Letter to the Editor

Innovation in Hemophilia Therapies — "And Miles to Go, before [We] Sleep"

Albert Farrugia, PhD[1,2]

[1] School of Surgery, QEII Medical Centre, The University of Western Australia, Western Australia, Australia
[2] Kedrion S.p.A, Via del Ciocco, Castelvecchio Pascoli, Lucca, Italy

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Address for correspondence Albert Farrugia, PhD, School of Surgery (QEII Medical Centre), The University of Western Australia (M509), 35 Stirling Highway, Crawley, WA 6009, Australia (e-mail: albert.farrugia@uwa.edu.au).

In a recent issue of this journal, several authors reviewed and discussed aspects of the current therapeutic era in hemophilia.[1–3] As the authors describe, this era is characterized by innovation and rapid change, such that technologies not approved or not yet fully embedded in the market may experience redundancy through competitors lagging only slightly behind each other in the development process.[1] This situation is to be welcomed, following previous eras of limited choice among sometimes unsafe products. However, as several of the authors highlight, "*economic issues must be considered,*"[2] and the path for transitioning these therapies to full market access remains uncertain. While the putative benefits of features such as extended half-lives are vigorously marketed to patients,[4] the personalized dosage regimens exemplified by Berntorp and Andersson[2] will require careful patient conversions, including extensive pharmacokinetic alignment, and consequent additional costs. In their recent thoughtful editorial, Croteau and Neufeld[5] propose that reduction and prevention of bleeding events is more important than the decreased infusion frequency, which is the intuitive and touted benefit of extended half-life products. It is likely that this principle will be increasingly embraced by the majority of funders. In this context, Berntorp and Andersson's hope that "*the goal to reach a zero A[nnualized] B[leeding] R [ate] ….is feasible*" needs to be tempered with the recognition that none of the "innovative" factor concentrates have demonstrated a superior annualized bleed rate (ABR) when compared with standard products.[6] Given the commitment of health technology assessors to focusing on patient-related outcomes, such as bleeding, when formulating advice for funders, it may be anticipated that reimbursement for therapies proposed, primarily as "more convenient," may be challenging. It should be noted that one major health technology assessment body has already determined that such considerations do not merit enhanced reimbursement relative to standard hemophilia therapies.[7]

Clearly, the major determinant in shaping the uptake of the new therapies will be the price of the product, at least until protocol development, based on patient-related outcomes, is optimized. In this optimization effort, treaters and other participants need to match the innovation offered by the new concentrates with equally innovative approaches to their use. This may include protocols transitioning patients using a multiplicity of products, as proposed by Croteau and Neufeld.[5] Such an approach will become increasingly relevant in the integration of gene therapy[1] and the pharmacological therapies reviewed by Mannucci et al,[3] none of which promise to obviate entirely the need for factor substitution therapy. Optimization of treatment may allow a more comprehensive assessment of the true costs, especially if bleeding and its sequelae is diminished, irrespective of the infusion frequency. In the interim, the plethora of new products on the market is resulting in a welcome level of competition, which is driving down the price of factor products, particularly of standard products and in countries with centralized purchasing and tender systems.[8] While the United States continues to be relatively resistant to these developments, stakeholders in the therapeutic landscape should ponder on the risks inherent in the uncontrolled escalation of hemophilia costs in the foremost global market under the banner of "innovation." Uptake of the new products in the United States has been modest thus far,[9] suggesting the hemophilia dollar is stretched even further in the United States. Overall, the developments described in the aforementioned issue of *Seminars in Thrombosis and Hemostasis*[10] continue to augment the progress of past decades in hemophilia therapeutics, but we have "miles to go, before we sleep."

Conflict of Interest
The author provides compensated services for companies producing therapies mentioned in this communication.

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