and/or production animals. The potential lack of efficacy arising from the use of illegal veterinary medicines in production animals has the potential for substantial negative impact on the efficiency of production with consequent increases in the price of food.

The consequences of the use of illegal veterinary medicines may result in a **loss of confidence** of pet owners, farmers and veterinarians in medicines and, more generally, in veterinary health care systems. This effect is also described for human patients using human medicines [4].

Wider economic effects. The wider consequences on Animal Health companies of illegal veterinary medicines which compete with authentic VMs is the **reduced incentive to invest and innovate**, and the diversion of their expertise and resources to counter and investigate illegal veterinary medicines. However, the **economic consequences are not confined to individual companies**. A 2016 analysis by the EU intellectual property office (EUIPO) and OECD working in conjunction with World Customs Authority (WCO) data for 92 economies has highlighted the impact on global trade of counterfeit and pirated products including pharmaceuticals [12]. This analysis excluded domestic seizures of IPR infringing goods (i.e. goods not seized by customs) and is therefore very conservative as many patent-infringing goods are seized domestically. The study estimates that the international trade in counterfeit and pirated goods in the EU amounted to 5% by value of imports across all product types. This compares with other estimates that suggest worldwide, an estimated 10% of all medicines are counterfeit [17]. Another relevant comparison is provided by the plant protection (pesticides) industry which has an estimated worldwide market of US $60 billion and, as for pharmaceuticals is underpinned by IPR and is highly regulated. The market share of illicit pesticides is estimated to be 10-15% or US $6-10 billion, globally [22] and 13.8% of EU sales [23].

Pertinent to the effects on society as well as individual companies, the EUIPO / OECD/ WCO analysis indicated that the relative impact of counterfeiting across industries is twice as high for a group of developed countries, including the EU and the US, than it is for the world as a whole. This is because of the much greater economic importance of intangibles, including **IP rights** (patents, trademarks, copyright, design rights), which are clearly relevant to pharmaceuticals including VMs. The report noted that counterfeit and pirated[2] trade is a major threat to any modern, knowledge-based economy, and given the fundamental importance of IP, that counterfeiting and piracy must be directly targeted as a threat to sustainable IP-based business models [12].

For governments, there are other substantial negative effects of illegal medicines including illegal veterinary medicines such as **reduced tax revenues and increased public expenditure** required to counter illegal veterinary medicines by regulators and enforcement agencies.

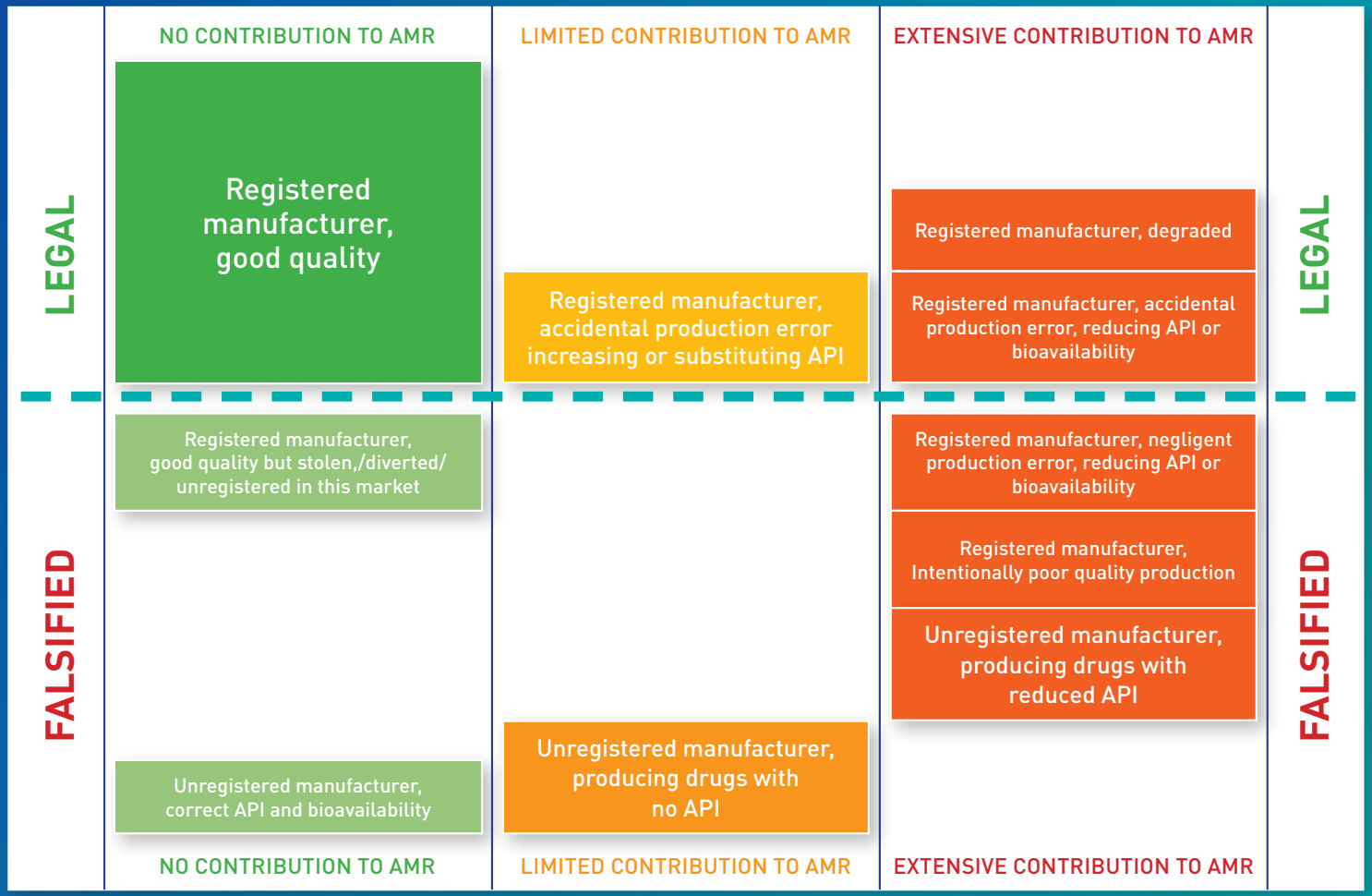
At a more health focused level, an important consequence of falsified and substandard medicines, either veterinary or human, is their **contribution to development of resistance to antimicrobial and antiparasitic products**, and which has 'One Health' implications for the health of both humans and animals [9, 10, 24, 25]. Illegal veterinary medicines are particularly likely to contribute to antimicrobial resistance development where they provide sub-therapeutic doses of API to animals. Illegal veterinary medicines that contain little or no API, or slightly substandard authentic VMs are less likely to contribute significantly to antimicrobial resistance development [10].

The O'Neill review on antimicrobial resistance (2015 and 2016) was commissioned by the UK Government and The Wellcome Trust, and it identified two specific aspects of the AMR problem which are particularly pertinent to illegal veterinary medicines: **The online sale of antimicrobials without prescription, and the supply of poor-quality and falsified antimicrobial drugs** [9, 10, 26]**.** As highlighted in the reports, the growing number of online pharmacies (human and veterinary) exploit gaps in the global regulatory mechanisms to offer antibiotics for sale around the world, often without prescription or clinical guidance – something that fuels dangerous self-medication habits (including owners medicating their animals) and encourages the development of drug-resistant strains of infection by increasing unnecessary and excessive antimicrobial use. Meanwhile, poor quality and falsified antimicrobials fuel the development of resistance by delivering sub-therapeutic doses, providing enough exposure to the drug for microbes to begin developing resistance, without properly treating the infection [9, 10, 26].

2 Counterfeit refers to fake, IP infringing goods. Pirated refers to unauthorised reproduction of copyright-protected works

Antimicrobial Resistance and Medicine Quality

Pisani for AMR Review, November 2015



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Business

The effects of illegal veterinary medicines on Animal Health companies are partially represented by the effects discussed above for animals, and people and society. Additional effects on businesses centre around the following three areas:

1. Direct cost to sales

Illegal veterinary medicines compete for sales of authentic products. Estimating value has to consider whether the counterfeited goods were offered through the primary market for authentic products where transaction value is usually close to replacement value, or through the secondary market (e.g. illegal internet sales) where the replacement value is likely to be lower. As discussed in sections 1.1 and 2.2, a conservative estimate of 3% of authentic sales has been assumed for illegal veterinary medicines on the basis that the VM market is relatively small and that the valuable market for authentic production animal products, at least in developed countries, is less likely to support large use of illegal veterinary medicines because of the higher risk of detection and large penalties. This contrasts with companion animal products where illegal veterinary medicines are growing in all markets facilitated by the rapid growth of e-commerce generally and by compounding in, particularly but not only, North America.

2. Reduced value of IPR and disincentive to invest in R&D

The potential negative impacts of illegal veterinary medicines on IPR value and confidence to invest were referred to in Section 2.2. Specific evidence for the disincentive to invest was reported in the Animal Health Global Benchmarking Survey 2015 which found that in the US, 10 pharmaceutical products had not been developed or progressed to approval due to pressure from illegal compounding [27].

3. Reputational damage

This was referred to in some responses to the surveys of Animal Health companies and national associations (Appendixes 1 and 2). An insightful analysis was provided from the plant protection industry and the interview with the Director of Anti-Counterfeiting for the industry body, CropLife International (Appendix 3). A pivotal point was that illegal products for the human pharmaceutical, animal health and plant protections industries are matters of safety, and for animal health this is animal, public and environmental safety. Animal Health companies and their industry must be prepared to show that they are actively addressing the question: **What are you doing about these illegal products?** Based on experience in CropLife International, this applies regardless of where the fake product is marketed. For example, a fake product bearing a company name or logo in an African country is just as significant as a fake product in the EU or the US, especially so when a senior staff member of that Animal Health company is faced with reporters.

Illegal veterinary medicines and distribution chains

All regions suffer from illegal veterinary medicines however, there are substantial differences in the predominance of individual distribution channels and the types of illegal veterinary medicines between regions and, in some cases between individual countries within regions (for example, illegal compounding is a problem in Italy but not in all EU countries). Information for this section represents a summary of the qualitative information obtained from the surveys and interviews presented in Appendixes 1, 2 and 3, together with desk research. A summary of the regional importance of distribution channels and types of product is shown in Table 1.

It should be appreciated that this qualitative information is subject to uncertainty because of the limitations of the input however it does indicate the major features of the illegal veterinary medicines landscape by region and type.

Regional profiles and trends

In the developed countries represented by the US, Canada, EU, Australia and New Zealand, the most important illegal veterinary medicines are for companion animals (equines, cats, dogs). In the US and Canada this is dominated by compounded pharmaceuticals and of greatest concern, to companies and regulators, are those produced from bulk API. The use of compounded products and autogenous vaccines for companion animals is growing. Veterinarians are heavily involved in promoting the illegal use of these products, and in their supply either providing compounded/vaccine products from their offices or prescriptions for owners to use at pharmacies, both physical and internet. The motivation of veterinarians is often likely to be a belief that they are servicing their clients by providing cheaper products without understanding the risks and implications of their actions.
There is also growing misuse of the medical device category for systemic administration of some compounded products.

Counterfeit, falsified and unregistered illegal veterinary medicinal products including bulk supplies are a particular problem for **companion animal parasiticides** in the US and Canada, and also in other developed countries. Their **supply is increasingly through unapproved internet pharmacies, other e-commerce sites (e.g. eBay, Amazon) and more recently via social media (Facebook, Twitter etc).** Supply of authorised VMs through illegal internet sites is a growing problem with companion animal products across all regions.

The situation for illegal veterinary medicines in **Australia, New Zealand and Japan** is that the full range of illegal veterinary medicines are found however, the scale appears to be less than in the US. Compounding is an increasing problem in Australia. Japan appears to have very few illegal veterinary medicines although there are some indications of underestimation of the problem.

North America and Europe

- Companion animal (equine, dog, cat) illegal veterinary medicines dominate over those for production animals (cattle, pigs, swine, poultry, sheep)
- Compounded pharmaceuticals for companion animals are a large-scale, growing problem in the US & Canada
- Veterinarians are encouraging use of illegal compounded products (often to provide cheaper products without appreciating the risks and implications)
- Companion animal compounded products are less important in EU
- Companion animal counterfeit, unregistered, falsified illegal veterinary medicines are important especially parasiticides
- Sales of companion animal registered products marketed illegally via internet are increasing
- Production animal illegal veterinary medicines are not, in general an important problem in the US and the EU (strong enforcement and large penalties)
- Some illegal antimicrobial compounded products for cattle (US, Canada) and for poultry (Italy)
- Some illegal supply of registered and counterfeit antimicrobials for production animals in the EU, including unauthorised parallel imports between member states

In the **developing countries** of Latin America (e.g. Brazil), Asia (e.g. China, India, Thailand) and Africa (e.g. South Africa and sub-Saharan Africa [11]) there are crucial differences in the pattern and scale of illegal veterinary medicine use compared with developed countries. This reflects the greater proportion of **production animal products** in these Animal Health markets, combined with usually less well-developed regulatory systems and enforcement. It should be noted that farmers in these countries producing for export markets (especially those in the EU and the US), are much more compliant in avoiding use of illegal veterinary medicines and in minimising the use of AM products in order to comply with regulatory and customer requirements. However, for the majority of farmers in these developing countries, compliance with regulation is much poorer. Furthermore, in many of these countries legal access to authentic production animal VMs is often limited by supply constraints and costs. This encourages the use of cheap, **bulk API** in feed or water (e.g. **AMs** for pigs, poultry, fish), **illegal compounding, illegal autogenous vaccines**, and counterfeit, falsified and unregistered products such as injectable AMs, trypanocides and a wide range of **parasiticides** including endectocides. Frequently, illegal veterinary medicines are supplied by unregistered pharmacies, traders and street sellers, and there is a growing market in the sale of illegal veterinary medicines via the internet.

For companion animal VMs in developing countries, it is often a challenge for veterinarians to legally access authentic VMs and therefore supply via e-commerce internet sites / internet pharmacies are important to facilitate access to VMs even though many of the products are likely to be of questionable authenticity.

Table 1. Illegal Veterinary Medicines (IVM): Regional Importance of Distribution Channels and Types of Product

	USA, Canada	EU (Denmark, France, Germany, Italy, Netherlands, UK)	Australia, New Zealand	Japan	Africa (RSA, Other)	Latin America (Brazil, Peru)	Asia (India, Thailand, China)
Distribution Channel							
Primary[a]**:** Licensed wholesalers, veterinarians, approved physical retailers (pharmacies, merchants)	+++	+	+	+/-	++	++	++
Primary: Approved internet retailer supplier/ pharmacy	+++	+	+/-	+/-	+	+/?	+
Secondary[a]**:** Unapproved physical retailer/ merchants	+	+	+	+	++++	++	+++
Secondary: Unapproved internet pharmacies	+++ ↑	+++ ↑	+	+/?	++	++++	+++
Secondary: Other e-commerce (e.g. eBay, Amazon, Alibaba)	++ ↑	++ ↑	+	+/?	+/?	++++↑	+++↑
Secondary: Social media (e.g. Facebook, Twitter)	++ ↑	++ ↑	+/?	+/?	+/?	+/?	+/?
Types of Illegal Veterinary Medicine Products for Companion Animals (CA) and Production Animals (PA)							
Illegal compounded pharmaceuticals: CA	+++ ↑	+ varies by country	+	?	+	++	+
Illegal compounded pharmaceuticals: PA	+	+ varies by country	+	?	++ ↑	++	++++[b]
Illegal autogenous vaccines	+ ↑	+ ↑	?	?	++ ↑	+	++
Other IVM: CA	++ ↑	++ ↑	+	+	+	++++	++
Other IVM: PA	+	+	+	+	++++ [b]	++++ [b]	++++ [b]

+ Importance: + low, ++++ very high (>10% of market). +/? Present but scale is unclear. ↑ Increasing trend. ? Unknown / Information is not clear.

a. Primary and secondary refer to legality of channel (see text)

b. Excluding livestock and aquatic animals for export to US or EU for which presence of illegal veterinary medicines is minimal..

Supply chain vulnerabilities, protection and resilience, and trends

Markets for infringing products, including human pharmaceuticals and illegal veterinary medicines, develop dynamically and have been affected by several economic developments over the past 10 years as has been highlighted by a recent OECD EUIPO report [12] for trade in IPR counterfeits. Some **major, interrelated patterns and trends** can be distinguished including:

- Growing economic importance of IP rights and consequently growing economic incentives for "free riding" e.g. counterfeit[3] and falsified illegal veterinary medicines
- Increased international trade
- Globalisation of value chains which results in international fragmentation of production and shifts attention to IP to help capture value in fragmented and complex production processes
- Rapid growth of e-commerce in global (and national) trade
- Increased pressure for cost reduction, for example veterinarians using illegal compounding and illegal autogenous vaccines, and animal owners using other forms of illegal veterinary medicines as low-cost replacements of approved, authentic VMs

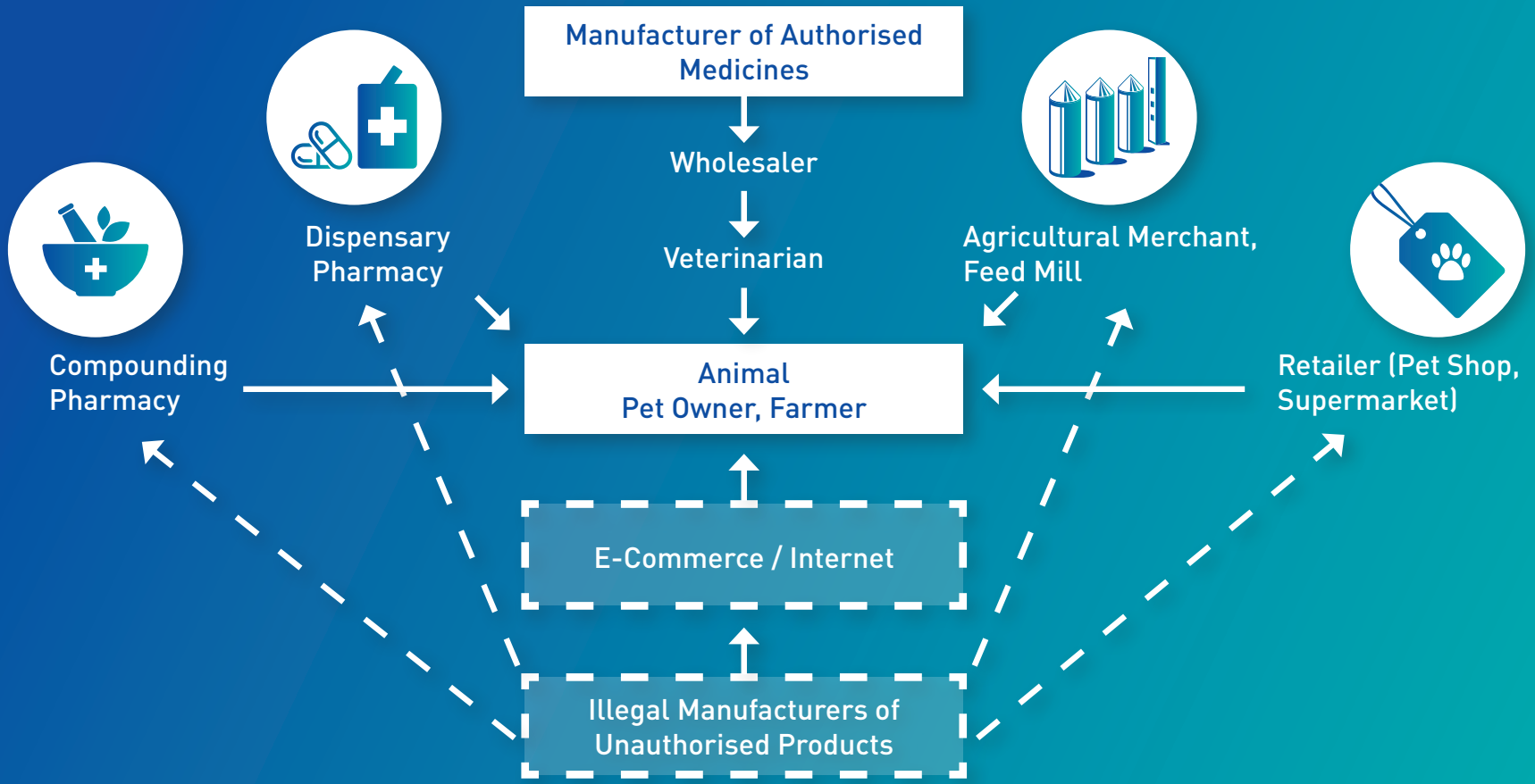
Complex, multinational manufacturing processes of authentic products contribute to increased vulnerability to counterfeiting of intermediates, including packaging and labels, as well as final products. Customs authorities collect data on the provenance economies of counterfeit trade (i.e. economies where the actual production of the infringing goods is taking place) and economies that function as a point of transit through which the infringing goods pass. Counterfeiters and pirates[4] tend to transport their products via complex trade routes, using several transit points. This is done for several reasons including:

- "Cleansing" of all documents and camouflaging the original point of production and/ or departure
- Establishing distribution centres for counterfeit and pirated goods (e.g. in free trade zones) and then forwarding in smaller orders to their final destination
- Processing of products (often in free trade zones), for example by adding counterfeit (or pirated) trademarks, repackaging or re-labelling

3 This section refers extensively to customs data and the term counterfeit is used advisedly to refer to products which break IP rights

4 Piracy refers to illegal reproduction of copyright protected material and it is often part of production of falsified products including some IVM

How do Animal Owners Access Veterinary Medicines?



Note that supply by e-commerce / internet also applies to approved, authentic veterinary medicines.

Therefore, it is often difficult for customs officers to determine the economies involved and particularly the provenance economy. Moreover, while imports of counterfeit goods may be targeted by local enforcement authorities, goods in transit are not within their scope which means they are less likely to be intercepted. The **seizure of quantities of counterfeit products, packaging and labels for** three well-known companion animal VMs in **the US** [28l] **and for a range of products the EU** [29] is consistent with the known practice of counterfeiters importing unlabelled products (which attract less attention and do not infringe trademark regulations) and then labelling with counterfeit logos or packaging into trademark-infringing packages in another economy that is closer to the destination markets and has weaker IP enforcement [12]. This is a known practice in the EU including with illegal veterinary medicines and is likely to be a risk in other regions, for example Mexico – US border.

The rapid growth of e-commerce in national and international trade has introduced clear benefits for businesses and consumers however, it also leads to risks in the context of trade in IPR counterfeit VMs and other forms of illegal veterinary medicines. Consumers are drawn to e-commerce sites because they are available continuously and access is relatively easy. E-commerce has therefore become a **major enabler for the distribution and sale of counterfeit,** pirated, falsified and other forms of illegal, tangible goods as it opens new possibilities to produce and distribute such goods in markets that were previously not readily accessible. For example, veterinary products in developed and highly regulated markets such as the EU and the US, were traditionally beyond the scope of most counterfeiters. In addition, counterfeiters are able to function across multiple jurisdictions, expanding their market and evading capture. They are able to take down (or authorities may take down) web-sites but then set up new websites overnight without losing their customer base. Some websites are of such high quality and sophistication that they rival those of the rights holder [12, 30].

Another feature of the increasing importance of e-commerce in national and international trade is the share of **small shipments**, mostly sent by post or express services, that is growing rapidly due to shrinking costs and growing demand from internet and e-commerce users. Small shipments are a **highly effective way to avoid detection and to minimise the risk of sanctions** against the perpetrators. This raises the cost of checks and detention for customs and the huge volumes of small international packages being traded has introduced significant challenges for enforcement authorities [12]. **Supply of illegal veterinary medicines direct to animal owners through illegal internet sites is therefore likely to continue to grow.**

Illegal Veterinary Medicines: Demand drivers

There are three main factors that drive demand for illegal products:

- The features of the product. Price and quality of the infringing product relative to that of the authentic product are key drivers to the decision to purchase.

However, not all purchasers will be aware that they are purchasing a counterfeit or falsified or otherwise illegal product. In the **primary market**, demanders (veterinarians or animal owners) wish for authentic products but may be deceived into buying illegal products if the counterfeiters have gained access to the normal supply chains (conventional physical distributors or approved internet pharmacies). This is also a recognised problem with human pharmaceuticals even in developed markets. In the **secondary market**, illegal veterinary medicines are purchased knowingly. In general, most purchasers of counterfeit products (especially non-professional purchasers such as companion animal owners) are not aware and do not even suspect that they are receiving illegal products [12].

- The individual consumer circumstances, for example their economic situation, and any concerns they may have regarding purchase or use of an illegal product such as illegal veterinary medicines.
- Risk of discovery, prosecution and penalty together with availability and ease of access to the illegal product.

For **veterinarians** in the US using illegal compounding for companion animals, there is minimal risk because of limited enforcement action by state and federal agencies, however there is significant professional risk for lack of efficacy and adverse safety reactions which is borne by the veterinarian and not the pharmacy.

For production animal and companion animal veterinary products, **direct access by animal owners** has become much easier in the last few years through the internet and e-commerce with the attendant risks of purchases of illegal veterinary medicine, knowingly or not. The **legal penalties** for companion animal owners are very low; the risks are from lack of safety and efficacy of the product administered to the animals. For production animal owners in developed countries (EU, US etc.), the risk of detection is considerable in the case of pharmaceuticals but less so for illegal vaccines and the penalties for use of illegal veterinary pharmaceuticals in production animals are high in these countries (legal penalties plus loss of market). However, in developing countries the risk of detection and the penalties are in general very low unless the production is for export markets.

Manufacture and access to illegal veterinary medicines

General illegal veterinary medicines

- Primary market participants (manufacturers of authentic VMs, and approved wholesalers, retailers, pharmacies (physical and internet), veterinarians, and end users / animal owners)
- Secondary market participants (manufacturers of illegal veterinary medicines, and unapproved retailers / merchants / internet pharmacies / physical pharmacies, and end users / owners)
- Internet and e-commerce (manufacturers of illegal veterinary medicines, unapproved internet sites and internet pharmacies, general retail sites (e-Bay, Amazon, Alibaba etc., social media, veterinarians, end users / owners)

Control by

- Customs / Border control authorities at entry ports in conjunction with other agencies e.g. Interpol / Europol / WCO, national enforcement agencies.
- Enforcement agencies in provenance and intermediate countries
- National enforcement officers at destination market
- Combined operations important including against illegal web sites

Illegal compounding and illegal autogenous vaccines

- Manufacturing and supplying pharmacies / laboratories / veterinarians
- Accessed via physical sites and internet
- Accessed by veterinarians and animal owners

Control by

- Regulators and enforcement agencies (federal and state)

Controlling illegal veterinary medicine markets: Recommendations

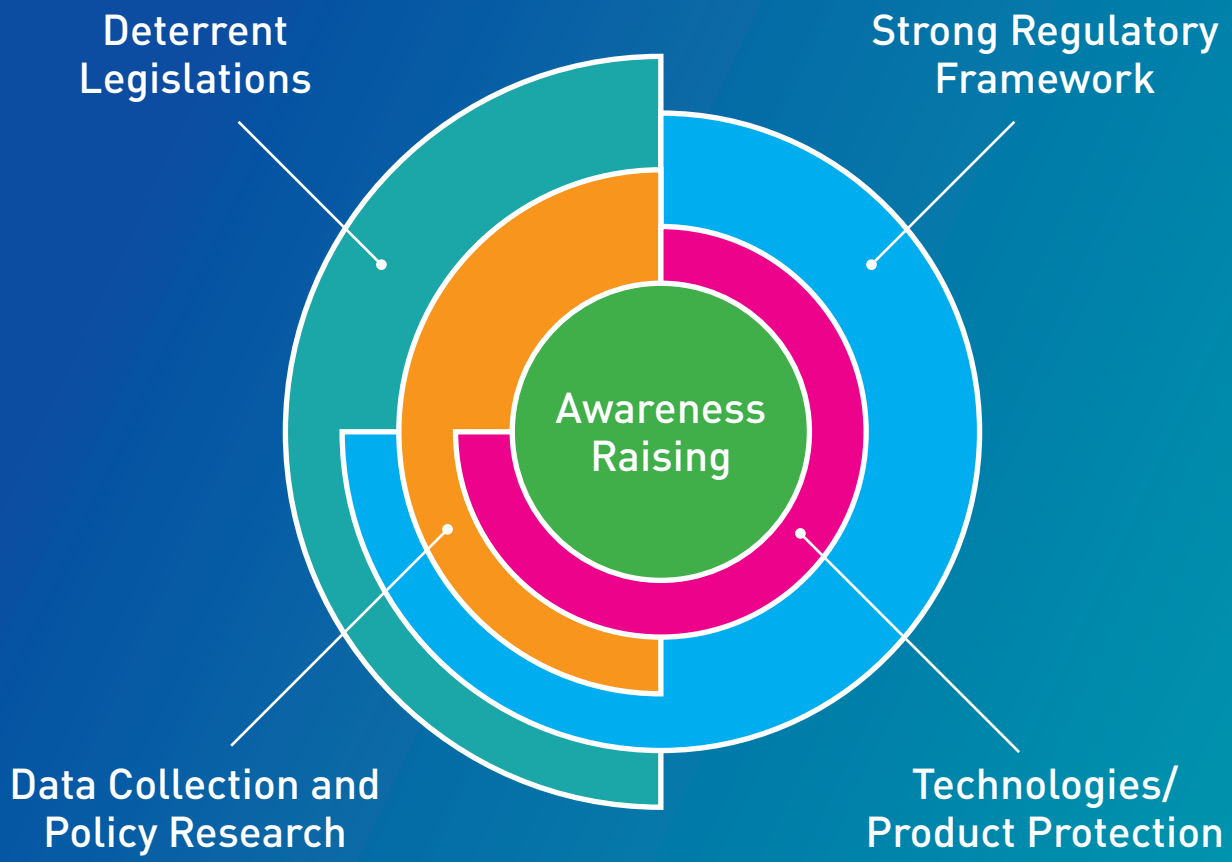
The fight against illegal medicines requires approaches that rely not only on their interception and prosecution of the perpetrators, which are inevitably limited in their scope, but also on prevention to reduce and contain the size of the counterfeit / falsified market. The overall objective is to lower the risks to animals and the public, and to increase the risks to traffickers.

The following excerpt from IRACM [31] provides a general overview of the strategies for prevention of counterfeit / falsified human medicines as adopted by "...various organisations around the world, governments, health agencies, associations and pharmaceutical companies in turn are taking individual or concerted actions that are effectively stemming the scourge and better protecting populations. These approaches are extremely varied and complementary, aiming to foster more ethical behaviour, to increase vigilance or to secure the pharmaceutical products and their supply lines. If such measures could be coordinated on a large scale and optimized in a comprehensive global strategy, the risk balance would certainly sway in favour of the patients and to the detriment of the traffickers."

The major elements of the IRACM strategy and that of other bodies such as WHO aiming to control illegal human medicines are:

1. Informing, training and advising healthcare professionals
2. Securing the supply chains
3. Organizing vigilance, monitoring incidents and systematizing feedback
4. Facilitating access to authentic medicines in developing countries
5. Educate and communicate to the general public

Tackling Illegal Veterinary Medicines



Falsified medicines respresent a serious threat to animals and society around the globe. It is a complex global health challenge, which requires an integrated, multi-stakeholder approach.

Source : IFPMA website

Awareness and engagement of animal health companies

Several company and regulatory respondents to the surveys and the interviews conducted for this report indicated the vital importance of engagement in the problem of illegal veterinary medicines. The strongest recommendations came from organisations representing human pharmaceuticals (IFPMA) [16] and plant protection (CropLife International) [33] which have seven or more years of experience of concerted action to draw upon. CropLife International's approach is considered successful. Its approach has been to **leverage smaller budgets against high advocacy** with governments and enforcement agencies (See Appendix 3 for additional information).

Visible and enduring support from Animal Health companies is considered essential to gain sustainable, long-term engagement with the issue by company staff not only at senior management levels but also in the field force / sales teams to identify and gather evidence of illegal veterinary medicines. Managers must then ensure that the evidence is validated and documented, and liaise with enforcement agencies and resolve appropriately. **Companies that take strong action against illegal veterinary medicines are less likely to be the victims of further illegal activity.**

Equally important is making information and case studies of illegal veterinary medicines available for collation (appropriately anonymised) and **publication by third parties**. This approach of third party publication helps to avoid the problem of illegal veterinary medicines being dismissed as merely a commercial issue and creates the necessary driving force for long-term raised awareness in the main stakeholders including key opinion leaders, regulators, enforcement officers, veterinarians and animal owners, as well as wholesale and retail distributors and pharmacies.

End-user and distributor awareness

The lack of awareness of illegal veterinary medicines and indeed of falsified human medicines is illustrated by the following recent reports [31]:

"A MarkMonitor survey of 4500 people from Great Britain, seven other major European countries, the US and China, has revealed that almost 30% of online consumers have been swindled when buying makeup, beauty products and medicine and may have put their lives at risk. Sixteen per cent of respondents said that they bought online medicines which turned out to be falsified. Thirty-four percent said they had experienced a bad reaction to the product, while 50% said they were alerted by bad quality. The survey results show that unintentional falsified health product purchases are highest in China, where 46% of consumers claim to have unintentionally purchased falsified products, followed by the Netherlands (28%) and Italy (27%)."

"According to an Alliance for Safe Online Pharmacies (ASOP) survey of 500 people, 55% of Americans have bought, or would consider buying, prescription medicines online. In addition, ASOP also found that 74%

of consumers who had purchased prescription medicines from an online pharmacy in the past would do it again. Fifty-three per cent of respondents perceive Canadian online pharmacies as risky but 20% would take the risk if the medicines were sold at a cheaper price. The investigation also revealed that those most likely to purchase online medicines are young people and regular social media users." Note that most Canadian pharmacies are not located in Canada and often in south east Asia [32].

For veterinary and human medicines, there are various national and international organisations that provide information on fake/falsified/counterfeit medicines including articles on safe use of internet pharmacies, identifying fake products and risks to safety and lack of efficacy. A list of relevant web sites is provided on page 51. Additional information may be found on individual national internet sites for regulatory authorities and enforcement agencies.

For **veterinarians and veterinary nurses** there is little specific information, however of relevance are the general recommendations for vigilance by healthcare professionals as provided by the International Institute of Research against Counterfeit Medicines in the following statement [31]:

"...while all the players in our healthcare systems share the responsibility, it is especially up to each and every individual to be vigilant. It must take several forms:

1. **A technical intelligence process:** For any type of medicine, pharmacists and doctors must pay heed to all the elements which might point to a counterfeit: an alteration in the appearance of a medicine (size, colour, shape or taste), its texture (for example, pills that are more friable), its packaging, any unusual side effects or the lack of efficacy of a treatment. They are also encouraged to know and regularly check the traceability methods and authentication procedures for healthcare products (Data Matrix codes, RFID marking, holograms, etc.).
2. **A public awareness platform:** Individually, day after day, healthcare professionals have the authority to inform patients about the very real threat linked to fake medicines. Their task is also to alert them to the risks they would be taking by buying the prescribed treatments in pharmacies in unauthorised distribution channels.
3. **A duty to inform:** As in all other professional fields, healthcare professionals are encouraged to inform themselves regularly about the security of the health system, any weaknesses in that security and the means available to help make it as reliable as possible.

For **distributors and wholesalers** of medicines there are guidelines on good distribution practice for human medicines published by, for example, the European Medicines Agency [34]. The International Chamber of Commerce (initiative for Business Action to Stop Counterfeiting and Piracy) has produced an analysis and guidance for intermediaries in the distribution of pharmaceuticals [35].

What Action Should be Taken Against Illegal Veterinary Medicines?

"We all have a role"

Regulation & Enforcement Agencies

- Effective regulation
  - Necessary government resources
- Rigorous enforcement
- Collaboration
  - Police
  - Customs
  - Regulatory agencies
  - Professional bodies
  - Manufacturers
- Private prosecution, legal action

E-Commerce & Internet Sites

- Raise awareness
- Cease or comply
- Popup warning on legitimate sites
- Full compliance with legal requirements

Manufacturers of Authorised Medicines

- Raise awareness
- Collect data
- Leadership in working with enforcement agencies
- Evaluate technology to support enforcement
- Protect patents and trademarks
- Protect reputation

Veterinarians, Retailers, Wholesalers, Feed Mills

- Raise awareness
- Report illegal products
- Work with enforcement agencies
- Be alert and informed
- Do not encourage illegal compounded products and vaccines

Farmers

- Awareness of risks of illegal products:
  - Efficiency
  - Safety
  - Residues
  - Environment
- Business risk if illegal products are used
- Report illegal products

Pet Owners

- Awareness of risks of illegal products to efficiency and safety
- Report illegal products

Engagement with enforcement agencies and regulatory authorities

The support and collaboration of Animal Health companies with customs authorities and federal / regional / national / state authorities to intercept and ultimately destroy illegal products, and to prosecute the perpetrators is clearly important to animal and public safety, and to maintaining pressure on the perpetrators and criminals. A key part of that support and collaboration is firstly, raising / maintaining awareness of illegal veterinary medicines; secondly, providing as much information as possible regarding suspicions of illegal veterinary medicines, and thirdly, facilitating the distinction of authentic and falsified goods (finished product, API, packaging and labels etc). This may include intelligence, data on, for example, bar codes and 2D-matrix identification, and technical support for analyses conducted using hand-held devices or in laboratories (e.g. Raman spectrometry for rapid identification which is of growing importance in customs operations).

The World Customs Organization Interface Public Members (WCO IPM) is a web and mobile platform allowing rights holders to share relevant product information with the only global security solution gateway allowing Customs officers to verify the authenticity of products online [36]. The aim is to support Customs agents in their day-to-day work in the fight against counterfeiting and illicit trade. However, the work involved in keeping WCO IPM updated with company product information may be significant.

Two centrally important organisations that work to coordinate intelligence and operations across borders, in addition to national agencies, are World Customs Organisation (WCO) and Interpol.

As an example of their work, each year Operation Pangea is held as an international week of action tackling the online sale of counterfeit and illicit medicines and highlighting the dangers of buying medicines online. Coordinated by INTERPOL, in collaboration with WCO, the annual operation brings together customs, health regulators, national police and the private sector from countries around the world [36]. Activities target the three principal components used by illegal websites to conduct their trade, which is the Internet Service Provider (ISP), payment systems and the delivery service. The operation has gained significant momentum since its launch in 2008. The first phase of the operation brought together 10 countries, a number that by 2015 had risen to more than 100. Although details are not available, it is believed that Operation Pangea may include illegal veterinary medicines. In France alone, in the one-week operation in 2015, there were medicines "...mostly without marketing authorization (720,000 unspecified drugs) but also counterfeit (273,000 tablets) and doping products (50,000 doses)."

Supply chain protection, defence activities and technology

Protection of the supply chain from illegal veterinary medicines should be based on inclusion of the following points.

1. **Awareness and vigilance** are the cornerstones of preventing growth and then reducing the volumes of illegal veterinary medicines. This should include all stakeholders: Animal Health companies, manufacturers (API, packaging, labels), distribution chain participants, wholesalers, pharmacies, veterinarians and animal owners. Developing a strong and effective **narrative** around illegal veterinary medicines is important for raising awareness and maintaining vigilance.
2. **Facilitate easy identification** of approved retailers, internet pharmacies and physical sites and authentic VMs. This should be particularly for use by veterinarians and animal owners. Regulatory agencies in some countries are already facilitating identification of approved physical suppliers and internet pharmacy sites. For human medicines only, the EU is in the process of adopting a common, EU-wide logo to identify legal online pharmacies. This should make it easier to distinguish between legal and illegal online pharmacies throughout the European Union.
3. **Simple nomenclature.** This is important to avoid confusion and mistrust not only for animal owners but also for front-line enforcement officers including customs and police. Definition and nomenclature is a vexed issue as illustrated by the changing systems used by different organisations. A single term, such as illegal, is readily understood. In investigation and data gathering, more detailed classification is required and needs to be agreed within the Animal Health industry. Examples of terms in common use include: counterfeit, fake, illicit, falsified, unregistered / unlicensed, substandard, spurious, falsely labelled, diverted, stolen, product tampering, illegal compounding, illegal autogenous vaccine, illegal medical device (for systemic delivery).
4. **Strong deterrence and adequate regulatory framework.** In developed and some developing countries adequate regulatory frameworks exist; their absence encourages illegal medicines including illegal veterinary medicines as observed in many developing countries. However, for a good regulatory framework to be effective regardless of where, it is essential to have well-resourced enforcement agencies, seizure of proceeds of crime and other penalties [16, 31, 32].
5. **Data collection and policy research**. Adequate data is essential to an in-depth understanding of the problem of illegal veterinary medicines, developing strategies that prioritise and direct the limited resources available, measuring success and identifying trends. Equally, it is possible to act against illegal veterinary medicines without a full data set.

The Pharmaceutical Security Institute is a not-for-profit, membership organization that collates and shares information on the counterfeiting of human medicines (counterfeiting used in the broadest sense) and may provide an example to the Animal Health Industry of third-party data collection [32].

PSI data for 2016 indicated that there were reported:

3,147 recorded pharmaceutical crime incidents in 2016

Incidents increased by +5% from 2015

Incidents were at an all-time high

Over the past five years, incidents increased by +56%

Half of the incidents involved more than 1000 dosage units

6. **Technology**. To mitigate the threat of counterfeit and falsified medicines, and ensure that patients receive safe and effective medicines, pharmaceutical companies have incorporated anti-counterfeiting technologies into their packaging and implemented campaigns to detect and disrupt the counterfeiters and criminals involved. A concise review of technologies has been provided by WCO [38].

Most of the technology systems are much more effective if they are used internationally in a harmonised manner. Some of the more advanced technologies for track and trace, and serialisation are not internationally harmonised. They also require considerable investment. The survey indicated that most of the larger Animal Health companies are using 2D matrix although, at present this may be principally for within company control, and by some large wholesalers. Some countries are using 2D matrix for monitoring AM use (e.g. The Netherlands). Overall, 2D matrix has a valuable role in supporting traceability however it is not a panacea for prevention or detection of counterfeit and falsified medicines. The WCO comments on 2D datamatrix were that:

- Value is mostly as confirmation of suspected illegal products that have been detected because of other alerts (e.g. packaging, intelligence, inconsistency with insured value)
- Requires a large and highly complex database which needs constantly updating by companies
- Needs all or large majority of manufactures (including generic manufacturers) to participate

A variety of technologies are available, for example:

- Tamper-evident seals, Product approval numbers etc. Simple and low cost. In an interview FDA commented that 'very few veterinarians look for a NADA number on a VM'
- Track and trace, serialisation systems
  - Alpha numeric & data matrix systems. 2D matrix allows products to be authenticated by Customs officers using smartphone applications
  - NFC (Near Field Communication) and longer-range RFID (Radio Frequency Identification) tagging solutions which allow products to be authenticated by Customs officers using smartphone applications
  - Image based authentication, visible or invisible digital information (such as a hologram) can be captured by a smartphone camera lens of the customs officers. The captured image will then be challenged and return a valid or invalid response

Beyond securing the supply chain and increasing patient safety, serialisation and product verification also allows additional supply chain benefits and the possibility of automated checking of expiry dates, improved pharmacovigilance, and reduced medication dispensing errors. However, although the **2D data matrix technologies'** technical detection rate was very high, the **operational authentication rate** in hospital pharmacies has been disappointing in terms of operational detection of counterfeit medicines, recalled drugs and expired medicines [39].

Of course, sophisticated criminals that are targeting high-value products will overcome some of these technologies but nevertheless they are likely to have a strong deterrent effect.

Methodology

This report is focused on qualitative analysis of the problem of illegal veterinary medicines. As previously noted, a quantitative analysis was not feasible. This was confirmed by comments from, for example, WCO, EUIPO and OECD when referring to the economic impact trade in counterfeit and pirated goods, and by WHO and IFPMA in relation to human pharmaceuticals, and CLI regarding plant protection products.

This study used qualitative, standardised surveys of the member companies of HealthforAnimals (Appendix 1, with responses received from 7 of 9 companies) and from National Associations of Animal Health companies (Appendix 2, with responses from 16 Associations from North America, Europe, Latin America, Africa, Australasia and Asia). The data received in response to the survey questions were not exhaustive for multiple reasons. For example, not all of the questions were answered by all participants and the quantity of information provided in response to each question varied considerably. In these surveys, examples of illegal veterinary medicines were requested and many of these are briefly detailed in the responses. Quantitative information on specific examples of illegal veterinary medicines was only provided in a small number of cases (although additional details may be available from some respondents). Nevertheless, there is a consensus in this report that illegal veterinary medicines are a growing problem.

The study also used interviews (Appendix 3) with key organisations to provide information on illegal veterinary medicines including regulators and enforcement agencies. Interviews were conducted with senior staff of organisations concerned with counterfeit and falsified human pharmaceuticals and plant protection products (each of which represent industries that are similar to VMs in being under-pinned by intellectual property and highly regulated). Senior members of the following organisations were interviewed: International Federation of Pharmaceutical Manufacturers and Associations, CropLife International, World Customs Organisation, UK Veterinary Medicines Directorate, US FDA Center for Veterinary Medicine (CVM), World Organisation for Animal Health OIE, Thailand Department of Livestock, Indian Federation of Animal Health Companies, World Small Animal Veterinary Association.

The report is based on the materials in the Appendices supported by extensive desk research and References.

List of abbreviations and acronyms

AM	Antimicrobial(s) (antibiotic)
AMR	Antimicrobial (antibiotic) resistance
API	Active pharmaceutical or biological ingredient(s)
AV	Autogenous vaccines
CA	Companion animals: Horses, dogs, cats
CLI	CropLife International
EMA	European Medicines Agency
EUIPO	European Intellectual Property Office
FDA	US FDA Center for Veterinary Medicine
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IP / IPR	Intellectual property rights (patents, trademarks, designs, copyright)
IVM	Illegal veterinary medicines (vaccines or pharmaceutical drugs) including illegally compounded animal medicinal products and illegal autogenous vaccines
n/a	Not assessed/available/applicable
OECD	The Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
OTC	Over the counter (products not requiring a prescription)
PA	Production animals: Cattle, pigs (swine), poultry, sheep
PSI	Pharmaceutical Security Institute
VMD	UK Veterinary Medicines Directorate
VM	Veterinary Medicine(s): Vaccine /immunological/ biological and pharmaceutical products
WCO	World Customs Organisation
WHO	World Health Organisation

Appendices

Appendices 1, 2 and 3 are produced as a separate document to this report.

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Health for Animals
global animal medicines association

HealthforAnimals represents the animal health sector: manufacturers of veterinary pharmaceuticals, vaccines and other animal health products throughout the world, as well as the associations that represent companies at national and regional levels.

The animal health industry provides value to society by protecting animals and as a consequence, humans, from diseases. Our products help keep pets and food-producing animals healthy. The public health benefits we bring include safer and more secure food supplies, more efficient production for increased food supply, improved sustainability, and prevention of the transmission of zoonotic diseases.

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