ANALYSES

Regulatory Considerations for Gene Therapy Products in the US, EU, and Japan

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Developers of gene therapy products (GTPs†) must adhere to additional regulation beyond that of traditional small-molecule therapeutics, due to the unique mechanism-of-action of GTPs and the subsequent novel risks arisen. We have provided herein a summary of the regulatory structure under which GTPs fall in the United States, the European Union, and Japan, and a comprehensive overview of the regulatory guidance applicable to the developer of GTP. Understanding the regulatory requirements for seeking GTP market approval in these major jurisdictions is crucial for an effective and expedient path to market. The novel challenges facing GTP developers is highlighted by a case study of alipogene tiparvovec (Glybera).

INTRODUCTION

In the last decade, the cost of genome sequencing has dropped from $100,000,000 to $1,000 per genome [1].

This five-log decrease over ten years, initiated in part by a scientific arms race in the late 1990s to first sequence the human genome, has yielded unprecedented access to the genetic code of our cells [2]. The unwinding of

Table 1. Definitions of gene therapy products in EU, US, and Japan.

Jurisdiction	Name	Gene Therapy Definition
EMA (EU)	Gene therapy medicinal product (GTMP)	*"a biological medicinal product (excluding vaccines) that:* *(a) Contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence and;* *(b) Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.* *Gene therapy medicinal products shall not include vaccines against infectious diseases."* Directive 2001/83/EC, Annex I, Part IV, as amended in Directive 107 2009/120/EC)
FDA (USA)	Gene therapy product	*"Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified* ex vivo *for subsequent administration to humans, or may be altered* in vivo *by gene therapy given directly to the subject. When the genetic manipulation is performed* ex vivo *on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect, or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight."* FDA. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998
MHLW (Japan)	Gene therapy product	*"The term "Regenerative Medicinal Products" (as "SAISEI-IRYOUTOU-SEIHIN" in Japanese) used in this act refers to the articles (excluding quasi-drugs and cosmetics) specified in the following items which are specified by the cabinet order.* *[…]* *(2) The articles which are intended to be used in the treatment of disease in humans or animals, and are transgened to express in human or animal cells."* Act on Pharmaceutical and Medical Devices, Chapter 1 Article 2-9* *translation from [24]

the human genome has created myriad new therapeutic opportunities for previously untreated diseases. Genome sequencing is complemented and its potential enhanced by the development of molecular techniques for artificial genomic delivery and modification, including viral-based transfection mechanisms and the CRISPR/Cas9 system [3].

The specific terminology for a gene therapy differs slightly in our jurisdictions of interest (Table 1); for the purpose of this review gene therapies will be generally referred to as a "gene therapy product" (GTP). GTPs face significant additional regulatory challenges when pursuing market approval due to the risks and concerns unique to gene therapies which must be accounted for during the regulatory process. These challenges are amplified by the novelty of gene therapies; the first gene

therapy in either the European Union (EU) or United States of America (US) alipogene tiparvovec (Glybera, uniQure; Amsterdam NL) was approved in 2012, and at time of publication only two more have received market approval since. In comparison, the first recombinant protein drug Humulin was approved 35 years ago (FDA), the first monoclonal antibody Orthoclone OKT3 31 years ago (FDA), and the first synthetic drug chloral hydrate was discovered 148 years ago (Germany) [4-6]. As the first rudimentary pre-market approval process for drugs in the US was established in 1938, small molecule drugs pre-date regulatory structures [7].

Understanding the regulatory framework that a gene therapy must navigate to achieve market approval is critical for both developers and scientists. The former need to plan their path to market accordingly and assess
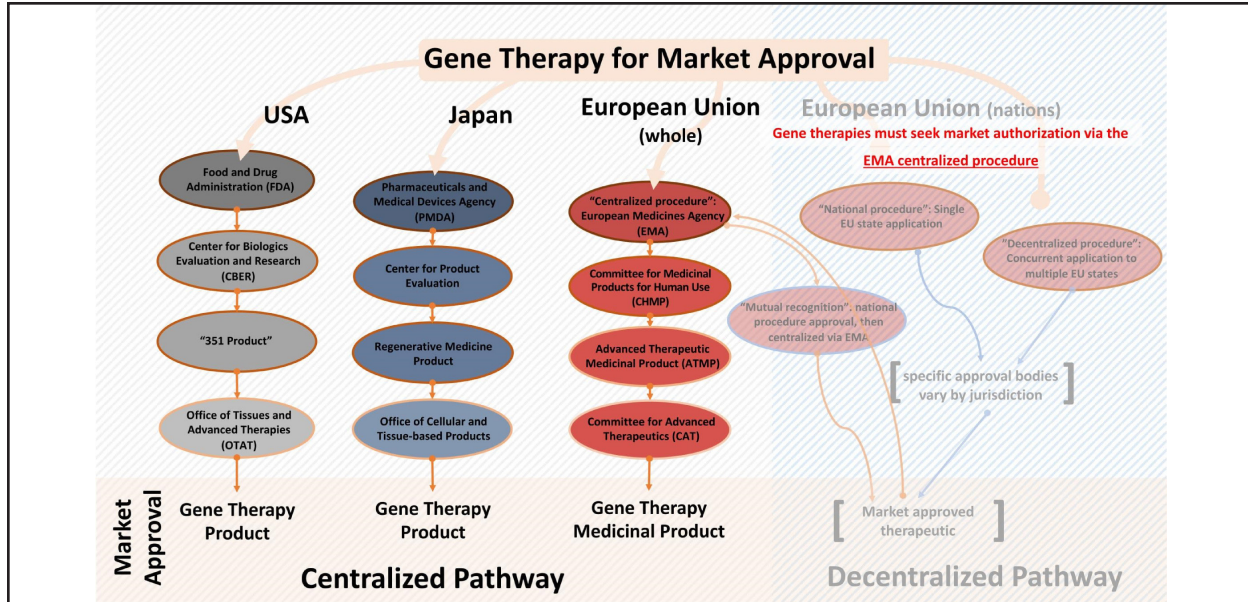
Figure 1. The regulatory structure of the US, EU, and Japanese regulatory bodies as relevant to gene therapies. Unlike the FDA and MHLW, the EMA is not a completely centralized approval body – developers may pursue market approval also via the "national procedure" (single EU state application), "decentralized procedure" (concurrent application to multiple EU states) or "mutual recognition" (first via a single EU state, then centralized via the EMA). However, ATMPs including GTs are mandated to seek approval under the centralized EMA pathway, along with specific therapeutics of certain modalities and indications.

candidates' translational viability, but scientists also need to understand the regulatory framework in order to inform their work in improving and optimizing gene therapies in the laboratory and ensure that they are translatable.

This review will cover the relevant regulatory considerations for the US, EU, and Japan. The US and EU were chosen due to their inherent relevance to Western drug developers. Japan is a significant jurisdiction and an interesting case study for the topic of this review due to their unique regulatory pathways available only to regenerative medicines, including gene therapies. Additionally, the US, EU, and Japan are the founding members of the International Conference of Harmonization, an international organization which develops scientific and regulatory documents on drug development for widespread international adoption. Therefore, these jurisdictions' regulatory outlook is especially influential on worldwide therapeutics development. The formal definition of a gene therapy in the jurisdictions of interest is given in Table 1. Within the general terminology, gene therapies are divided into two broad classes: *in vivo* and *ex vivo*. *In vivo* gene therapy is the direct modification or insertion of genetic information to cells within a tissue body; *ex vivo* gene therapy is the genetic manipulation of cells *in vitro* which are then delivered into the patient. As *ex vivo* gene therapy necessitates the introduction of significantly manipulated cellular products into the patient, these products must

generally comply with both cell-based medicinal product and gene therapy product guidelines and regulation. Only regulation directly relevant to gene therapy will be covered in this review, however, *ex vivo* GTPs are also subject to cell therapy considerations and regulations. The regulation of cell-based medicinal products has been recently reviewed [8-10].

GENERAL REGULATORY ENVIRONMENT

Within the EU and US, GTPs are regulated within the same general regulatory framework as other types of therapeutics [11]. Japan's regulatory agency, the Ministry of Health, Labour, and Welfare (MHLW), has a special regulatory framework for "regenerative medicinal products" under which gene therapy products are categorized and regulated (not to be confused with "regenerative medicine," a separate category defined in the Japanese regulation solely for academic or clinical research products where market approval will not be sought). As the Japanese regulation of GTPs differs significantly from the US and EU, further specifics of this jurisdiction's practices will be discussed separately in this review under **Japanese Regenerative Medicinal Products**. An overview of the regulatory hierarchy for GTPs in the jurisdictions of interest may be found in Figure 1.

The United States of America

The U.S. Food and Drug Administration (FDA) has jurisdiction over a variety of products including food, tobacco, vaccines, and therapeutics in the US. Within the FDA, therapeutics are regulated under either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). CBER is responsible for the regulation of human gene therapy products [12]. Within CBER, oversight of gene therapy products falls to the Office of Tissues and Advanced Therapies (OTAT), which before restructuring in October 2016 was known as The Office of Cellular, Tissue, and Gene Therapies (OCTGT) [13]. In addition to regulatory review, OTAT also releases regulatory policy and guidance documents, many of which will be referenced in this publication [14].

Biologics, and therefore GTPs, are regulated under Section 351 of the Public Health Services Act and are therefore commonly referred to as "351 Products." A 351 Product is defined by exclusion; it is a biologic which does not meet the criteria of 361 Products as defined in the same legislation. 361 products cover products including tissue and bone transplants and are referred to as "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) [15]. They must meet the following requirements: minimal manipulation; homologous use; not combined with another article; either no systemic effect and do not rely on metabolic effect of living cells; or have a system effect and rely on metabolic effect of living cells but are for autologous, first or second-degree blood relative or reproductive use [16]. The mechanism of genetically modifying a cell precludes 361 Product classification, as genetic modification has a systemic effect and depends on the metabolic activity of living cells. Therefore, GTPs are regulated as 351 Products. As a 351 Product, GTPs must receive pre-market approval and meet Good Manufacturing Practice (GMP) requirements, among others.

The European Union

The European Medicines Agency (EMA) is the centralized regulatory body of the EU. Within the EMA, The Committee for Advanced Therapies (CAT) provides an expert opinion on the drug's application dossier and gives a recommendation for approval or rejection. This decision is reviewed and ratified by the Committee for Medicinal Products for Human Use (CHMP). GTs are classified as Advanced Therapeutic Medicinal Products (ATMP) which are governed under the ATMP Regulation (Directive 2001/83/EC, as amended by Regulation (EC) No. 1394/2007). ATMP Regulation covers gene therapy medicinal products (GTMP), Somatic Cell Therapy Medicinal Products (CTMP), Tissue Engineered Products (TEP), and Combined ATMPs, which are a combination of a medical device with one or more of the previous categories. ATMPs must comply with EU pharmaceutical regulations and therefore receive pre-market approval. A non-pharmaceutical product meets the following criteria: "*It is not substantially manipulated; cells are used for the same essential function in the donor and recipient (sometimes called 'homologous use'); it is not combined with a medical device or an active implantable medical device.*" If these criteria are not met, the product is regulated as an ATMP [17]. The classification is tasked to CAT, which provides a non-binding recommendation as to whether a specific product should be considered an ATMP. As with 351/361 Product designation, any GTP would be considered a gene therapy medicinal product (GTMP), and therefore an ATMP, due to the mechanism and cellular effect of gene therapeutics. The regulation of a Combined ATMP is determined by its components, following a categorical hierarchy defined by the EMA: GTMP over TEP over CTMP. Therefore, an *ex vivo* gene therapy would be classified as a GTMP, even though the final therapeutic product would be cell-based like CTMPs [17].

Unlike the FDA and MHLW, the EMA is not a completely centralized approval body. Developers may pursue market authorization in individual EU member states; GTPs are mandated to seek approval under the centralized EMA pathway, as are all other ATMPs are along with other therapeutics of certain modalities and indications. (Figure 1) [18]. However, within the ATMP Regulation there is a special provision entitled hospital exemption, which allows small scale custom ATMP treatments for rare, specialized diseases to be used in patients without market authorization. The product must be prepared on a non-routine basis, and be used within the same hospital in which it is produced under the exclusive supervision of a medical practitioner. A controversial example is the work of Dr. Paolo Macchiarini. At Karolinska Instituet in Stockholm, Sweden, Dr. Macchiarini implanted tissue-engineered tracheas combined with cellular products into patients with cancer and other forms of esophageal damage under the hospital exemption clause. Numerous issues with the experimental treatment were later revealed, including that animal studies were not robust nor sufficiently supportive of human trials, inadequate patient consent procedures, and inconsistent and perhaps not experimentally justified material use for the synthetic tracheas. The failure of the grafts is implicated in the death of multiple patients, including those who were not in critical condition and therefore likely would have had fewer complications should they not have received the transplant at all [19].

Table 2. FDA Guidance Available for Gene Therapy Products. Only includes regulation and guidance specific to gene therapy products. Reference abbreviation provided is not official nomenclature and is only for the purposes of this review.

Title	Reference (non-official)	Year
Recommendations for Microbial Vectors used for Gene Therapy	FDA-1	2016
Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products	FDA-2	2015
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products	FDA-3	2015
Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products	FDA-4	2015
Preclinical Assessment of Investigational Cellular and Gene Therapy Products	FDA-5	2013
Potency Tests for Cellular and Gene Therapy Products	FDA-6	2011
Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	FDA-6	2008
Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors	FDA-7	2006
Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events	FDA-8	2006
Guidance for Human Somatic Cell Therapy and Gene Therapy (superseded by 2013 guidance)	FDA-9	1998

GUIDANCES ON PRE-CLINICAL AND CLINICAL DEVELOPMENT OF GTPs

GTPs present challenges and risks in their development and use in patients. The manufacturing process must be defined and validated to ensure product standardization, batch comparability and sterility. As many GTPs are dependent on viral delivery mechanisms, meeting these requirements may be more complicated than with small molecule therapeutics and other biologics. Toxicity and immune response of the component parts of the GTP, even if the part does not confer the therapeutic effect, should be addressed. Immune responses are a significant concern with some types of GTPs, tragically highlighted by the death of Jesse Gelsinger. In 1999, Mr. Gelsinger received an experimental GTP consisting of the corrective gene for ornithine transcarbamoylase deficiency delivered via recombinant adenoviral vector, the attenuated cold virus. He later died of a massive, systemic immune response to the vector [20]. The safety of the delivery mechanism and the gene therapy itself must be thoroughly evaluated during the development of a new GTP. This includes rigorous product definition and standardization, toxicity, and immune response studies to all component parts of the GTP, shedding studies, and genomic integration sites. Even after market approval, long-term structured monitoring of some types of GTPs is necessary due to the unique long-term risks posed by GTPs, especially those which have the propensity to integrate in the genome and therefore may inadvertently induce deleterious mutations.

To address GTP-specific concerns and ensure product safety, homogeneity, and compliance, the EMA/CAT and FDA/OTAT have made available multiple resources for developers (Table 2, Table 3). Relevant FDA and EMA documents are referenced for each section. For the purposes of this review the FDA guidance documents have been labeled FDA-1 to 9 for further reference to Table 2.

Product Quality

(FDA-6; EMA/CAT/80183/2014, EMA/CHMP/BWP/187338/2014)

Standard Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) requirements apply to GTPs, with some additional considerations tailored to GTPs. Starting materials should be controlled, including using viral seeds if appropriate. Potency can be challenging to determine for GTPs. Potency is defined by the FDA as "the specific ability or capacity of the product...to effect a given result." Additional challenges may be due to factors such as the inherent variability of the starting materials, lack of reference standards, multiple active agents, and the possibility for these to interfere or synergize in an unpredictable or undesirable

Table 3. EMA Guidance Available for Gene Therapy Products. Only includes regulation and guidance specific to gene therapy products.

Title	EMA Reference	Year
Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products	EMA/CAT/80183/2014	2015
Management of clinical risks deriving from insertional mutagenesis	CAT/190186/2012	2013
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	CAT/CPWP/686637/2011	2013
Design modifications of gene therapy medicinal products during development	CAT/GTWP/44236/2009	2012
Quality, nonclinical and clinical aspects of medicinal products containing genetically modified cells	CHMP/GTWP/671639/2008	2012
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products	CHMP/CAT/BWP/353632/2010	2011
Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors	CHMP/GTWP/587488/07	2010
Questions and answers on gene therapy	CHMP/GTWP/212377/08	2009
ICH Considerations General Principles to Address Virus and Vector Shedding	CHMP/ICH/449035/09	2009
ICH Considerations - Oncolytic Viruses	CHMP/GTWP/607698/08	2009
Follow-up of patients administered with gene therapy medicinal products	CHMP/GTWP/60436/07	2009
Non-clinical studies required before first clinical use of gene therapy medicinal products	CHMP/GTWP/125459/06	2008
Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products	CHMP/GTWP/125491/06	2008
Guideline On Safety and Efficacy Follow-Up - Risk Management of Advanced Therapy Medicinal Products	EMEA/149995/2008	2008
Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors	EMEA/273974/05	2006
Development and Manufacture of Lentiviral Vectors	CHMP/BWP/2458/03	2005
Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (superseded by EMA/CAT/80183/2014)	CPMP/BWP/3088/99	2001

manner, complex mechanism(s) of action, and the *in vivo* fate of the product, which can be challenging to determine and variable. Special care should be taken to detect and avoid contamination from adventitious agents, for example extraneous viral contamination.

Pre-Clinical Assessment

(FDA-5, FDA-9; EMEA/CHMP/GTWP /125459/2006).

The FDA OTAT evaluates the following GTP products: non-viral vectors, replication-deficient viral vectors, replication-competent oncolytic vectors, microbial vectors, and *ex vivo* genetically modified cells. The following should be detailed and justified in a pre-clinical program design: animal species selection and the model of disease or injury; proof-of-concept studies,

toxicology, product delivery considerations, GLP, adherence to reduction, refinement, and replacement of animals, and development of the product for later phase trials such as further safety and changes in formulation of the product. Animal selection should take into consideration the permissiveness/susceptibility of the candidate species to infection and replication of the viral vector and the response of the specific species to the expressed transgene. The document also provides a list of safety considerations specific to GTPs:

"*a. Toxicities due to the components of the final formulation (e.g., liposomes and various excipients/ contaminants).*

b. Toxicities due to the ROA [route of administration] *used.*

c. Aberrant localization to non-target cells/tissues.

d. Level and persistence of vector and expressed transgene.

e. Level of viral replication in non-target cells/tissues.

f. Immune activation or suppression.

g. Immune response directed against the vector.

h. Phenotype/activation state of target cell(s).

i. Potential for insertional mutagenesis or oncogenicity.

j. Potential for germline transmission.

k. Potential horizontal transmission of replication competent vectors from the patient to family members and health care providers (i.e., shedding)."

The EMA requires at minimum the following additional pre-clinical studies for GTMPs: integration (if applicable), germline transmission (see: EMEA/273974/2005), target tissue selectivity, immunogenicity and immunotoxicity, delivery devices, and excipients contribution, reproductive toxicology, oncogenicity/tumorigenicity, and environmental risk/shedding. These requirements can vary depending on the type of GTP product and the variant risks inherent to them.

Clinical Development

(FDA-3; CHMP/GTWP/212377/08, EMEA/CHMP/GTWP/587488/2007, EMA/CAT/GTWP/44236/2009, CHMP/EWP/83561/2005, EMA/CAT/80183/2014)

In general, GTPs follow the same standard principles of any therapeutic entering clinical trials in the EU or US. Dependent on their mechanism of action, GTPs may require additional risk consideration when undertaking human studies due to their unique mechanism of action. Specific risks include uncontrolled delivery of the gene, interference of normal function of cells and tissue, and the long-term integration of the gene into the genome. In GTPs utilizing an integrating vector, these adverse events may lead to the subsequent potential inactivation or activation of neighboring genes; of particular concern is the activation of proto-oncogenes (see: *Delayed Adverse Effects*). Developers should heed special monitoring considerations including: immunogenicity, duration of the product in the body, shedding, clonal outgrowths if applicable, and the effect on children linear development and maturation. Inherited genetic disorders are often already expressed in children, for example, Duchenne's muscular dystrophy. Therefore, it is critical to understand the potential effect on pediatric patients. Differential vulnerabilities to the vector may exist between special patient populations, *e.g.* pregnant women, children, and the elderly.

Additionally, it should be noted that determining safe and optimal dosing can be more challenging in GTPs.

Dose scaling from animal models to humans may not be as predictable as they are with small-molecule therapeutics, therefore extra care should be taken to minimize risk of dosage errors in humans.

Some GTPs utilize viral-based delivery technologies, for example adeno-associated virus. Briefly, AAV is a low immune-reactive with a predictive integration pattern in chromosome 19. Numerous serotypes of AAV exist, which vary in their inherent tissue tropism and immunogenicity. The further described GTP Glybera utilized AAV1 to deliver the gene product to the patient [21]. These may necessitate or benefit from the concomitant use of immunosuppressive agents, whose choice and efficacy should also be validated clinically. There is some allowance for modifying a GTP during an ongoing clinical trial without invalidating previously-acquired data. This is possible if the new GTP shares critical properties with the previous version, such as the gene product and tissue tropism.

Often GTPs are indicated for orphan diseases, in which case developers should follow guidance available for designing clinical trials for small populations (CHMP/EWP/83561/2005: *Guideline on Clinical Trials in Small Populations*).

Shedding

(FDA-2, FDA-4; EMA/CAT/80183/2014, EMEA/CHMP/GTWP/125491/2006)

Shedding studies evaluate how a viral or bacterial based GTP is excreted or released from the body, with concern towards contamination of others and the environment due to this shedding. These studies should be conducted to determine the risk of a GTP being transferred from the patient to an untreated person in close contact, such as a health care professional. Developers should prepare a shedding report for delivery to the FDA, as outlined in the guidance document. Additionally, some types of GTPs may require the submission of an Environmental Assessment to determine the risk of the GTP on the environment.

Delayed Adverse Effects

(FDA-8; EMA/CAT/190186/2012, EMEA/149995/2008, EMEA/CHMP/GTWP/60436/2007)

GTPs are prone to delayed adverse effects due to the persistent biology activity of the genetic material. Additionally, insertional mutagenesis may cause the development of a malignancy years after treatment. Such serious adverse events have been previously reported in GTP clinical trials. Five patients treated with genetically-modified autologous HSC transformed with a gamma retroviral vector for the treatment of X-linked severe combined immunodeficiency developed T-cell lymphoid

leukemia 2 to 5.7 years after treatment [22-23].

A series of guidance questions can be used to determine whether a specific GTP has a high risk of delayed adverse events:

Question 1: "*Is your gene therapy product only used for* ex vivo *modification of cells?*"

Question 2: "*Do pre-clinical study results show persistence of vector sequences?*"

Question 3: *"Are vector sequences integrated?"*

Question 4: *"Does the vector have potential for latency and reactivation?"*

If the answer to Questions 2 or 4 is "no," the risk of gene transfer-related adverse events is low and there may not be necessity for the developer to provide a structure for long-term monitoring of patients. If the answer to Questions 3 or 4 is "yes," the developer should incorporate long-term monitoring into their design study.

For example, AAVs do not have the propensity to integrate and therefore GTPs dependent on this technology do not require long-term monitoring. Additionally, integration studies should be considered if the vector system has the capacity to permanently integrate into the cellular genome and has a long *in vivo* duration. Integration studies inform the developer and regulatory agency of the risk of insertional mutagenesis caused by for example the inadvertent activation of a proto-oncogene.

REGULATORY INCENTIVES AND SUPPORT IN THE EU AND US

The FDA and EMA offer programs aimed to expedite the development of critical medicines. The indications of interest to the developers of GTPs are often life threatening or debilitating and currently without an effective treatment, and are therefore often able to qualify for regulatory support mechanisms.

Japan, the US, and the EU offer orphan designation, and there is a common EMA/FDA application for developers pursuing orphan designation for their therapeutic candidate. Orphan designation is available for any drug which is indicated for a rare disease. A "rare disease or condition" is defined by the FDA as either affecting less than 200,000 people in the United States, or affecting a higher number but is without a reasonable expectation that a therapeutic for the indication will bring significant financial returns to justify its development [24]. Developers will receive benefits including tax credits equivalent to 50 percent of the clinical trial costs, market application fee waiver, and seven-year market exclusivity [25]. In the EU, a therapeutic candidate may be considered an "orphan medicinal product" if it is indicated for a life threatening or debilitating condition which is not more prevalent than 5 out of 10,000 people, or is more

prevalent but unlikely to generate significant returns on the investment. The therapeutic candidate must offer a significant benefit over current treatment modalities. Benefits of orphan drug designation by the EMA include scientific advice, ten years of market exclusivity, and fee reductions [26]. Glybera, discussed further in this review, received orphan designation. In addition to standard orphan designation, Japan also offers a regenerative-medicine-specific orphan designation if the regenerative medicine product affects a patient population of less than 50,000 and offers significant potential medical benefit. These therapeutics receive financial and advisory benefits and priority review by the MHLW [27].

The FDA offers four expedited programs for drugs which treat serious conditions where there is an unmet medical need: Fast Track designation, Breakthrough Therapy designation, Accelerated Approval, and Priority Review designation [28]. Fast Track provides the developer increased access to the FDA, rolling review of the Biologic License Application (BLA) or New Drug Application (NDA), and eligibility for Accelerated Approval and Priority Review. Breakthrough Therapies receive the Fast Track benefits in addition with intensive guidance during the drug development process from an early stage. Accelerated Approval grants market approval to drugs based on their effect on a surrogate endpoint, with the condition of meeting the requisite clinical endpoints in Phase 4 confirmatory trials. A surrogate endpoint is a biomarker or biomarker(s) which predict the meeting of a desired clinical endpoint in a clinical trial. Priority Review designation commits the FDA to reviewing the drug's application within six months, in comparison to ten months under standard review. The details of these programs are provided in *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.

The EMA offers Priority Medicines (PRIME), Accelerated Assessment and Conditional Marketing Authorization. While the specifics of these programs vary, they are generally analogous to FDA Breakthrough Therapy designation, Priority Review, and Accelerated Approval, respectively.

JAPANESE REGENERATIVE MEDICINAL PRODUCTS

The Japanese government recently passed a set of legislations to promote the development of Japan as an international hub of medical research and therapeutics development, possibly due in part to the important role of Japanese scientists in the discovery of induced pluripotent stem cell (iPSC) [29]. Of specific relevance to regenerative medicines, and therefore GTPs, are the *Regenerative Medicine Promotion Law* (RMP, May

> ## Glybera (alipogene tiparvovec)
>
> **Company:** uniQure N.V., Amsterdam, Netherlands
> **Indication:** familial lipoprotein lipase syndrome
> **Regulatory status:** conditional market approval by EMA in 2012, withdrawn from market in 2017; request for further data from FDA [31]
> **Cost:** $1 million/patient [36]
> **Time in clinical trials:** 7 years (2005-2012)
> **Type:** AVV1 carrying LPL^{S447X}
> **MOA:** reduces chylomicron concentration, which reduces incidence of acute pancreatic attacks in patients [32]
> **Issues:** Clinical trial data did not lead to approval in USA; cost for patient; closure of obligatory phase IV post-market study for economic reasons in Europe; small patient population [37]

Figure 2. Case Study on Gene Therapy Product Glybera.

2013), the *Act of Safety of Regenerative Medicine* (RM Act, November 2013), and the *Act on Pharmaceuticals and Medical Devices* (PMD Act, November 2013). This legislation and statements from the MHLW have demonstrated their interest in promoting iPSC-based therapeutics development [30]. The RMP guarantees broad governmental protection and support of regenerative medicines at all stages and the RM Act gives more granular regulation on the clinical development of regenerative medicines, regulating logistical aspects to regenerative medicine development such as risk classification and processing facility requirements [11]. The PMD Act gives the strongest distinction of Japan's regulatory environment from the US and EU. This act creates a therapeutic category "regenerative medicine products," under which GTPs fall (Figure 1). Most interestingly, it creates separate drug approval pathway for these regenerative medicine products, effectively providing a shortcut through the clinical trials process [30]. Developers may seek conditional marketing approval after Phase II trials if their candidate has demonstrated safety and probable efficacy in a small sample size. Phase III data is collected while the drug is commercially available. The market approval is time-limited: within seven years from the initial approval, the drug will be re-analyzed and granted final market approval if the data is favorable.

POST-MARKET CHALLENGES: CASE STUDY OF GLYBERA

At time of publication, only four GTPs have received market approval in the either US or EU: Glybera (uniQure; Amsterdam, NL), Strimvelis (GlaxoSmithKline; Brentford, UK), Kymriah (Novartis; Basel, CH) and Yescarta (Kite Pharma; Los Angeles, CA, US). Additionally, Luxturna (Spark Therapeutics; Philadelphia, PA, US) is expected to receive market approval in early 2018. Glybera provides useful case studies for any developer of GTPs. Navigating the path to approval, in itself, does not guarantee a medicinal product's success, and commercial, rather than regulatory, challenges have in some cases resulted in product failure. These too must be considered prior to and throughout development.

In 2012, Glybera (alipogene tiparvovec, see Figure 2) was recommended for approval, becoming the first GTP on market in either the EU or US [31]. Glybera is an *in vivo* AAV1 GTP indicated for lipoprotein lipase deficiency (LPLD). LPLD is an autosomal recessive disease caused by the loss-of-function of a critical protein. Patients with LPLD do not have a functional copy of the lipoprotein lipase enzyme and therefore cannot breakdown triglycerides, leading to a variety of health complications including possibly life-threatening pancreatitis [32]. The AAV1 delivers an intact DNA transcript of the deficient LPL protein to the patients' cells. Both the CAT and the CHMP initially gave negative opinions on its market authorization candidacy before eventually approving the product [33]. As of late 2016, it had only been used commercially in one patient [34]. Glybera sponsor uniQure announced in early 2017 that the company would voluntarily withdraw the product from the EU market for logistical reasons [35]. Not only the first market approved GTP, Glybera was also the most expensive drug in the world, with an estimated cost of $1 million per treatment [36]. The large price tag in combination with a very small patient population, the curative action of the drug (therefore no repeat revenue from regular treatment), and inability to enter the US market due to FDA skepticism of the drug's efficacy have proved Glybera financially unappetizing for uniQure [37].

CONCLUSION

Gene therapies offer the potential to improve prognosis and potentially cure certain diseases. However, the uncertainty and therefore risk surrounding this novel approach results in a regulatory landscape that in the view of some is overly stringent and complex. Ensuring that patient benefit is maximized requires both: i) that regulators remain flexible and reactive to the demands and challenges uniquely posed by GTPs, and ii) that those developing GTPs operate optimally within the constraints of the regulatory system. This article focusses on the latter, and hopes to serve as a guide for those

interested in, or currently developing, gene therapies. An understanding of the regulations surrounding GTPs is essential to success in the area, and consideration of the core principles detailed in this article at the earliest possible stage of development will inevitably increase the likelihood of much needed gene therapies entering the clinic. Regulations are in place to ensure that the risk/benefit ratio of medicinal products is optimized, and this should also be the view of any entity developing GTP. GTP developers must act within the constraints imposed by regulatory bodies to improve the likelihood of their success; however, they should also remain aware of the shared goal, and work with regulators to define and improve the criteria for successful products. With a collaborative approach, regulations will evolve to best represent the needs of the stakeholders concerned – most importantly, the patients.

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