About the Validation of Animal Models to Study the Pharmacodynamics of Generic Antimicrobials

To the Editor—The systematic review by Tattevin et al [1], including 37 heterogeneous articles about the equivalence of generic antibacterials, concluded that more evidence is necessary before revising the marketing authorization process of these products. They cite 5 articles in

which the neutropenic mouse thigh infection model (NMTIM) [2–6] was the main experimental tool to invalidate the regulatory assumption that bioequivalence guarantees therapeutic equivalence [7]. Surprisingly, Tattevin et al disregard the results from the NMTIM, arguing that it "is not validated for the evaluation of the efficacy of antimicrobial agents" and asserting that the rabbit endocarditis model is the "gold standard" for such purposes. We beg to disagree.

The Food and Drug Administration Animal Rule is supported by a solid regulatory guideline [8], although it does not mention the term "validation." The validation of animal models comes from the demonstration of their face validity, or similarity to the symptoms, pathophysiology, and therapeutic response of human disease [9]. Construct validity is also required, meaning that the model has a rational basis [10]. Of paramount importance is the translation of the results to humans, or predictive validity [10], which is the statistical comparison of pharmacodynamic parameters to demonstrate reliability and relevance. Reliability requires repeatability (intralaboratory) and reproducibility (interlaboratory), and relevance relates to the accuracy (sensitivity and specificity) of the model to predict the biological response. In this regard, the predictive validity can be tested by the systematic examination of animal results, and by comparing these with human reference data [10].

It is widely known that modern concepts on antimicrobial pharmacodynamics were translated to humans from the seminal experiments of William A. Craig with the NMTIM [11]. Recently, Ambrose et al summarized the vast amount of rodent-derived data and compared it with the findings from humans, demonstrating that the pharmacokinetic/pharmacodynamic (PK/PD) indices and their magnitudes for microbiological and clinical effectiveness are essentially the same [12]. In contrast to the thoroughness of this predictive validation of the NMTIM, the rabbit endocarditis model is restricted to cardiac valve infection, and experts advice a higher degree of caution to extrapolate its results because it lacks both reliability and relevance [13–15]. Some of the major drawbacks are that (1) the starting inoculum at the infection site is never measured, but it is crucial to quantify critical PD information, such as bacterial growth, inoculum effect, and postantimicrobial effects [11, 16]; (2) the lack of a dose-response curve prevents the determination of PK/PD indices necessary to translate to humans [15]; (3) the low metabolic activity and limited multiplication of microorganisms in vegetations change the PD of some antibiotics [15]; and (4) the intrinsically large variance reduces the statistical power to compare response to different compounds [17].

The NMTIM resembles sepsis and the rabbit model imitates endocarditis; therefore, both models have face and construct validity. Regarding in vivo testing of generics, reliability and relevance have been demonstrated only with the NMTIM [3, 5, 6], validating its use to accurately determine therapeutic equivalence [2] or nonequivalence [3–6, 18]. In contrast, predictive validation is missing in Tattevin et al's model [19].

Note

Potential conflicts of interest. A. F. Z. has received personal fees from Sanofi, Roche, Allergan, Pfizer, Novo Nordisk, Stendhal, RP Pharma, and CIDEIM. O. V. has received personal fees from PROCAPS. All other authors report no potential conflicts.

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