IX products that went into effect in February 2012. In fact, it is the EMA BPWP guidelines that require pediatric data to be included in the initial MAA. If this requirement were not in EMA BPWP guidelines, deferral of the studies in the PIP until after approval of the adult indication would be possible.

The primary concern of the authors is the delay of product availability to European patients, and it appears justified by examining recent late-stage development timelines for Baxter's recombinant coagulation factor IX product. The product was submitted for approval to the US Food and Drug Administration in August 2012 and was approved for treatment of adults following a 10-month review (http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm358781.htm (accessed 3 March 2014)). Four months after US approval, the company submitted the European MAA, including the report of the pediatric study, which was also submitted to the US Food and Drug Administration in the same time frame[2]. Thus, the requirement to include pediatric data in the initial MAA resulted in the drug being submitted in Europe 14 months after being submitted in the United States.

Although this recent evidence corroborates the opinion of Peyvandi *et al.* that approval of new hemophilia treatments will happen later in the European Union than in the United States because of requirements to include pediatric data in the initial MAA, the requirements originate from the EMA BPWP guidelines for factor VIII and IX products, not from the Paediatric Regulation and PIP. This is an important distinction to make so that researchers do not disparage an initiative whose goals are to evaluate safety and establish appropriate dosing in the pediatric population so that this information can be included in drug labeling to assist physicians in their treatment of children.

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Peyvandi *et al.* reply:

We were pleased that our opinion piece[1] triggered the interests of the Pediatric Center of Excellence at Quintiles[2] and the European Medicines Agency (EMA)[3]. Our writing did refer to the manner in which clinical studies are planned, but we have not suggested that these studies are unnecessary in pediatric patients. Our main point was that if studies in children are a prerequisite before coagulation factor concentrates become available in adults, then adults will face an undue delay in access to new drugs, particularly because pediatric studies take a long time owing to the small number of children with inherited coagulation disorders.

It is true that 50 years ago patients with hemophilia seldom reached adulthood. However, these patients currently enjoy a normal life expectancy. As a result, managing hemophilia in the aging adult in the presence of considerable co-morbidities (e.g., heart disease or cancer) has become a major challenge[4]. So it is important that these adult patients have access to new drugs with no undue delay.

Mentzer *et al.*[3] state that coagulation factors with a long half-life are potentially more interesting for prophylactic use than on-demand use and thus more relevant for pediatric use than adult use. However, most adults in the European Union with hemophilia are now treated prophylactically (as many as 60% of adults with severe hemophilia are). The prophylactic regimen entails at least three intravenous administrations each week[5] that are usually self-administered despite arthropathy in the shoulders, elbows and hands. Many of these individuals have damaged veins due to a lifetime of needle sticks and concomitant vein scarring, which subsequently results in considerable difficulties for successful self-infusions.

Mentzer *et al.*[3] correctly point out that the risk of immunogenicity, the main current complication of hemophilia treatment, is more relevant in children than adults. To evaluate the immunogenicity of new products, the most suitable cases would be previously untreated patients (PUPs). However, PUPs are very few in number, making their recruitment an obstacle in conducting such clinical studies[6]. Accordingly, the EMA currently requires clinical trials in at least 50 and 20 previously treated children (PTPs) aged <12 years for factors VIII and IX, respectively, for 50 exposure days (i.e., a day on which treatment is administered). With long-acting factors, administrations take place less frequently, so it will also take more time to complete the studies. All these aspects add to the delay before new factor products become available in adults, a snag that can be overcome by relaxing the requirement for pediatric trials and allowing clotting factor concentrates to be used in adults after studies in adults are completed.

We agree with Huff[2] that adequate planning, including early interactions with regulatory agencies, would make it possible to provide timely access in adults; this could help provide sufficient information to support use in children. However, this approach will not overcome the delays we mentioned in our piece because for now, children cannot be included in clinical trials until adult studies have been completed. Therefore, there remains a mandatory delay in initiating pediatric studies.

In conclusion, we fully agree with the urgency of completing clinical trials in pediatric populations, and we believe that doctors should be vigilant against prescribing drugs to children off-label. However, these objectives should not detract from the health of adults with hemophilia. In the context of hemophilia, we believe that a rigid adherence to the principles of the Pediatric Investigation Plan does more harm than good.

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