

REACTION to the review article ‘The consequences of generic marketing on antibiotic consumption and the spread of microbial resistance: the need for new antibiotics’

This letter to editor article is on the Review article by Toutain, P.-L. & Bousquet-Melou, A. (2013)

The purpose of this letter is to comment on some statements and opinions in the paper by Toutain and Bousquet-Melou (this Journal, 36, 420–424; 2013) and to raise some critical questions to specific sections of their review article. Informing the public with coherence and correctness is crucial to fight antimicrobial resistance with positivism.

The European Group for Generic Veterinary Products (EGG-VP) is much concerned about the issue of antibacterial resistance and is in contact with the European Union (EU) authorities as well as national authorities and stakeholders with the aim to propose solutions and to set appropriate measures in place. The industry takes its responsibility seriously by providing approved, high quality, safe and effective medicines, while promoting responsible use of antimicrobials and thereby preventing their inappropriate use.

The crucial role and benefits of generic veterinary medicines in society are undeniable. These products only enter the market if they have been approved in the EU by the competent authorities. Generic products create an appropriate, competitive environment, while increasing the range of choices available for veterinarians, farmers and pet owners, without compromising on quality, safety and efficacy of the medicines. In this way, generics certainly contribute to a high level of health and welfare for all animals and the environment.

In our view, the cited article of Toutain and Bousquet-Melou presents some statements, quotes and opinions, without providing in all cases the appropriate evidence. The authors refer arbitrarily to human and veterinary medicines, not always clearly indicating to which of them they refer. Furthermore, it is uncertain to which geographical areas the authors are referring to.

This ambiguity causes incomprehensibility and possible misinterpretation, and hence, we would like to take the opportunity to clarify some of the issues from a European perspective, referring exclusively to veterinary medicines.

GENERICS, ‘ME-TOO’ DRUGS,* ANTIBIOTIC CONSUMPTION AND RESISTANCE

First of all, a clear distinction between a generic veterinary medicinal product and a so-called well-established use product should be made.

*Addition to class Authorizations; in the USA only and mainly in human medicine.

What is a generic veterinary medicinal product (VMP)?

- According to Article 13(1) of Directive 2001/82/EC (as amended), it is a product with a full chemical/pharmaceutical package and refers to a reference product (originator) which is or has been authorized for not less than eight years in a EU Member State or the European Union. Contrary to what the authors state, the applicant needs to present for a generic (antibiotic) product a full environmental risk assessment report as appropriate.

What is a so-called well-established use (WEU) product?

- According to Article 13a of Directive 2011/82/EC (as amended), this is a product with a full chemical/pharmaceutical package and refers to the safety and efficacy information in published scientific literature in the case that the active substance has a well-established use for more than 10 years in the European Union. Pharmacokinetic (PK) and residue data as well as ecotoxicity information need to be product related as well as a part of the full package.

In the current EU veterinary medicines legislation, there are provisions to apply for a marketing authorization according to the generic or WEU principles. Companies prepare their files according to these provisions, and the Competent Authorities assess these accordingly. These procedures in the European Union are based in the highest transparency standards and scientific level, and should not be questioned. They are considered as a reference model worldwide and have also earned the trust of European citizens.

In the article, reference is being made to *old antibiotics* which – according to the authors – *have shortcomings concerning dosage regimens and extensive excretion to the environment*. The only possible interpretation to this statement is that there are many originators in the market, which should not have been authorized and/or renewed subsequently.

The authors state that *flooding the market* with different generics may lead to a higher consumption of antimicrobials. This is not correct. Statistics available at European Medicines Agency and Heads of Medicines Agency indeed show that the number of generic marketing authorizations has steadily increased during the last few years in Europe, but contrarily to the authors statement, this had not led to an overall antibiotic consumption in recent years. This is demonstrated in the conclusions of the third ESVAC report (Anon., 2013): From 2010 to 2011, a considerable (10%) decrease on the use of antimicrobials was observed in most EU member states. Furthermore,

simply linking general use (sales) data to resistance levels may not be appropriate and scientifically sound. These data do not provide the necessary information about the field use of antibiotics in animals and whether the recommendations for prudent use were respected or not.

Regarding the prescribing habits of the veterinarians, the authors do want us to believe that these are primarily financially driven. This might have been the case in some areas in the past, but the statement is certainly not valid anymore. The Heads of Medicines Agencies and the Federation of Veterinarians of Europe recently undertook a survey De Briyne *et al.* (2013) to gain a better insight into the decision-making process of veterinarians in Europe when prescribing antibiotics. In this survey, involving over 3000 veterinary practitioners from 25 European countries, the contrary was true; economic factors were the least important factors in their prescribing behaviours. Responses also indicate that no single information source is universally considered as critical, and training, published literature and experience were the most important parameters that determined the choice of an antibiotic. Factors recorded, which most strongly influenced prescribing behaviour, were sensitivity tests, own experience, the risk of developing antibacterial resistance and ease of administration. Of course, the efficacy of the antimicrobial agent (generic or originator's) is crucial, and ineffective antimicrobials are not used/prescribed by practitioners. Practitioner will always use/prescribe the medicine which is likely to be effective.

The simple fact that generics are cheaper than the originator is evident, as the originator needs to submit a full file with all associated costs. After a data protection period of 10 years, the first generics can be authorized. The statement that ... *competition between generics and also between generics and branded antibiotics leads to more aggressive promotion for the use of antibiotics both in human and veterinary medicine...* is not substantiated and certainly not true for the European situation.

Suggesting that generics *can favor the illegal promotion of bad veterinary practices (such as totally unjustified indications, advertising etc.)* is a provocative statement that demolishes the many efforts of both the generic industry and competent authorities to get the optimal Summary of Product Characteristics (SPCs) in Europe. The authors also assume that *authorities are promoting the authorization of generic antibiotics*; without providing evidence in support of such a strong statement.

GENERIC ANTIBIOTICS: BIOEQUIVALENCE AND THERAPEUTIC EQUIVALENCE

Toutain and Bousquet-Melou (2013) refer to a series of articles from a Colombian research group. The Colombian article (Vesga *et al.*, 2010) claims that generic products prove to be inferior in one preclinical mouse model *proving* that, although the active ingredient seems to be the same, the activity can be different, leading the authors to conclude that generics are not efficacious, whereas the originator is. In response to the article

of Vesga *et al.* (2010), the Food and Drug Administration (FDA) performed additional studies and concluded that all the batches tested (originator as well as generics) fulfilled the qualifications, according to the United States Pharmacopeia (USP) and British Pharmacopeia (BP) requirements. Moreover, the theory of Vesga *et al.* (2010) was investigated and disapproved later (Hadwiger *et al.* (2012).

The omission of the FDA reaction is a major shortcoming in this review article.

Concerns expressed in the article about stereochemistry are unreasonable, as no Competent Authority will allow a producer, nowadays, to register a generic active pharmaceutical ingredient (API) with a different stereochemistry (chirality) than the originator; polymorphism is also addressed in the conduction of bioequivalence studies, and residual solvents are strictly regulated. Therefore, the concerns expressed in the article are unsubstantiated.

The authors' concerns on the quality of generics are thus in various aspects unjustified and even misleading. They entirely neglect the fact that a generic product referring to a reference product of 20 years old needs to comply with today's rules and regulations, which are, in most cases, more stringent than those at the time of the original product's authorization.

OLD VERSUS MORE RECENT ANTIBIOTICS

The authors stress the need of new antibiotics in veterinary medicine. Many European and global initiatives are currently ongoing to define the best way forward in order to fight antimicrobial resistance. No final outcome is available so far. It may be the case that only the new and/or more recent antibiotics may be reserved for human medicine. Apart from novel antibiotics or formulations yet to be developed, other options to preserve effectiveness of the current antibiotics and to limit the resistance should be considered (such as appropriate duration of antibiotic administration), and various recommendations are made for the prudent use of currently available licensed antibiotics. Promoting strict adherence to these recommendations might be far more productive than blaming generics. Many stakeholders are putting a lot of efforts into this enormous task of finding solutions, and these should be acknowledged.

CONCLUSIONS

The European legislation of veterinary medical products includes provisions for generics and WEU products. Industry and competent authorities act according to these requirements. Suggesting that these products incentivize bad practices jeopardizes the discussions on antimicrobial resistance. Attempts to question the pharmaceutical quality of generics do miss the scientific basis on which generic antimicrobials are approved and in fact undermine the authors' own statement: 'It is not the

intention of this communication to challenge the very principles of generics. . . .’

Antibiotics are essential for animal and human health, and antibacterial resistance is a complex issue. Intensive research is conducted to better understand the factors contributing to mechanisms and spreading of resistance between animals, humans and animals and humans. The issue is far more complex than the introduction of generic antibiotics, and only a common effort of all stakeholders involved in the ‘one-health’ policy can be successful to contain antibacterial resistance.

ABOUT THE EGGVP – THE EUROPEAN GROUP OF GENERIC VETERINARY PRODUCTS

EGGVP is the association representing the pharmaceutical industry of generic veterinary medicinal products in Europe and is actively involved in veterinary medicinal products policy. The 22 EGGVP members are marketing authorization holders of generic veterinary medicinal products. EGGVP membership is mainly composed of small and medium sized companies.

EGGVP is a member of the European platform for the responsible use of animal medicines (EPRUMA).

E. VECINO

EGGVP (European Group for Generic Veterinary Products)
Brussels, Belgium

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