Pediatric requirements in Europe stymie help for hemophilia

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The European Medicines Agency requires that drug developers submit a 'pediatric investigational plan' to ensure that there is adequate information about how children fare on experimental medication for many indications before they go to market. But this requirement places an undue constraint on the makers of new hemophilia drugs and threatens to create an unreasonable delay in access to these therapies among adults with this disorder in the EU.

Hemophilia—one of the most well known but also rare inherited disorders—predisposes individuals to excessive bleeding due to a deficiency in coagulation proteins. Thankfully, there are several ongoing clinical trials testing modified, long-acting products to treat this life-threatening disorder. In December, the US biotechnology company Biogen Idec and its partner Swedish Orphan Biovitrum presented promising results from a clinical trial of the drug Alprolix (rFIX-Fc), a type of factor IX recombinant clotting protein bioengineered by Fc fusion technique[1]. Meanwhile, data have confirmed that the plasma half-life of this drug and the companies' similar factor VIII product, Eloctate (rFVIII-Fc)[2], exceeds that of currently available products, thereby providing longer-lasting protection from bleeding.

These drugs and others like them have the potential to dramatically transform the treatment of hemophilia by substantially reducing the frequency of injections. But a tangled web of regulations in Europe requiring pediatric trials and sequential testing of certain hemophilia drugs before products are approved for adults creates a uniquely difficult climate for bringing new therapies to market for this illness. Regulators should introduce more flexibility into current rules such as these.

Patients are waiting eagerly for advancements in treatment—and approval from the US Food and Drug Administration (FDA) for Alprolix might come within the first half of 2014. Unfortunately, with the current regulations in Europe, individuals with hemophilia who reside there are not likely to receive access to new therapies as quickly as people in the US. That is in part because the European Medicines Agency (EMA) requires clinical trials in children prior to authorization of a new coagulation concentrate for use in adults, in accordance with a so-called pediatric investigational plan or PIP—a regulation it instituted in 2007. This creates a severe disadvantage for adult patients in Europe because they have to wait for data from studies involving children. By contrast, the FDA requires clinical testing only in adults for medications to be used in adults.

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Given the rarity of hemophilia, such pediatric trials will take years to find sufficient numbers of patients for these trials. According to estimates, cases of severe hemophilia A afflict only 1 in 30,000 babies born in Europe[3]. Drug development for hemophilia in Europe faces a special hurdle because the EMA's Blood Products Working Party (BPWP) has specifically outlined, in guidelines that went into effect in February 2012, a sequential clinical trial process for factor VIII and factor IX products. These guidelines require that companies conduct clinical trials in patients aged 12 years or older to assess the immunogenicity of factor VIII and factor IX products before testing them in a younger pediatric population. They also stipulate that data are required from at least 50 and 20 previously treated patients for factors VIII and IX, respectively, for 50 exposure days (meaning days on which injections of the drug are given). Given that the new long-lasting hemophilia drugs are administered only a week or longer, this translates into a prolonged stretch of time before testing can begin in those aged less than 12 years.

This delay is problematic because there is an urgent need for coagulation factors that are long acting and may be less immunogenic. The short half-life of the currently approved coagulation therapies necessitates frequent intravenous administration—about two to three times per week for prophylaxis—which may hinder venous access and lead to other problems at the site of injection. More seriously, about 30% of people with hemophilia A eventually develop neutralizing antibodies against the coagulation factor concentrate, rendering the therapy ineffective. Ultimately, we estimate that adult hemophilia patients in Europe face a delay of about two years in benefitting from new products compared with US patients, during which time complications due to the frequent schedule of injections may arise. Even a delay of months could create problems for people with hemophilia, many of whom currently receive intravenous replacement therapy of coagulation factors either at the time of bleeding or as a prophylactic regimen to prevent bleeding.

The PIP is a laudable initiative, as it will reduce off-label prescription to children of drugs licensed for use in adults. By compelling manufacturers to test drugs in more parts of the population, it will also help reduce the chances of unforeseen side effects from medicines that are widely prescribed to younger patients. However, this cannot be applied across the board, and programs to protect children should not disadvantage adult patients.

In conclusion, even though it is explicitly stated that the PIP requirement should not significantly delay approval of products for adult patients, the current EU guidelines are doing exactly this. The PIP requirement, combined with the conditions outlined by the BPWP, makes matters worse. Abandoning the EMA's requirement of testing new clotting factor concentrates in children before these drugs can be used by adults will help to ensure that new and improved drugs for hemophilia therapy will be available in Europe at the same time as in the US, Canada and other countries.

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