The issue of comparing the rates of inhibitor development in previously untreated patients with severe hemophilia A who are treated with plasma-derived Factor VIII concentrates (pdFVIII) or recombinant Factor VIII (rFVIII) is influenced by numerous and unavoidable biases. These biases essentially depend on the observational nature of the data and on the recognition that factors other than the type of product might be implicated. In this framework, the meta-analysis by Franchini et al\(^1\) represents the most comprehensive and updated attempt to shed light on this controversial topic.

In the discussion of the results of this meta-analysis, one key of interpretation has not been considered by the authors but deserves, in our view, to be pointed out. The question essentially is: Do these results represent no proof of difference or proof of no difference?

When a traditional meta-analysis generates a nonsignificant result, the need to differentiate between no proof of difference or proof of no difference is increasingly being recognized\(^2\)–\(^5\); in fact, in the first case the results should be viewed as inconclusive (i.e., no demonstration of anything) while in the second case a statistical proof is obtained that no difference exists (i.e., demonstration of equivalence or noninferiority).

To address this specific question, we have reanalyzed the results described by Franchini et al by carrying out a formal equivalence test based on 95% confidence intervals (CIs). The objective was to compare the inhibitor development rates between pdFVIII and rFVIII; the main assumption of our analysis was that the margins for equivalence are set at 0 to 4.0%.

Fig. 1 summarizes our reanalysis. To determine the 95% CIs shown in Fig. 1, we first repeated the proportion meta-analysis of Franchini et al and we exactly confirmed the meta-analytic results published by the Italian authors (details on our repeated meta-analysis with study-specific crude rates and Forest plots can be seen from our institutional Web site at http://www.sifact.it/firenze/sth-messori-supplement.pdf);
confirmation of the crude rates was a prerequisite for undertaking our equivalence analysis. The main result of our equivalence analysis was that the pooled rate difference of +6% for rFVIII versus pdFVIII (i.e., the difference between the two point estimates of 29 vs. 23%, respectively) is associated to a standard error of 5.335% and to a 95% CI ranging from −4.46 to +16.46%. According to our reanalysis, the published data reported by the Italian authors clearly represent no proof of difference.

More importantly, our results show that these data do not support the conclusion of proof of no difference (i.e., equivalence) unless one extends the definition of equivalence up to an unrealistic margin of 0 ± 17.0%. Another unsettled question is that the need to differentiate between different products containing rFVIII further increases the difficulty in studying this topic.

We conclude that, despite the inclusion of the best evidence currently available, we still do not know whether or not rFVIII is associated to an increased rate of inhibitor development as compared with pdFVIII. Finally, while we admit that most of the considerations presented herein were implicit in the article by Franchini et al, we think that making these points more explicit is worthwhile.

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Conflict of Interests
None declared.

References
2 Arruda MA. No evidence of efficacy or evidence of no efficacy. JAMA Pediatr 2013;167(3):300–302
6 Ahn S, Park SH, Lee KH. How to demonstrate similarity by using noninferiority and equivalence statistical testing in radiology research. Radiology 2013;267(2):328–338