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Molecular Therapy

Endgame: Glybera Finally Recommended for Approval as the First Gene Therapy Drug in the European Union

In an Editorial published earlier this year in *Molecular Therapy*,[1] I described the regulatory uncertainty surrounding the evaluation of Glybera (alipogene tiparvovec) by the European Medicines Agency (EMA). Glybera is an adeno-associated viral vector engineered to express lipoprotein lipase in the muscle for the treatment of lipoprotein lipase deficiency. As with a typical TV serial, its regulatory saga has now had four acts, leading recently to a final recommendation by the EMA to approve Glybera in the European Union.[2] Although this is excellent news for the gene and cell therapy communities and for companies working in this area, the regulatory process that led to this positive outcome is still not without problems.

Amsterdam Molecular Therapeutics submitted its original application to the EMA in January 2010. The specialty Committee of Advanced Therapies (CAT), established by the EMA to review gene and cell therapy products, recommended against a marketing authorization for Glybera, and this view was consequently adopted by the Committee on Human Medicinal Products (CHMP), which makes final recommendations for marketing authorization in the EU. Amsterdam Molecular Therapeutics responded by requesting reexamination of the application, which led to the CAT's reversing its earlier ruling and recommending approval of the drug. It was therefore a great surprise when, in October 2011, the CHMP once again rejected marketing authorization based on its view that "the dossier had not provided sufficient evidence of a persistence of effect in lowering blood fats in a clinically relevant manner and there were too few patients from whom sufficiently long-term data were available." Indeed, lipoprotein lipase deficiency is an ultra-orphan disease affecting only one in a million people. According to publicly available information, the clinical results were based on only 27 patients. Following the negative decision, Amsterdam Molecular Therapeutics faced severe financial problems, and a new private company (UniQure) was established with rights to Amsterdam Molecular Therapeutics' assets.

Apparently after intensive lobbying and some political pressure, in January 2012 the European Commission, which usually ratifies CHMP recommendations, unexpectedly asked the committee to reexamine Glybera for an indication restricted to lipoprotein lipase–deficient patients who have experienced either severe or multiple pancreatitis attacks, which are serious problems in these patients. Further analysis showed that patients receiving Glybera experienced significantly fewer pancreatitis attacks than they had before treatment. The third review resulted in a CHMP vote of 16 to 15 in favor of marketing authorization—1 vote shy of the absolute majority (in this case 17) necessary for a positive opinion. Thus, the third round of review produced a negative opinion, even though a narrow majority on the CHMP was in favor of approval. Evaluation of Glybera for the restricted indication had limited the clinical material to 12 patients, and the CHMP was concerned that the data showing a reduction in postprandial plasma chylomicrons was apparently derived from only 5 patients. Recognizing "the difficulty of obtaining data in this rare disease," the CHMP invited UniQure to request reexamination for a fourth time, which resulted in the CHMP's handing down a majority vote on 19 July in favor of authorization. Apparently, the CHMP concluded that the benefits of Glybera in this subset of patients were greater than the known risks. This positive decision should be ratified by the European Commission later this year.

This lengthy and tortuous approval process raises several questions. Frequent reapplications are very time-consuming and expensive, which in this case led to the demise of Amsterdam Molecular Therapeutics, although thankfully private investors were able to continue the process. Nevertheless, investors will shy away from supporting biotech companies unless greater clarity

and predictability can be achieved in the process of regulatory evaluation and approval. The Glybera saga also highlights problems specific to ultra-orphan drugs—because obtaining large-scale phase III data with a very limited number of patients is virtually impossible, procedures to handle these indications must be further developed.

Reapplications are not entirely uncommon during the regulatory evaluation of traditional small-molecule drugs and monoclonal antibodies. However, it is noteworthy that the first three products that have been evaluated by the CAT and the CHMP have required reapplications and reexaminations. Among these products, a chondrocyte cell therapy product was eventually approved, whereas an adenoviral thymidine kinase gene therapy for malignant glioma was not. Clearly, researchers and investors developing gene and cell therapies must be prepared for a prolonged and iterative evaluation process. Despite these problems and difficulties, the final opinion in favor of Glybera is encouraging news for the gene and cell therapy communities, and hopefully evaluation of the twists and turns of the plot of this saga will help to streamline the regulatory processes of other gene and cell therapy products so that this new area of medicine can eventually fulfill its promise in human medicine.

Seppo Ylä-Herttuala
Associate Editor

REFERENCES

1. Ylä-Herttuala, S (2012). The need for increased clarity and transparency in the regulatory pathway for gene medicines in the European Union. *Mol Ther* **20**: 471–472.
2. European Medicines Agency. Press release: European Medicines Agency recommends first gene therapy for approval <http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001574.jsp&mid=WC0b01ac058004d5c1> (20 July 2012).