Reply to Zuluaga et al

TO THE EDITOR—We thank Zuluaga and colleagues for their interest in our systematic review on the efficacy and quality of generic products of antibacterial agents approved for human use [1], and we appreciate the opportunity to respond.

Zuluaga and colleagues, who performed the 5 published studies in which the neutropenic mouse thigh infection model suggested that bioequivalence does not guarantee therapeutic equivalence [2–6], aimed at defending the validity of this model for that purpose [7]. Although we agree with most of the points they raised, we do not think these points support their conclusion that the neutropenic mouse thigh infection model is adequate to compare the efficacy of generic products of antibacterial agents face-to-face, or, when available, with the innovator.

First, Zuluaga and colleagues stated that validation of animal models comes from the demonstration of their similarity to the symptoms, pathophysiology, and therapeutic response of human diseases. However, there is no convincing evidence to date that the neutropenic mouse thigh infection model fulfills these criteria. Second, they cited the landmark articles from William A. Craig [8] and Ambrose et al [9], but these authors mostly advocated that these “animal pharmacokinetic-pharmacodynamic (PK/PD) models serve as the cornerstone of the preclinical assessment process for antibacterial agents, and dose and dosing interval selection” ([9], p 79). Among the references cited in these 2 reviews, there is no article in which these models were used for the comparison of the bactericidal activity of one antibacterial agent vs another. Neutropenic mouse thigh infection models are mostly used to identify the PK/PD measure that maps most closely to the bactericidal activity and the presence and duration of persistent effects. This usually implies dose-fractionation studies (eg, studies comparing the efficacy of a same daily dose administered with different dosing intervals), to identify optimal dose and dosing intervals [8, 9]. When the objective is to compare the bactericidal activity of different antibacterial agents, the rabbit model of endocarditis has a much longer track record [10]. Last, some of the major drawbacks attributed to the rabbit endocarditis model by Zuluaga and colleagues are not accurate: (1) the starting inoculum at the infection site may be measured in the rabbit model of endocarditis [11]; (2) the inability to determine PK/PD indices with the rabbit endocarditis model is not an issue, as this is not among its objectives, PK/PD parameters being more easily predicted from rodent models [8, 9]; and (3) the high requirement of the endocarditis model, in terms of bactericidal effect within the vegetations [12], is an asset for the comparison of antibacterial agents, as these stringent conditions reinforce the discriminative power of these experiments [13].

Again, our systematic review does not advocate for the indiscriminate use of generic products of antibacterial agents; our main finding was that there is no convincing evidence to date that the marketing authorization process of generics should be reinforced [1], due to the heterogeneity of findings, and the limited validity of the main studies suggesting that bioequivalence does not guarantee therapeutic equivalence [2–6].

Note

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