The authors suggested that biosimilar quality might be inconsistent over time and suggested that track-and-trace capabilities might encourage consistent quality. Product quality is tightly regulated by the FDA, both for reference biologics and biosimilars. Each batch of every biologic must meet predetermined release specifications before it can be used to treat patients. These tight regulatory requirements ensure product quality and consistency over time for all biologics.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported being employees of Sandoz Inc.


In Reply Drs Frankel and McKay first note that the FDA is able to ensure biosimilar and reference biologic quality through pre-release specifications. But these specifications cover only a subset of all measurable quality attributes. If FDA testing were adequate to predict all emergent quality-related safety issues with biologics, then there never would have been cases of pure red blood cell aplasia associated with Eprex1 or HX575, which are biosimilar versions of epoetin-α, nor would there have been deaths due to contaminated heparin in the United States in 2008.2

Second, even though the argument is often repeated that biosimilars must match the variability of the reference product, this has not been the case for biosimilars in Europe thus far. Biosimilars have been licensed with measurable differences in posttranslational modifications outside the variability of the reference product. In some cases, these differences were in critical attributes that affect the pharmacology of the product. The regulatory approval in these cases was based on the totality of the evidence (ie, clinical efficacy and safety testing) as opposed to matching the variability of the reference product.

Third, it is not true that “accurate predictions about the safety and efficacy of the biosimilar can be made based on the history of the safety and efficacy of the reference product.” Any differences between products (reference and biosimilar candidate) have to be evaluated and explained—first through an analytical process. Immunogenicity is one of the areas that analytics cannot resolve, which is why clinical trials are expected to be required for all biosimilar approvals.

At some point in the future, we expect that scientific understanding will progress to a point at which there will be no need to conduct clinical trials for some molecules. The larger point is that the FDA approves drugs as safe and effective using the logic that there is more benefit than harm or risk across the population of patients. One challenge is that immune systems exhibit variation across patients and what may be fine for the majority of patients may not be fine for 1 particular patient. Postmarketing surveillance will help manufacturers with less variability.

Fourth, a biosimilar manufacturer should not assume that its biosimilars are approved for the same indications as the reference product. An example is infliximab: Health Canada did not approve the biosimilar for all indications (although the Europeans did). The record is not clear on why, but presumably the studied indication by the biosimilar manufacturer was not the most sensitive one or the unapproved indications used a different mechanism of action than the approved indications.

Biosimilars offer patients tremendous promise and their use must be established in a safe and effective manner.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Chandra reported being a consultant to Precision Health Economics, which receives payments from Amgen and other life sciences companies that market biologics and biosimilars, and also reported serving on the Congressional Budget Office’s Panel of Health Advisors. Dr Vanderpuye-Orgle reported being an employee of Precision Health Economics.


To the Editor We wish to retract the article “Effect of Perindopril on Large Artery Stiffness and Aortic Root Diameter in Patients With Marfan Syndrome: A Randomized Controlled Trial,” published in the October 3, 2007, issue of JAMA, based on inadequate validation of primary data sources and data misrepresentation. An independent review was conducted by the Baker IDI Heart and Diabetes Institute following an admission of scientific misconduct by the first author (Anna A. Ahimastos, PhD) in relation to the data included...
in another study that has since been retracted. This review resulted in our decision to retract this additional article. We do not believe that management guidelines for Marfan syndrome have been changed as a result of this small clinical trial.

While clinical governance procedures have been strengthened since publication of this study, the Institute has commenced a review with the purpose to further strengthen current audit practices and to minimize any possible risk of recurrence of such behavior. We were not found to be involved in any research misconduct, but we do acknowledge the responsibility for our authorship of this article and for supervising the overall study and sincerely apologize to the editors, reviewers, and readers of JAMA. We are committed to correcting the public record, notifying relevant stakeholders, and implementing practices to prevent recurrence.

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CORRECTION

Clarification of Sentence: In the In Reply letter entitled “Promise of Precision Medicine” published in the October 27, 2015, issue of JAMA, a sentence in the second paragraph is incorrect. In the second paragraph, the second sentence should be “In fact, the cost of sequencing a human genome has decreased almost 1 million fold, and the National Human Genome Research Institute regularly updates a graph showing how much faster the cost of human sequencing has decreased than the law defined by Gordon Moore. (The law by Moore, co-founder of Intel, describes how the number of transistors on an integrated circuit doubles every 18 months.)” This article was corrected online.


Incorrect Data in a Table: In the Review entitled “Diabetes: Advances in Diagnosis and Treatment” published in the September 8, 2015, issue of JAMA, there were incorrect data in Table 1. The fasting glucose range for “Prediabetes” should have been “100-125.” This article was corrected online.


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