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Gene therapies need new development models

As with other medicines, the approval of gene therapies should hinge on a risk–benefit analysis for the patient, argues **Fulvio Mavilio**.

Is gene therapy finally becoming a reality? The European Commission is poised to authorize, for the first time in the Western world, the commercialization of a gene-therapy product. Called Glybera (alipogene tiparvovec), it is designed to treat a rare genetic defect involved in fat metabolism.

Success has been a long time coming. Gene therapy was first administered more than 20 years ago, to a child who had a rare disorder of the immune system called adenosine deaminase (ADA) deficiency. Since then, it has struggled to find its place in medicine amid a roller coaster of successes and setbacks, hype and scepticism that has little precedent in modern times. Although the approval of Glybera is a positive move, it is unlikely to herald a new age of gene therapies — not without significant changes to the system. It is no coincidence that no gene therapy has yet been approved in the United States and that no other gene-therapy product is being considered by regulators in Europe.

Here is why. The design, development and manufacture of products such as Glybera — a virus engineered to carry a correct copy of the defective gene — is complex and done mostly in academic centres. Yet legislation introduced in the past decade in Europe and the United States demands that these products be produced under the same rules that cover conventional drugs, in establishments operated with industry-like standards and certified by government agencies.

This is a formidable challenge for academic centres, which tend to lack the necessary human and financial resources. So why is the development of gene therapy focused there, and not in industry, which seems better suited?

The first reason is the financial uncertainty generated by the complex, confused and poorly harmonized regulatory environment — as the history of Glybera shows. At first, the application for its authorization received a negative opinion from two committees at the European Medicines Agency (EMA): the Committee for Advanced Therapies (CAT) and the Committee for Human Medicinal Products for Human Use (CHMP). Only when another body, the Standing Committee of the European Commission, asked the EMA to reconsider the application in a restricted indication did the CHMP eventually recommend approval under "exceptional circumstances", requiring post-marketing studies and the set-up of a restricted-access programme. The Dutch firm Amsterdam Molecular Therapeutics, the inventor of Glybera, did not survive the process, and became known as uniQure after refinancing.

Lack of resources is a second reason. For many years, the drug industry stayed away from gene therapy, perceiving it as a dangerous technology of dubious efficacy that was too complex to develop and targeted too small a market.

There are some positive signs, because this last perception, at least, is changing: the industry now recognizes that rare diseases and orphan-drug legislation provide attractive opportunities. Some recombinant proteins and monoclonal antibodies originally developed as orphan drugs have been repurposed for larger indications.

An example of how academia and industry could cooperate comes from the recent alliance between the drug giant GlaxoSmithKline (GSK) in London, and the charity-funded San Rafaelle Telethon Institute for Gene Therapy (TIGET) in Milan, Italy. GSK gained an exclusive licence to develop and commercialize the ADA treatment, and will co-develop with TIGET gene therapies for six more genetic diseases. The contribution of public or charity-funded organizations in early development phases lowers the cost and risk of investing in diseases with a tiny market, and gives the industry access to technologies that can be expanded to more profitable applications, thereby repaying the investment and allowing resources to be fed back into rare diseases. Unfortunately, promising therapies for hundreds of orphan diseases are unlikely to attract similar industrial interest.

So, how do we ensure that scientists will continue to develop such treatments? Should they all turn to the 'hospital exemption', which permits experimental therapies to be manufactured and used under the responsibility of a physician without regulatory supervision?

That should not become standard practice. Governments, funding agencies, scientists and patients' associations must together come up with new models. Public funds could be used to pay for centralized manufacturing facilities or to subsidize enterprises with the necessary expertise to get involved, as is done for vaccines. And regulators should look again at product definition and the pathway to market.

The complex combination that forms the basis of the ADA therapy makes it somewhere between a biotherapeutic and a transplantable organ, so it hardly meets the definition of a 'medicinal product' and should therefore be regulated differently. Moreover, the amount of preclinical data and post-treatment monitoring currently required to authorize a treatment is hardly justified when preclinical models are uninformative and patients have no therapeutic alternatives.

The major factor in deciding whether to authorize an experimental treatment should be a risk–benefit analysis for the patients. Applying a different standard to gene therapy is unfair, slows down its development, discourages investment and ultimately denies people the right to have timely access to possible cures. ■

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