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Quality control programmes for veterinary antimicrobial medicines

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ABSTRACT

The health benefits of the antimicrobial's use is inherently associated to the risk of antimicrobial resistance (AMR), an ever-increasing multifactorial problem, closely related with injudicious use of antimicrobials, and the lack of new antimicrobial medicines on the market, particularly for veterinary use. Currently, an increasing number of regulatory "One Health" action plans on AMR are running worldwide, already based on monitoring and surveillance systems for resistance and antimicrobials consumption. Such plans are still not mandatory in the European Union member States (EU-MS), but post marketing annual programmes for quality controls of medicines are, to verify and ensure full compliance with the marketing authorizations. The European "risk level" sampling is not based on the conventional risk-ranking process of severity factors *vs* the probability of occurrence, but instead, on the conviction that in the European Union (EU) all medicines are produced under good manufacturer practices (GMP) and rigorously controlled for quality by the marketing authorization holders (MAH).

The present paper links poor-quality antimicrobials and AMR, highlighting examples of regulatory initiatives on this subject outside the EU, particularly those resulting from the World Health Organization (WHO) recommendations. It also intends to trigger a discussion on the role of such quality control programmes, particularly for antimicrobials, beyond the control at any stage of the quality parameters of a marketed medicine, to reflect whether or not it might be relevant to other regulatory coordinated actions against AMR.

1. Introduction

The main use of an antimicrobial is the rapid eradication of a pathogen causing an infection in humans or in animals. As a defense mechanism, antimicrobial resistance (AMR) has been ever anticipated, occurring also due to a continuous use of low antimicrobial doses, by selecting microorganisms with higher minimum inhibitory concentration (MIC) values, like in infection's prevention or control, and for growth promoting purposes. This last usage is forbidden in the European Union (EU) since 2006 (EU, 2003) and in the United States of America (USA) since 2017 by the Veterinary Feed Directive (FDA, 2015). The amplification and spread of resistant bacteria are specifically significant after administration of oral formulations of veterinary antimicrobial medicines (VAM) by exerting potentially higher selection pressure due to their impact on the animals' gut flora (Acar and Moulin, 2006). Oral route is however the most practical way to administer VAM to food-producing animals, via the feed or water, either for treatment, prophylaxis or metaphylaxis (Mason et al., 2008; Weese et al., 2015). Antimicrobial medicines, when subject to degradation under inappropriate transport or storage conditions or manufactured poor-quality, either deliberately or as the result of a production error, with insufficient active substances and reduced delivery, may be as critical and resulting in sub-therapeutic levels. Overall, the impact of the quality of the antimicrobial medicines on AMR is of great uncertainty. Low levels of antimicrobials may be less harmful in promoting resistance than intermediate levels, but only very recently researchers started to look systematically for evidence of poor-quality medicines, and have already found critical results. Lawrence and Jeyakumar (2013) consider that under-dosing may occur due to several factors that may influence the absorption and the disposition of an antimicrobial, preventing it from reaching target microorganisms with the most appropriate dose (Stojančević; et al., 2014). Some of these factors are related to the treated animals while others may be related to the quality of the medicines, like solubility, bioavailability, permeability, which may accelerate AMR emergence by exposing larger bacterial populations to subtherapeutic doses of antimicrobials (Bourlioux et al., 2003; Lin and Wong, 2017; Martinez and Amidon, 2002; Vaddady et al., 2010). To investigate such link, data on quality deviations need to be

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analised, by implementing systematic detection and traceability of the antimicrobial medicines out of specifications. These non-compliances have recently emerged as a less frequently examined source of underdosing concentrations across many countries. However, AMR have no boundaries, and efforts to optimize the use of VAM and antimicrobial medicated feed should promote official controls' reinforcement from manufacture throughout the full supply chain until the use in animals (Nwokike et al., 2018). Poor-quality VAM or antimicrobial medicated feed, may both result from a manufacture error, a nonconformity of the degradability over time, or from incorrect formulation, may having each cause different impact on AMR. At relatively low-intensity exposures, there is little amplification of any pre-existing, less susceptible population because little pressure is exerted upon the system. As intensity increases, the susceptible population is killed, but there is maximal amplification of the less susceptible portion of the population. Moreover, considering the fragmented and increasingly globalized nature of the pharmaceutical market, this probability increases considerably to a point where poor-quality active substances may unwittingly be made into poor quality medicines, in some GMP manufactures (Pisani, 2015). Although disease-specific data indicate that poor-quality medicines may be a driver in the development of AMR, comprehensive data on the extent to which it contributes to resistance are still lacking (Nwokike et al., 2018).

2. The medicines quality control programmes

Most of the antimicrobial classes' effects depend on the pharmacokinetic/pharmacodynamic (PK/PD) parameter(s), the type of antimicrobial activity and the mechanism(s) of action. VAMs with one or more active substances are developed to be used in one or more animal species with different physiological and metabolic profiles (EMA, 2016a; EMA, 2016b), with variable and often unpredictable concentrations at the site of infection (Leekha et al., 2011; Martinez et al., 2012). Dose and duration of therapy can influence the likelihood of resistance selection and amplification, (Martinez et al., 2012). Thus, poor-quality of VAMs, with compromised identity and strength, apart from failing to meet their quality standards and/or specifications, are likely to create subtherapeutic results and rise treatment failures that may be incorrectly attributed to resistance. However, target bacteria may be only weakly inhibited by suboptimal dosing regimens, but altering significantly microbiota composition during long-term treatments subpopulations of resistant bacteria may be selected and re-emerge over treatment (Langdon et al., 2016; Olofsson and Cars, 2007). It can especially occur via the oral route, due to the significant amplification, dissemination, and circulation of resistant bacteria in the gut flora (Zhang et al., 2013), an important potential link between animal and human resistance (van Den Bogaard et al., 2000). The VAM quality, formulation, and dosing regimens, may though contribute for resistance selection pressure based upon exposure-response relationships sufficiently relevant to implement or develop the existing quality control programmes and increase the antimicrobial's sampling. Several approaches to ensure quality medicines, addressing simultaneously the poor-quality medicines, have already been suggested worldwide, through for example the “Prevent, Detect, Respond Model” proposed by the WHO, already merged into global strategies and national action plans on AMR, in some countries. Such goal requires the reinforcement of regulatory mechanisms in all countries, to ensure the access of quality antimicrobials, (both for human and veterinary), by ensuring good manufacturing practices and monitoring manufacture processes of quality-assured antimicrobials. This post marketing regulation is supposed to be coordinated all throughout the antimicrobial active substances and the antimicrobial medicines supply chain, enabling regular conduction of surveys on quality, as a tool to estimate also the extent of antimicrobials non-prescription sales and their drivers, equally important for tackling AMR. For any quality control programme, appropriated laboratory systems are essential, and already provided for action plans on AMR, also in some countries outside the EU or the USA, like for example Bangladesh, Indonesia and South Africa. The “Promoting the Quality of Medicines Programme”, running since 2009, was established to strengthen medicines quality surveillance systems in low and middle-income countries, and feed the open access “Medicines Quality Database”, with nearly 15 000 medicine quality test results, mostly antimicrobial products, from 200 sentinel sites across Africa, Asia and Latin America (Nwokike et al., 2018). There are no similar available databases in the EU-MS, except at the European Medicines Agency (EMA), where antimicrobials are not considered a risk criterion for sampling and testing the quality of medicines, and the numbers of quality test results are incomparable. National data from quality controls of VAM are not public in EU-MS that usually publish quality alerts only.

2.1. The European quality control programmes

In the EU, the veterinary medicines are subject to a community marketing authorization procedure submitted to the EMA or to the competent national authorities (NCAs) for national marketing authorizations, under the same quality requirements to ensure the homogeneity of the finished product and the actual manufacturing formula (EC, 2001). The EU mandatory veterinary medicine's quality assurance system, should guarantee the quality of the finished product in all parts of the distribution chain (EMA, 2016a), coordinated by EMA/EDQM (European Directorate for the Quality of Medicines) only for medicines authorized by the European centralized procedure, and by the NCAs for the others (EMA, 2007). The European sampling plan of the medicine quality control system is annually established, for medicines already marketed for 3 years, and based on risk criteria related to the active substance, the manufacturing process, the route of administration, the target population, and eventually, with any marketing authorization variation. The sampling procedure is the same for human and veterinary medicines, except for veterinary-specific medicines or formulations, such as medicated premixes, top-dressing and miscible oral powders, teat dips, spot-on and multispecies presentations (EMA, 2005; EMA, 2007; EMA, 2009) and only the involved NCAs, EMA and MAH know the selected medicine(s) to be tested. The community sampling and testing programme has been running in the European Economic Area (EEA) since 1997 to ensure that the quality control methods are as satisfactory as authorized, to investigate any suspected quality defects, or to detect/confirm counterfeits. Its risk-based selection criteria may also consider risk's proposals from the EU-MS that might have been identified, in medicines (human and veterinary) or to patient profiles. Particular attention is given to the inherent variability of the production processes, poor product stability, presence of toxic impurities, problematic bioavailability, and biological standardization of potency, but also relates sales, reduced stability, low dosages, narrow therapeutic windows, long treatment indications, pharmaceutical forms and any relevant data from previous controls (EMA, 2005). New generic and recent innovative medicines may be also be relevant factors, but no EU-MS has ever requested EMA to include antimicrobials as an AMR risk factor in the Community Quality Control Programme. The first one ran in 1998–1999, with 9 medicines, (human and veterinary), under the selection criteria of the therapeutic categories, market availability, stability and manufacturing processes (EMA, 2008) and a risk-based approach upon the probability of an adverse outcome from testing and any consequences from eventual severe impacts. Only the number of the tested medicines (Table 1) were reported without details, being the “risk level” just defined as a “health risk” (EMA, 2008; EMA, 2013). Between 1998 and 2007, a total of 280 medicines were tested (EMA, 2008), and between 1998 and 2000, half of the 45 tested medicines, revealed some unidentified “issues” (EMA, 2008). In 2008, the tested medicines followed the authorized specifications and there were no instances of quality defects raising immediate concern for public or animal health (EMA, 2010a). However, in 2009, one “out of