From Lipoproteins to Chondrocytes: A Brief Summary of the European Medicines Agency's Regulatory Guidelines for Advanced Therapy Medicinal Products

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SINCE JUNE 2012, the European Union (EU) has witnessed two major regulatory milestones in the fields of gene, cell, and tissue therapy. In July 2012, the European Medicines Agency (EMA) approved the Western World's first-ever gene therapy product (Glybera [alipogene tiparvovec]; uniQure, Amsterdam, The Netherlands); more recently, in April 2013, the EMA approved the EU's first-ever combined tissue-engineered product (MACI [matrix-induced autologous chondrocyte implantation]; Genzyme, Cambridge, MA). The recent spate of positive clinical results in both gene and cell therapy suggests that there will be more of these approvals in the near future (European Medicines Agency [A]). This brief commentary uses Glybera, MACI, and the first-ever EMA-approved cell therapy product (ChondroCelect; TiGenix, Leuven, Belgium) as case studies to elucidate the EMA's current regulatory guidelines for the development of gene, cell, and tissue therapy products.

Based in London, the EMA was set up in 1995 with funding from the EU and the pharmaceutical industry. The Committee for Medicinal Products for Human Use (CHMP) was established by the EMA in 2004 and is responsible for preparing official opinions on all questions concerning medicines for human use. If the CHMP concludes that the quality, safety, and efficacy of the medicinal product are sufficiently proven, it adopts a positive opinion. The positive opinion is sent to the European Commission, where it is transformed into a marketing authorization (MA) valid in Iceland, Liechtenstein, Norway, and all EU member countries. This allows the MA holder to market the medicine and make it available to patients and health care professionals throughout Europe.

Until 2007, the term "medicines" broadly applied to all products of chemical (i.e., small molecules) and biological (i.e., monoclonal antibodies) origin. In 2008, the EMA developed a consolidated regulatory framework specific for advanced therapy medicinal products (ATMPs). ATMPs comprise gene therapy, somatic cell therapy, and tissue-engineered products. To assist in the implementation of ATMP specific guidelines, the EMA established the Com-

mittee for Advanced Therapies (CAT) in 2009 (European Medicines Agency [B]). The CAT is an independent multidisciplinary committee that functions in various capacities along the regulatory pathway. Before submitting a marketing authorization application to the EMA, an ATMP sponsor may engage with the CAT at any step in the clinical development pathway (Fig. 1). These discussions are not legally required but provide ATMP sponsors a valuable opportunity to obtain guidance from the CAT on a myriad of issues including ATMP classifications, scientific advice requests, and collaboration with the EMA's Innovation Task Force.

After submission of a marketing authorization application (MAA) (Fig. 2), the CAT's primary responsibilities are to assess the quality, safety, and efficacy of ATMPs and to provide the CHMP with a recommendation for approval or refusal of the MAA. EMA regulations mandate that the CHMP reach a formal decision on approval/refusal within 210 days of submission of the MAA; the clock is stopped, if necessary, to ask the applicant for clarification or further supporting data. The CAT publishes a monthly report on all of its activities. According to the April 2013 report a total of 10 MAAs have been submitted since 2009 (European Medicines Agency [C]). Of these applications, there have been four positive draft opinions, which have resulted in marketing authorizations for three ATMP products (ChondroCelect, Glybera, and MACI), two negative draft opinions, and four withdrawals. There are currently three pending MAAs.

The first gene therapy product to receive a positive opinion from the CAT and the CHMP was Glybera, an adeno-associated viral vector encoding the gene for lipoprotein lipase (LPL) protein (European Medicines Agency [D]). LPL deficiency is a rare (i.e., orphan disease) autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for mutations in the *LPL* gene; LPL deficiency affects approximately one or two people per million. In March 2004, Glybera was granted an orphan medicinal product designation. This designation allows a pharmaceutical company, in this case Amsterdam Molecular

FIG. 1. Committee for Advanced Therapies (CAT) specific involvement in regulation of advanced therapy medicinal products (ATMPs) before submission of a marketing authorization application (MAA). Adapted from European Medicines Agency ([A] and [C]).

Therapeutic (AMT, Amsterdam, The Netherlands), to benefit from incentives from the European Union to develop a medicine for a rare disease, such as reduced fees and protection from competition once on the market. The EMA's Committee for Orphan Medicinal Products (COMP) examines applications for orphan designations.

AMT subsequently submitted an MAA for Glybera in December 2009. In June 2011, the CHMP and the CAT adopted negative opinions on the MAA, concluding that AMT had not provided sufficient evidence of a persistence of effect in lowering blood fats in a clinically relevant manner and that there were too few patients for whom sufficiently

FIG. 2. Timeline outlining Committee for Advanced Therapies (CAT) and Committee for Medicinal Products for Human Use (CHMP) specific involvement in regulation of advanced therapy medicinal products (ATMPs) after submission of marketing authorization application (MAA). Adapted from European Medicines Agency ([C]). EC, European Commission; EMA, European Medicines Agency.

long-term data were available. During reexamination of the MAA, at AMT's request, the CAT considered that there was scope for approval of Glybera with additional postmarketing studies, but the CHMP maintained its negative opinion in October 2011. In January 2012, during a meeting of the Member States Standing Committee on human medicinal products, the European Commission (EC) asked the EMA to reevaluate the application for Glybera in a restricted group of patients with severe or multiple pancreatitis attacks due to LPL deficiency. After detailed scientific discussions in both committees, the CAT adopted a positive draft opinion in June 2012, which was then endorsed by the CHMP in July 2012. The CHMP's positive opinion on Glybera was subsequently sent to the EC for adoption of the MA. AMT was acquired by uniQure in April 2012 and currently holds the MA for Glybera. The MA allows Glybera to be intramuscularly injected, at 1×10^{12} genome copies/kg body weight, in patients diagnosed with LPL deficiency and suffering from severe or multiple pancreatitis attacks. It should be noted that Glybera was granted an MA under exceptional circumstances, meaning that it will need to meet certain specific obligations and will have to be reviewed annually by the EMA (European Medicines Agency [D]).

Two ATMPs have been approved by EMA for the treatment of full-thickness articular cartilage defects of the knee. ChondroCelet (TiGenix) was the first-ever cellular product to complete its developmental cycle, from research to clinical approval, as an ATMP under the guidance of the EMA (European Medicines Agency [E]). ChondroCelet is manufactured from autologous chondrocytes isolated from biopsy material that is subsequently positioned in the cartilage defect with a collagen membrane. TiGenix submitted their application for licensing in June 2007. In June 2009, the CAT offered a positive draft opinion based on the data submitted and discussion within the scientific committee, which was subsequently endorsed by CHMP, resulting in the granting of market authorization.

A second chondrocyte-derived ATMP, MACI (Genzyme), recently became the first combined tissue-engineered product to receive CHMP approval after a positive recommendation by the CAT (European Medicines Agency [F]). MACI is also produced from isolated autologous chondrocytes, but differs from ChondroCelet in that the autologous chondrocytes are seeded on a three-dimensional cell-free porcine scaffold for implantation. The seeded scaffold is then shipped to the surgical center, where it is trimmed to match the articular cartilage defect, and cemented in position with a fibrin glue. MACI was found to be superior to microfracture in improving pain and joint function in an open randomized trial. The benefit-to-risk ratio was considered positive and therefore the CHMP granted marketing authorization for MACI in April 2013. Before consideration by the CAT, MACI had been available since 1998 in a number of European countries including Austria, Belgium, Denmark, Germany, Greece, Ireland, Italy, Holland, Norway, Portugal, Spain, and the United Kingdom, in accordance with local regulations.

This year, the CAT expects to review three or four MAAs for ATMPs. This compares with three initial applications for MAA received in 2012, which led to the authorization of Glybera. Although the number of MAAs for advanced therapies is still limited, the research and development pipeline is large (European Medicines Agency [A]). As a conse-

quence, a high number of MAAs for advanced therapies is expected over the next 5 to 10 years (Maciulaitis *et al.*, 2012). Among the ATMPs under development, three-quarters are cell-based medicinal products with the remainder representing gene therapies. Most of these products are being developed for cancers, cardiovascular diseases, and hematology-related conditions. Interestingly, according to the EMA, most of these ATMPs are under development by noncommercial sponsors (60%) and micro-, small, and medium-sized enterprises (SMEs; 38%) (European Medicines Agency [A]; Maciulaitis *et al.*, 2012).

Author Disclosure Statement

No competing financial interests exist.

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Received for publication May 16, 2013;

accepted May 23, 2013.