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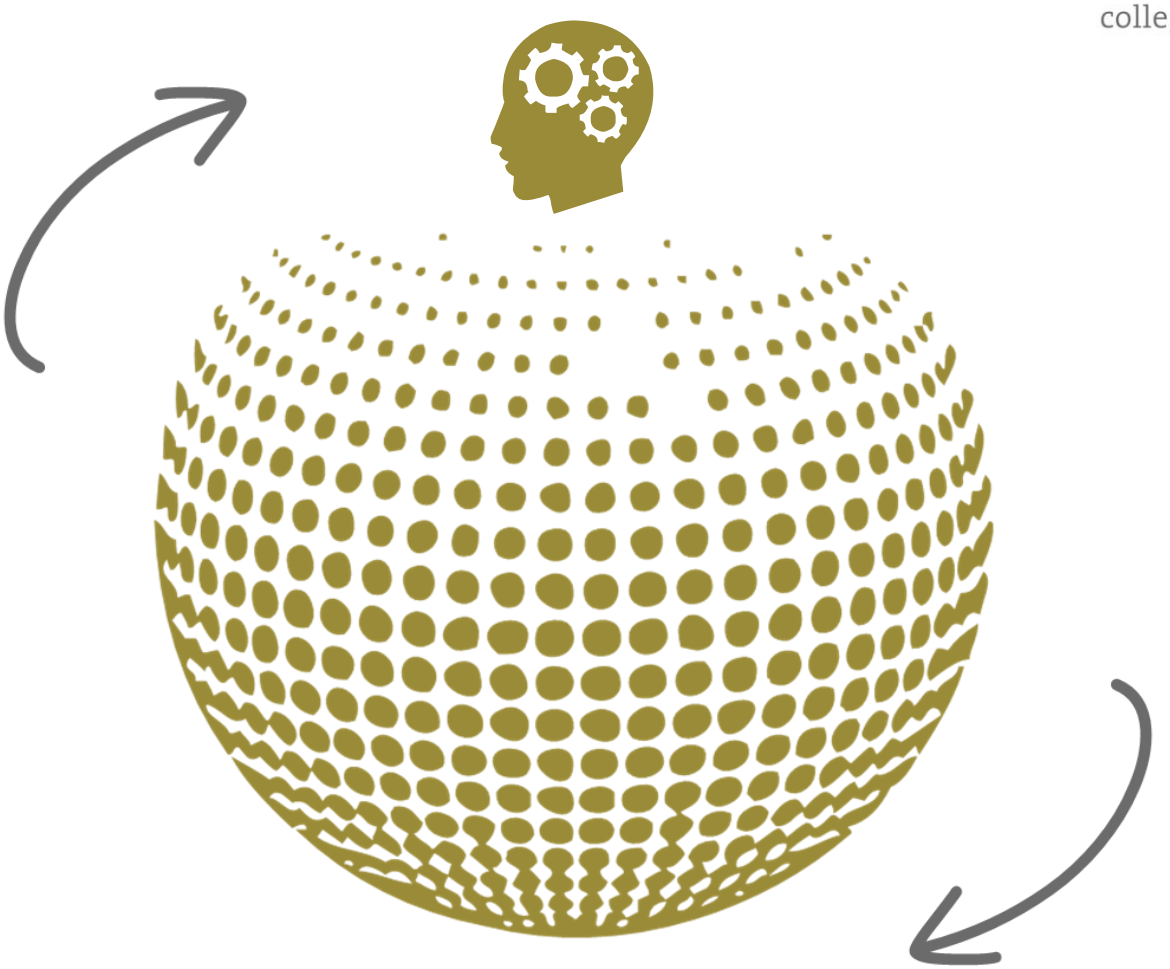

White Paper

Successful market access for gene therapies – strategic challenges and possible solutions

AUTHORS

Dr. Esther Kenfack
Prof. Dr. med. Matthias P. Schönermark, M.D., Ph.D.
SKC Beratungsgesellschaft mbH
Pelikanplatz 21
30177 Hannover
Germany
Phone: +49 511/ 6468 14 – 0
Fax: +49 511/ 6468 14 – 18

schoenermark@skc-beratung.de

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1. The advance of gene therapies and the resulting challenges

Gene therapy – what is it?

The gene therapy field focuses on somatic gene transfer

The German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) defines gene therapy as the use of gene transfer to introduce genes into cells or tissue, with the goal of utilizing the functions of these genes to provide therapeutic or preventative benefit. Genes are introduced into cells or tissue with the help of what are known as vectors (Figure 1). In genetic engineering, a vector is a means of transport generally made up of the four DNA building blocks: adenine (A), thymine (T), guanine (G) and cytosine (C). Genetic therapy contexts often refer to viral vectors – virus particles that have undergone targeted modification and adaptation to allow transmission of genetic material into cells and tissue. Only somatic gene transfer (introduction of genetic materials into cells) is permitted in Germany; genetic interference with germ line cells is prohibited under Section 5 of the Embryo Protection Act (ESchG). Egg and sperm cells develop in the germ line, and genetic modifications within it would be passed down to the offspring, which could have irreversible consequences. The German Genetic Engineering Act (GenTG) also create a framework intended to protect humans, animals, and the environment against the harmful effects of genetic engineering processes and products, while also establishing an ethical framework for genetic engineering research, development, and testing.

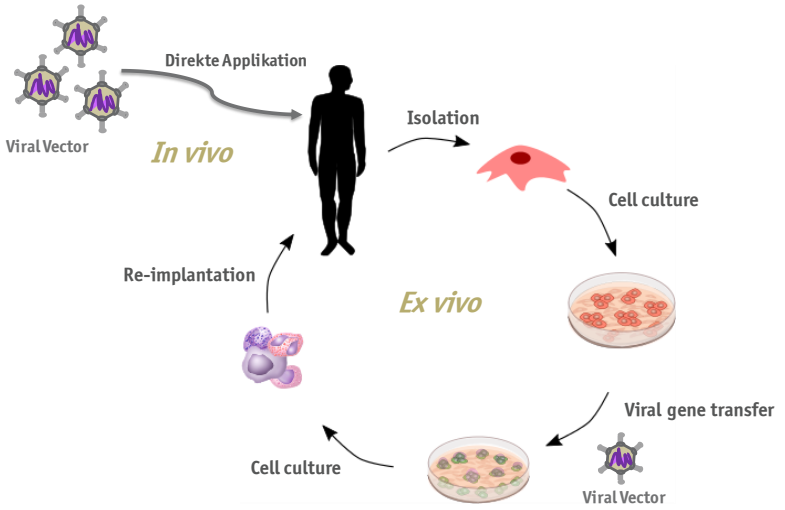

Figure 1: Schematic presentation of a somatic in vivo and ex vivo gene therapy using viral vectors. Source: SKC

News in the field of gene therapy research

Genome editing technologies have a great potential, which is currently being researched and tested

Viral vectors, such as retroviruses, lentiviruses, adenoviruses, or adeno-associated viruses (AAV) form the basis of modern gene therapy; they have been used in experimental treatments since the 1980s, and have been approved by drug regulation authorities for sale since 2012 (Glybera®, the first gene therapy approved by the EMA). Numerous other highly innovative "surgical tools" that also work on the molecular level are still in the development stage. But although **genome editing technology** has only blossomed some 30 years after virus-based gene therapies were first used, its development has progressed rapidly thanks to the availability of new (bio-)medical technologies. Gene editing procedures using zinc finger nucleases, TALENs (transcription activator-like effector nucleases), and CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats; CRISPR-associated proteins) have a great deal of scientific potential, and are in the process of revolutionizing the field of gene therapy. CRISPR/Cas9 technology allows scientists to modify genetic material within cells (to add, eliminate, or correct certain genes or gene segments) in a more time-saving, highly selective, precise, and cost-effective manner than was possible using previously available methods. Patients with **hereditary conditions**, in particular, will greatly benefit from the new methods in the future. Nowadays, scientists are continually publishing new information in renowned scientific journals like *Nature*, demonstrating what impressive potential gene editing technologies hold in the field of medical applications. Yet here, too, the question remains as to how far is too far with these new methods – for example intervening in patient germ lines without their consent, and with no way of reversing the procedure or the changes associated with it. Thus, in order to create a uniform, transparent understanding of which procedures are

allowed or forbidden, the scientific community has called repeatedly for the creation of a voluntary international moratorium, with the goal of defining all forms of molecular-genetic procedures on the human germ line more clearly, and preventing these to the greatest possible extent ("Human gene editing – Toward responsible evaluation of a new technology", from the International Working Group Genetic Engineering Report (IAG) by the Berlin-Brandenburg Academy of Sciences). While germ line therapies are generally prohibited and punishable by law in Germany, researchers in China and America, among other places, are already using genome-editing tools to modify genetic material in human embryos – a practice that has not gone uncriticized. As with germ line therapy, somatic gene therapies entail a certain degree of uncertainty with regard to long-term risks, which have yet to be explored extensively. Since genetic surgery in general involves both **opportunities and risks** (and, accordingly, has both proponents and opponents), it remains to be seen which side of the coin will play the greater role within the international scientific community in the future, without losing sight of ethical justifiability or therapeutic goals (treating and preventing illness and disability).

International approvals of gene therapies – a look at America (US FDA) and Europe (EMA)

The first gene therapy approved in Europe was Glybera®

The world's first therapy based on gene alteration was approved for use in China back in 2003. Gendicine®, a genetically modified adenovirus developed to treat tumors in the ear, nose, and throat area, was approved on the basis of primary phase I and II studies – which, at the time studies began (prior to 1999), was still sufficient to apply for approval there. In Europe and America, however (and, since 1999, in China as well), completed phase III clinical trials are usually required for gene therapy approval. In July 2012, **Glybera®** (alipogentiparvovec) by UniQure, and Chiesi after having obtained marketing rights, making it the world's first gene therapy approved on the basis of phase II/III studies. The gene therapy has EMA (European Medicines Agency) approval in Europe as a treatment for the metabolic disorder lipoprotein lipase deficiency; it uses AAV vectors to replace the lipoprotein lipase (LPL) gene in affected patients, whose LPL does not function correctly. Approval for Glybera® was not extended – due to the small number of patients, among other reasons – such that it was withdrawn from the European market in October 2017; the application for approval in the United States was withdrawn in 2015. It was not until December 2015 that **Imlygic®**, a weakened herpes simplex virus type 1 (HSV-1), became the next gene therapy to receive approval. Imlygic® is indicated for the treatment of adults with unresectable, locally or remotely metastatic melanoma without bone, brain, lung, or other visceral involvement. In May 2016, **Strimvelis®** became the first *ex vivo* gene therapy using autologous

stem cells to receive EMA approval. Strimvelis® is indicated for use in children with adenosine desaminase severe combined immunodeficiency (ADA-SCID) who cannot find matching stem cell donors. This was followed by the first CAR-T cell-based therapies to receive approval from the US Food and Drug Administration (FDA): **Kymriah®** (tisagenlecleucel), by the Swiss pharmaceutical company Novartis (approved in August 2017), and **Yescarta®** (axicabtagene ciloleucel) by Gilead Sciences (approved in October 2017). Both therapies received an EMA approval in August 2018 and are based on anti-CD19 CAR-T (chimeric antigen receptor) cell therapy, which uses genetically modified immune cells (T-lymphocytes, or T-cells) from the patient's own body to detect and eliminate cancerous cells. Kymriah® is used to treat aggressive forms of acute lymphatic leukemia (ALL) in children and young adults up to the age of 25; Yescarta® is indicated for adults with recurrent and refractory diffuse large B-cell lymphoma (DLBCL, a non-Hodgkins lymphoma, or NHL) who have not responded to at least two other treatment methods. About a year later (May 2018), Novartis' Kymriah® obtained FDA approval with status *Priority Review* for a second indication, as a treatment for adult patients with recurrent and refractory diffuse large B-cell lymphoma (DLBCL) who are not suited to, or relapse following, an autologous stem cell transplant. Kymriah® is also undergoing accelerated assessment by the European Medicines Agency as a treatment for both children and young adults with recurrent/refractory B-cell ALL, as well as for adults with r/r DLBCL who are unsuitable for autologous stem cell transplantation. At the end of last year (December 2017), **Luxturna®** (voretigene neparvovec-rzyl) by Spark Therapeutics received FDA approval, making it the first directly applied (*in vivo*) gene therapy approved to treat a genetic illness caused by a defined mutation. Almost a year later, in November 2018, Luxturna® was also approved in Europe. The therapy is an AAV vector which transports a corrected version of the RPE65 gene into the retinas of patients with hereditary retinal dystrophy resulting from mutations in the RPE65 gene, thus improving their vision. **Zynteglo™** (betibeglogene autotemcel) was approved by the EMA in May 2019 and is indicated for the treatment of patients with transfusion-dependent ß-thalassemia (TDT). Until now, Zynteglo™ has not yet been approved in the US and is thus the first gene therapy to be available on the European market only. In June 2019, Zolgensma®(onasemnogene abeparvovec-xioi), a recombinant adeno-associated virus-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA), was approved in the US. The therapy has also recently been approved in Europe (May 2020).

In the US, Kymriah® became the first CAR-T cell therapy to receive approval

With Luxturna®, gene therapies have also begun conquering the field of ophthalmology

Challenges involved in the development and introduction of gene therapies

The number of gene therapy products in the pre-clinical and clinical stages has doubled in the past several years. Several individual fields, such as oncology (cancer treatment) and treatment of hematological diseases, have emerged as preferred areas of potential gene therapy research; many such treatments are already in advanced phase II and III clinical trials (Figure 2). Analysis shows that, in addition to large pharmaceutical companies like Novartis, and Pfizer, a growing number of smaller companies are specializing in gene therapy products. Most new projects begin at small companies with risk distribution-based business models. Once a *proof of concept* has successfully been demonstrated, these projects are sometimes taken over by more established companies, as was the case with Luxturna®. Moreover, pharmaceutical companies also have at least twice as many phase I/II studies in the pipeline, with a focus on gene and cell therapies that will move to phase III within the next several years.

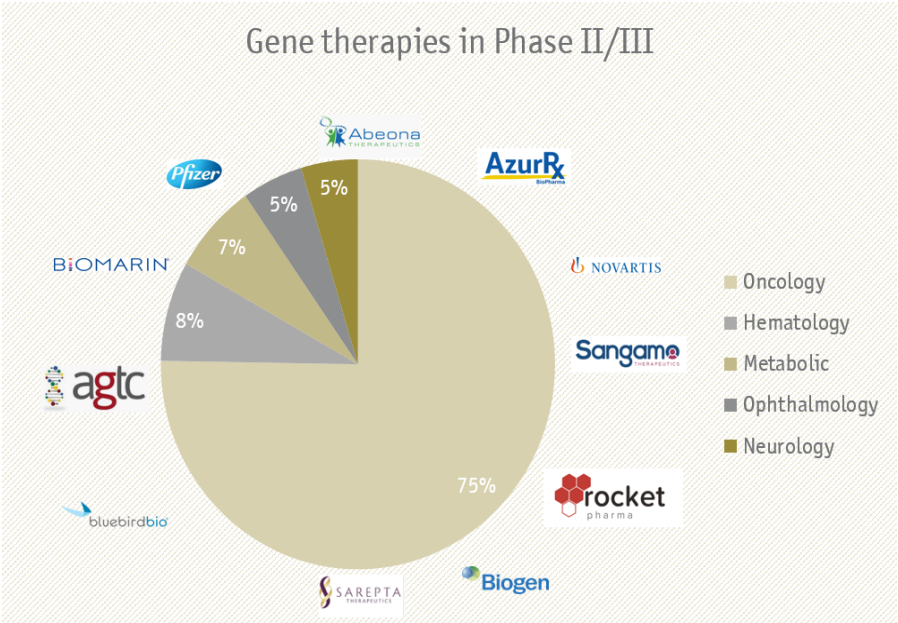

Figure 2: Numbers and indication of gene therapies in phase II and III. Analyses have shown, that more than 50% of gene therapies are developed for the treatment of oncological diseases and R&D as well as distribution is often under the lead of big pharma companies and young ambitious companies in the USA. Besides oncological diseases, hematological treatments are also found in the further advanced clinical trials. Source: www.clinicaltrials.gov, SKC-Analysis. This information is provided without liability.

The most significant challenges are in relation to evidence and adequate reimbursement

The FDA and the EMA have already approved five one-time gene therapies between them, although no uniform regulations are currently in place to clarify how usage of these one-time therapies is to be regulated or monitored, nor how they are to be covered by insurance. The costs associated with developing, implementing, and completing clinical trials for these products are enormous, which raises questions regarding adequate reimbursement and also poses new

challenges for both pharmaceutical companies and payers. Given the rarity of the diseases in question and the fact that gene therapy approaches have not yet been extensively evaluated, new requirements have arisen in terms of approval processes in Germany, particularly the AMNOG [Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganization Act)] process (pharmaceutical product benefit assessment and subsequent price negotiation) (Figure 3).

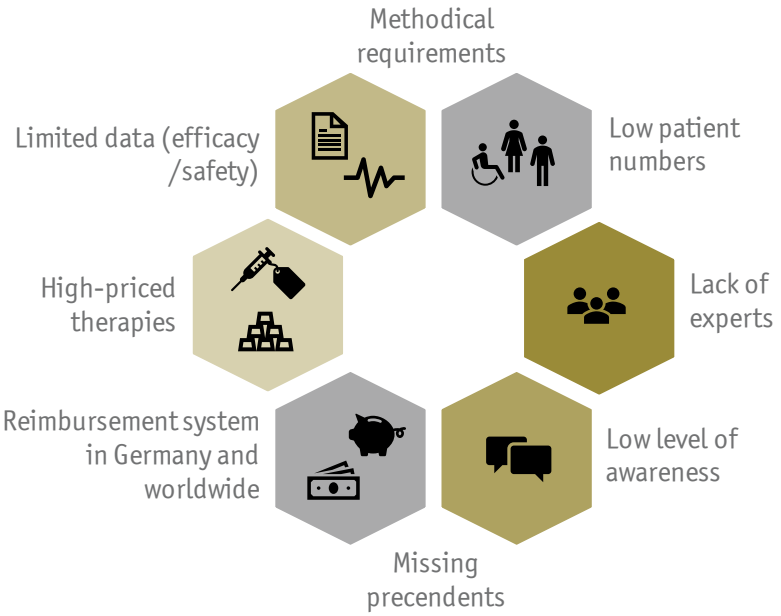

Figure 3: Challenges in the approval and benefit assessment process of gene therapies. Often a multitude of uncertainties regarding the studies and available data but also the lack of persons involved are a combined challenge, not only for pharmaceutical companies but also for the authorities and payers involved in the processes. Source: SKC-Analysis

In 2016, the US Institute for Clinical and Economic Review (ICER) identified three **key obstacles** facing gene therapies. The first of these is the issue of **generating evidence.** Orphan drugs are often faced with limitations in this regard due to the very low number of potential patients; the fact that placebo controls are sometimes not ethically justifiable (e.g., Glybera®, 60 painful injections per one-time treatment), resulting in single-arm study designs; and study designs being too short to research long-term safety and efficacy, resulting in a lack of data in this regard. **Assessing therapeutic value** represents another obstacle. Do the therapies offer added value by providing potential healing that will improve patient quality of life, reduce the need for alternative therapies, and increase productivity? How can this added value be measured, and at what point is adequate assessment of this value possible? As yet, sufficient evidence is not yet available on these assumptions that would allow a conclusive

In the field of gene therapy, demonstrating the value of the therapy is of essential importance

assessment of gene therapy compared to alternative therapeutic options. Determinations of whether a product has "particular value" can be made for small groups of patients based on the severity of the condition, the time of its development, the burden it represents, the individual development costs per patient (as in the case of autologous CAR-T cell therapies, for example), and the return on investment. In addition to difficulties with generating evidence and assessing the value of individual therapies, **affordability** is also playing an increasingly important role in the field of innovative therapies; this topic will be discussed in more detail in a later section.

Gene therapies also need to be integrated into the existing regulatory network, or else new regulations need to be established under which gene therapies can be introduced and covered. The key to the success of future therapeutic approaches lies in finding new strategies for bringing innovative forms of therapy **in line with regulatory institutions and the reimbursement system**. Overall, gene therapies raise a number of **critical issues** as regards regulatory requirements as well as reimbursement, particularly when used to treat rare conditions; in order to ensure a successful launch both in Germany and worldwide, these issues need to be considered during the pre-launch phase:

Successfully obtaining market access for gene therapies entails a variety of challenges

- The **small number of patients**, who will need to be **identified** (specific diagnoses are often difficult) and **recruited** (treatment is usually only symptomatic);
- The fact that many of these **medical conditions are not well-known**, meaning that the **unmet medical need** will need to be established and presented especially early on in the process in order to maximize **awareness**;
- The **small number of (clinical) experts** in the specific area of expertise in question, though it is important to win these over and **involve them in the ongoing process** as early as possible;
- The **limited amount of data** often available **at the time of market launch**, especially as regards evidence of the safety and efficacy of the therapy (one-armed study design, phase II studies, short monitoring periods, etc.);
- The **methodological requirements** on clinical studies, such as **numbers of clinical trial subjects**, a system for **categorizing severity of the condition**, or the need to incorporate **validated patient-relevant endpoints**;
- The one-time but usually extremely high **cost of applying the therapies**;
- The **current reimbursement systems** in Germany and around the world;
- The **lack of successful precedents** to provide orientation for authorities and businesses.

In light of this wide range of challenges, this document will present the positions relevant to the approval and reimbursement of gene therapies at the national and international levels, and then build upon these positions in order to identify the strategic options and room for maneuver available. From the perspective of the pharmaceutical company as well as those of the payer, the approval authorities, and the national agencies, it seems logical to use a **collaborative approach** when adjusting or re-developing regulations and systems in response to the future challenges posed by these new, innovative therapies, in order to guarantee that patients receive optimum care.

2. Regulatory considerations

Early dialog among stakeholders seems particularly advisable in the case of pioneers in the field of gene therapy

With many rare medical conditions and several very serious, i.e., life-threatening illnesses, there is still a high unmet need for curative treatment options. This increases the willingness to approve such therapies and bring them to market as rapidly as possible (even on the basis of a smaller amount of evidence), albeit while taking into account the special characteristics of the therapies. Companies planning to conduct gene therapy studies should thus enter into dialog with regulatory authorities as well as insurance providers early on, in order to discuss optimum study design and address related issues, such as the question of satisfactory results and *outcome measures*. Although randomized clinical trials (RCT) represent the gold standard for clinical trials, the limited number of study participants and the occasionally invasive procedures that would be necessary on control-group patients often make them difficult to implement in gene therapy studies. Since RCTs are not always possible, adaptive study designs, randomized evaluations, and cross-over studies are proposed. As with regular trials, gene therapy studies pose questions of potential late-onset adverse effects as well as of long-term efficacy (durability), which cannot yet be identified and investigated over the course of the short studies. These limitations play a role in the high level of uncertainty surrounding these clinical trials in terms of efficacy, benefits, and safety.

Various authorities have already begun working – some of them quite intensively – to investigate potential new design requirements on gene therapy clinical studies, in order to identify and implement any necessary adjustments to the existing directives and guidances. The following section provides a brief summary of the adjustments previously planned and implemented at the national (PEI, BfArM, DFG, G-BA) and international (FDA, EMA, NICE) levels.

International perspective - FDA (USA)

Market approval process for gene therapy products - authorities involved in the USA

Marketing and approval of gene therapies in the USA require submission of a BLA (biologics license application)

In America, the Department of Health and Human Services (DHHS) is responsible for monitoring clinical studies. Other organizations operating under the umbrella of the DHHS include the Office for Human Research Protection (OHRP), the FDA, and the National Institute of Health (NiH)'s Office of Biotechnology Activities (OBA). The FDA serves as the primary legislative supervisory authority on issues of American public health, and thus oversees the safety and efficacy of medical products before they become available to patients. Specifically, and among other things, the protocols submitted by (for example) pharmaceutical companies for purposes of investigation and application for market approval of gene therapy products (GTP) are subject to review by the Recombinant DNA Advisory Committee (RAC), which is organized within the OBA. The market approval process for novel gene therapies is faced with particular regulatory challenges due to their novelty, and due to the still unidentified risks associated with such therapies. In the USA, the regulation of therapeutic products is under the jurisdiction of the FDA, specifically the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), with the latter being responsible for the field of gene therapy. Within the CBER, in turn, the Office of Tissues and Advanced Therapies (OTAT), formerly the Office of Cellular, Tissue, and Gene Therapies (OCTGT), is responsible for the regulatory supervision of gene therapy products and the adoption of regulatory guidances. Biological products ("biologics"), which include GTPs and other products with similarly increased risk potential, are regulated under Section 351 of the Public Health Service Act, or PHSA, which is why they are often referred to as "351 products". However, before a gene therapy can be clinically tested in order to obtain market approval, an investigational new drug (IND) application must be submitted and an Institutional Review Board (IRB) must grant permission for studies to be conducted on patients. Studies and all related process steps must be carried out in accordance with good manufacturing, tissue, and clinical practices (GMPs, GTPs, and GCPs). Gene therapy products can only be marketed following submission and approval of a biologics license application (BLA) on the part of the pharmaceutical company or the FDA. Along the way, the FDA provides the companies with guidances which, among other things, are intended to provide assistance with clinical gene therapy studies. The CBER also offers companies scientific and regulatory consultation [INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER ProducTs) meeting, Pre-IND meeting, etc.] so that they can address open questions and potential obstacles early on in a targeted manner.

FDA guidances and recommendations for gene therapy products

Gene therapies are faced with several special challenges beyond those involved with "conventional" pharmaceuticals (see Figure 3), such that the approval process necessarily differs from the one for conventional therapies. GTP production must be clearly defined, and must be carried out on the basis of standardized processes; the safety of the therapy plays an essential role both during product development and after approval. *Gene Therapy Regulation: A Proactive Approach* was published in 1996, and names the FDA, the NIH, and its subcommittee, the RAC, as the regulatory institutions for gene therapy research and application. The fundamental regulations on gene therapies are similar to the ones on those conventional medical products falling under the category of *biologicals*. One key difference, however, lies in study design: gene therapy studies are permitted to involve sick subjects (as opposed to healthy subjects) in phase I trials in order to investigate the safety and efficacy of the product. The reasons for this include, in particular, the presumably unknown risk posed by the therapies. It also enables scientists to collect preliminary evidence early on regarding the bioactivity of the gene therapy product (Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products - Guidance for Industry, 2015).

Sick test subjects can be involved in gene therapy studies from Phase I onward

An overview of several existing **gene therapy-specific guidances** is provided in summary form in Table 1, covering key issues such as product safety (toxicity, immune responses, safety of the gene transfer and the mechanism *per se*, time the virus remains in the body, analysis of genetic integration sites, monitoring long-term risks), product purity and efficacy, product homogeneity, and FDA regulation compliance. Biologicals are regulated using a scientifically based, risk-based approach, making it possible to determine the extent to which the criteria can be upheld. Conversely, gene therapy products, which involve a potentially greater risk profile for side effects, are subject to stricter controls. More detailed information and original guidance documents are available on the FDA homepage under *Cellular & Gene Therapy Guidances*.

Biologicals are regulated based on a scientifically based, risk-based approach

GTPs are often the only therapeutic option available to patients with rare or life-threatening conditions. In order to give these patients quicker access to what may be life-saving therapies, the FDA has developed four accelerated approval process programs for products that represent treatment options for serious illnesses: fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval. Section 3033 of the 21st Century Cures Act for cell and gene therapies recently also made available the option of classification as a regenerative medicine advanced therapy (RMAT designation). The prerequisite for this is that the therapy be designed to treat

Gene therapies for serious illnesses can undergo accelerated approval processes in the USA

a serious or life-threatening condition, and that preliminary clinical evidence indicates that the product could cover the existing unmet medical need (Figure 4). Thus far, roughly 15 gene therapy products have been granted RMAT status and thus gained access to the accelerated FDA approval process. The first gene theray was LentiGlobin (Zynteglo™) from the US company bluebird bio, used to treat ß-thalassemia (a rare genetic condition causing a reduced production of hemoglobin). Zynteglo™ has already been approved by the EMA, and the FDA approval is expected in the second half of 2020. Unlike other fast-track processes, RMAT therapies need no evidence to show that the product represents a significant improvement over existing products. Besides the expedited review programs, medical products treating rare (orphan) diseases can also obtain orphan drug status ("*Orphan Drug Designation*"). Once a product has received orphan drug status, the pharmaceutical company receives aid in the form of a tax credit of up to 50% of the clinical development costs, a credit to waive the application fees, and seven years of market exclusivity for the product in question.

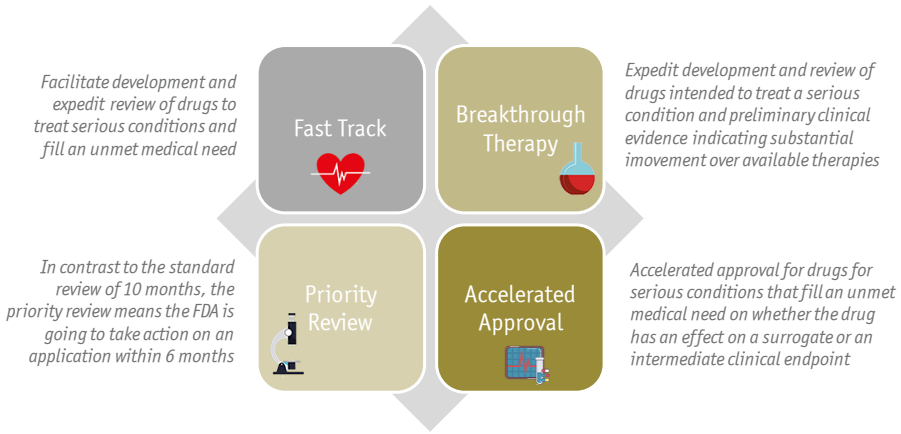

Figure 4: Overview – FDA´s expedited programs – Fast Track Designation, Breakthrough Therapy Designation, Priority Review Designation, Accelerated Approval incl. the RMAT Designation for cell and gene therapies (Guidance for Industry - Expedited Programs for Serious Conditions - Drugs and Biologics). Source: FDA

The regulatory authorities have recognized the medical change and the potential inherent in innovative therapies, which is why the FDA is in the process of adapting its traditional ways to develop concepts that fit the requirements on new gene therapy methods.

New concepts are formed on the basis of scientific standards, and the FDA hopes to position itself as a bridge rather than an obstacle in their implementation. In February 2019, a policy concept was developed within the political framework for regenerative medicine, with the goal of establishing shorter procedures for gene therapy products. Furthermore, three disease-specific guidances were published in 2020 to aid companies developing gene therapy products, and to create a framework delineating the safety and benefit standards to which innovative products will need to adhere. The CBER regularly publishes policy agendas presenting documents planned for the coming year; the hemophilia-specific guidance "Gene Therapy for the Treatment of Hemophilia" has already been announced. For instance, a guidance on gene therapy for neurodegenerative diseases has already been announced. Furthermore, the FDA has taken into account the recent developments in gene therapy and will publish later this year a guideline on the "Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing". Dr. Gottlieb reports more than 600 active IND applications falling under the category of gene therapies. Scientists at the Massachusetts Institute of Technology (MIT) estimate that around 40 of these gene therapies (of 932 current candidates) will receive approval by 2022. The assumption is that around 45% of those products are being developed to treat different types of cancer.

„We need to make sure that we're taking policy steps to enable these innovations to efficiently advance to benefit patients, while we maintain our gold standard for ensuring the safety and efficacy of new products."

Dr. Scott Gottlieb, FDA commissioner
19th December 2017

FDA requirements on long-term follow-up examinations of gene therapy study participants

Even after approval has been granted, pharmaceutical companies are still obligated to fulfill the FDA's post-marketing requirements. Among other things, these include documenting and reporting any adverse effects developing after market introduction, as well as complying with additional **post-marketing obligations**, such as initiating phase IV clinical trials. The FDA CBER has recently updated the guidance document on the "Long Term Follow-Up After Administration of Human Gene Therapy Products", which now replaces the document on "Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events". This document provides a framework for assessing potential risks and long-term effects of gene therapy supported by long-term observations made so far. In addition, the guidance document makes supplementary recommendations on the following subjects:

One essential requirement set by the FDA is the initiation of Phase IV clinical trials

- The generation of **suitable data** from pre-clinical and clinical studies to assess the potential long-term risks of gene therapies;
- Specific advice regarding the **duration and design of long-term monitoring**;

- Instructions for determining the likelihood that **long-term monitoring** of study participants **will generate scientifically significant information** and the recommendation to **create a registry**.

The FDA generally recommends conducting long-term monitoring

The FDA does not generally insist upon **long-term monitoring for gene therapies**, meaning that it is not necessary in cases involving, for example, a minor risk of late-onset side effects developing after one year following gene therapy. However, long-term monitoring is recommended for any gene therapy study, regardless of the vector or gene modification used. If, over the course of continuous observation, concerns arise regarding therapy-related risks, long-term monitoring may become necessary. It is also required if pre-clinical toxicity studies suggest that transgenic expression could result in late-onset toxicity; if the modified gene represents a functional replacement of the original gene, and the modified gene product is potentially immunogenic; or if clinical trials suggest that the vector remains in the body or an increased risk of long-term effects. The latter is a factor because the longer the vector remains in the cell / the body, the greater the risk of side effects. In addition, for gene therapy products using the gene editing method, off-target effects in long-term observations should be carefully monitored.

Post-treatment monitoring should continue for a minimum of 15 years

According to the FDA's Biological Response Modifiers Advisory Committee (BRMAC), long-term monitoring should be conducted for a **period of at least 15 years**, though a shortened monitoring period can be useful in individual cases, as long as the duration is appropriate to the circumstances of the study in question. Some study participants may be less suited to long-term monitoring than others, for example due to low life expectancies, generally poor health, other comorbidities, or the influence of other medications / treatments. The company is obligated to collect and maintain adequate, accurate medical histories for each and every study participant. The FDA provides recommendations in this regard as well, for example on what information should be obtained and documented over the long-term monitoring period. However, scientists and other interested parties are called upon to provide additional information regarding the FDA document on long-term monitoring of patients who have received gene therapy.

International View – EMA (Europe)

Market Approval Process of Gene Therapy Products – Institutions Involved in Europe

The main responsibility for the approval process at the EMA is borne by CHMP and CAT

In addition to somatic cell therapeutics and biologically engineered tissue preparations, gene therapeutics also belong to the **group of advanced therapy medicinal products** (**ATMP**). The classification of new medical products as ATMP is conducted by the Committee for Advanced Therapy Medicinal Products (CAT). These must be approved centrally at the European level so that market authorization in all member states of the European Union is ensured. The basis for the approval is Regulation No. 1394/2007. The central approval process is coordinated by the EMA. Within the process, the benefit/risk ratio is examined with the involvement of CAT. Here, the CAT is responsible for the initial review and forwards its approval recommendation to the Committee for Medicinal Products for Human Use (CHMP), which in turn forwards a recommendation based on this to the European Committee. The European Committee ultimately makes the decision about issuing the approval. The procedure and the evaluation by the various committees and the EMA are explained in the "Procedural Advice on the Evaluation of ATMPs" document; an overview is presented in Figure 5.

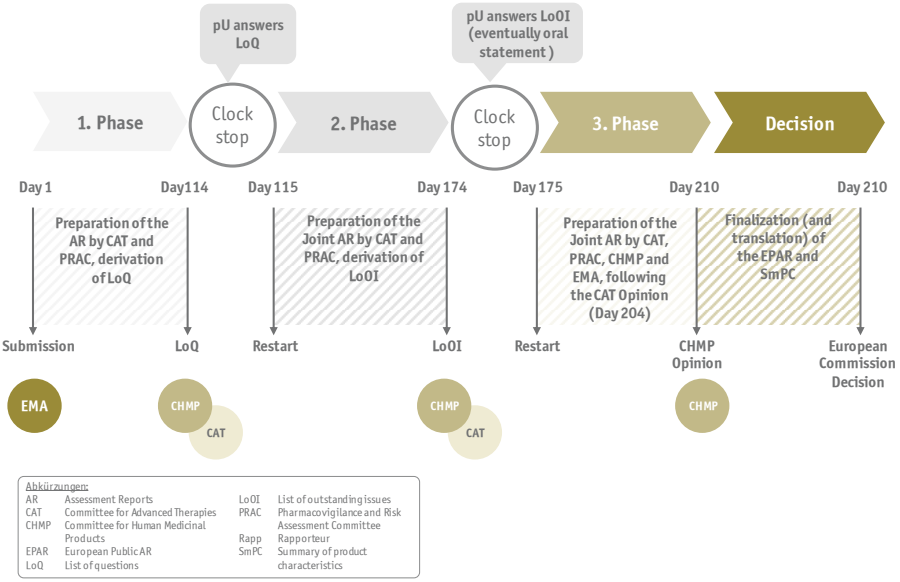

Figure 5: Overview of the centralized approval process of the EMA (simplified scheme). During the clock stops within the approval process the pharmaceutical company is able to address potential uncertainties and identified risks and define their position. Source: EMA, SKC-Analysis

In general, ATMPs must fulfill the same requirements as "normal" drugs during the approval process, however, some additional special aspects should also be taken into consideration. One particular characteristic of ATMPs is, for example, that they need to be tracked all the way from the place of manufacture to

the administration. These data must be kept by the market authorization holder for at least 30 years. For this reason, the EMA provides scientific advice on this aspect with regard to the establishment of systems for security surveillance. Furthermore, the EMA also offers the possibility to accelerate the approval of medicinal products. Hence, an **Accelerated Assessment** can be applied for if the product is of great interest for public health, especially with regard to innovative therapies including gene therapies. If application for an Accelerated Assessment is granted, the CHMP will evaluate the marketing authorization application within 150 days instead of 210 days. Since March 2016, the EMA has launched the **PRIME** (priority medicines) scheme, which enables an early dialog between the regulatory authority and developers of promising medicines to optimize plans and speed up the evaluation process so that these medicines are available to patients earlier. Once a drug candidate has been selected for the PRIME scheme, the developer is assigned a member of the CHMP or CAT to act as a contact person and provide regulatory guidance prior to submission of the marketing authorization application. The PRIME scheme also offers the possibility of an Accelerated Assessment or **Orphan Designation**. In the latter case, the EMA hopes to create financial incentives for the development of therapies for rare diseases by granting developers advice on marketing authorization, market exclusivity once the drug is on the market and fee reductions.

EMA guidelines and Particular Characteristics with respect to ATMPs and/or Gene Therapies

The EMA is currently revising one of the essential guidelines for the Market Access Process of ATMPs on the basis of precedence

Overall, the EMA offers specific guidelines for gene therapy products, of which two are currently being revised by the EMA. In addition, it should be noted that an environmental risk assessment is mandatory for gene therapies under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms (GMOs). In particular, the first revision of the guideline regarding the assessment of the safety and efficacy after successful market approval and the risk management of the ATMPs, the draft version of which was published in February 2018[1], shows that the increase in gene therapies is also prompting the EMA to adjust its methods in order to support the pharmaceutical companies in the development and the approval process and to satisfy the new requirements. The basis of the guideline is Article 14 (4) of Regulation (EC) No. 1394/2007, according to which the EMA is supposed to develop a guideline for the follow-up phase of ATMPs. The revised guideline is supposed to incorporate the experience of previous market authorization procedures. The focus of the revision here is on the following aspects: With respect to the methods

[1] The version is currently under revision.

for identifying risks and effectively mitigating their consequences for patients, attention should be paid to identifying these risks as early as possible in order to be able to incorporate the insights into the entire process. The overarching goal should be to prevent or minimize risks. With this in mind, work should be performed using the risk-based approach in order to be able to address the respective safety and efficacy aspects in the risk management plan (RMP) (Figure 6).

Figure 6: Risk Based Approach and risk management plan according to the "Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products" of January 2018. Source: EMA, SKC-Analysis

The potential risks of gene therapies should be assigned to the four phases of manufacture, handling, administration, and clinical follow-up

The risks should be assigned to the four phases – manufacture, handling, administration, and clinical follow-up. In particular, risks related to quality characteristics, storage, and distribution (risks regarding the transmission of diseases, tumorigenicity, storage, transportation, and distribution) must be addressed during the **manufacture**, whereas risks related to patient-associated diseases or comorbidities, as well as potential interactions with other medications (unwanted immunogenicity; risks associated with intended and unintended genetic alterations of the patient's cells; early and late consequences of transplants, differentiation, migration, and proliferation; risks associated with infection from vectors used in gene therapy; risks related to clinical follow-up care, e.g., immunosuppression, or in order to treat potential complications) have priority during **handling**. By contrast, risks of **administration** relate to the medical or surgical procedures and/or the administration of the medication (infusion, transfusion, implant). By contrast, the **clinical follow-up** is given a special significance. Here, the focus is on, for example, late complications such as the occurrence of malignancies or acquired autoimmunity.

Requirements by the EMA for clinical follow-up of ATMP studies

The seamless acquisition of additional data after launch should be ensured

Generally speaking, applicants, meaning the pharmaceutical companies where applicable, must ensure the acquisition of additional safety and efficacy data even after market approval. This can be done via **extension studies**, **additional clinical studies**, as well as via **registry data**. It should be noted here that while observational studies are more likely to take place than randomized controlled trials, overall there is still a general desire for a high level of internal validity. This can be achieved, for example, by including control groups, such as an untreated or placebo-treated group. When clinical trials are initiated, various approaches to study design and analysis should be included in order to ascertain early or late complications as well as to be able to document a gradual increase or decrease in **efficacy over time**. It is necessary that these dynamics are taken into account in the planning of such follow-up studies. Here, the studies should be designed according to the specific characteristics of the product, and not according to the general characteristics of the product classification. When initiating the follow-up study, the aspect of the **reality of care** must be taken into account and therefore generation of registry data seems reasonable and becomes a requirement, in particular, for results regarding long-term efficacy, for example, in order to document the maintenance of clinical benefit or healing of the patient. It is important to note that the study subjects from the phase I studies and participants from compassionate use programs should also be monitored in order to enable the **comprehensive generation of long-term data**. In order to ensure follow-up monitoring, it is recommended, according to the opinion of EMA, to include the **HOW** of the follow-up monitoring early on in the process. The pharmaceutical company's plans, for example, to set up registries or to use other sources of data for follow-up monitoring, should be sufficiently developed during the pre-launch phase in such a way as to enable **seamless follow-up monitoring** after the market access. Thus, potentially required agreements with other stakeholders, e.g., HTA (health technology assessment) authorities or patient representatives, should have already been made by the time that approval has been granted. The relevant guideline specifically for gene therapy approaches is "Follow-up of patients administered with gene therapy medicinal products" (CHMP / GTWP / 60436/07). A separate follow-up for acquiring data on safety and efficacy is not required. Instead, it is recommended that additional data acquisition be consolidated, in particular, once phase IV studies have been set up. The number of patients, however, is determined by the size of the patient population. Thus, in a study with a multitude of patients, a subset for the further study program may be sufficient if the selection of the subset can be scientifically justi-

The dynamics of the long-term efficacy must be ascertained using post-launch data acquisition

fied. For rare diseases, on the other hand, the "Clinical trials in small populations" guideline (CHMP / EWP / 83561/2005) can be used as the basis for determining the number of patients to be monitored. No universally valid duration for the follow-up has been specified; instead this depends on the individual product. In particular, when a maintenance effect needs to be determined or demonstrated, or if late onset side effects are probable, a long follow-up monitoring period is essential. For viral vector-based gene therapies, approx. 15 years are generally estimated, whereby the **exact duration cannot be determined until the market authorization** has been issued. The overarching goal of the follow-up is to ascertain the dynamics of the efficacy of the treatment, i.e., the issue of whether a treatment needs to be repeated, and if so, when that is. Thus, in the post-launch phase for gene therapy approaches, the focus is on the sustainability of the efficacy in addition to the monitoring of immunogenicity, the evaluation of the risk of insertion and a possible activation of an oncogene in the modified cells as well as the monitoring of the application (particularly for *in vivo* treatments). In order to mitigate risk, additional aspects can be utilized and submitted as part of the Marketing Authorization Application (MAA) and/or RMP. For example, the treatment location can be specified (e.g., limited to specialist centers) or the provision of training materials for healthcare professionals, pharmacists, patients, caregivers, and relatives can be specified.

The duration of the follow-up has not yet been ultimately determined; the initial recommendation is 15 years

In anticipation of the revision to this guideline, a multi-stakeholder meeting planned by the EMA regarding ATMPs already took place in May 2016. The purpose of this meeting was to reveal the various challenges involved in developing ATMPs such that in-depth research into innovative therapies can continue to be carried out just as before. During the discussion, a request was made, among other things, for increased incentives and regulatory support. This way, the initiation of ATMP-specific instructions, workshops and training sessions (e.g., on the comparability of therapies), as well as the promotion of novel development tools (organoids, extrapolation, modeling/simulation, biomarkers) could serve as important tools for simplifying the **process of market approval for gene therapy approaches**. A streamlining of the EMA's internal regulatory processes for ATMPs and/or the increased usage of instruments that enable **early access** (e.g., PRIME [priority medicines], adaptive pathways, scientific consultations, certification, and HTA-parallel consulting) along with an overview of the different national requirements of the individual EU states could be seen as an additional incentive and aid for the pharmaceutical companies. A portion of these proposals have already been implemented with the revision of the first guidelines and the CAT has also initiated a temporary working group specifically for gene therapies, which is responsible, among other

The EMA is in close contact with the stakeholders in order to address the challenges of ATMPs

things, for preparing and updating the guidelines and the reflection paper. The existing regulations, guidelines, and recommendations are summarized in the appendix in Table 2.

National View – PEI, BfArM, DFG and G-BA

The national authorities responsible for issuing approvals for medicinal products for human use in Germany are the Paul Ehrlich Institute (PEI) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). While the legal basis for the approval of medications is regulated on the one hand by the EMA at the European level, national regulations make reference to the German Medicines Act (Arzneimittelgesetz, AMG), among others. Uniform legal framework conditions for these products have gradually been created within the European Community. Just like with the EMA, gene therapies fall under ATMPs in Germany as well and they are likewise regulated via Regulation (EC) No. 1394/2007 of the European Parliament and the Council on ATMPs. This represents a supplement to Directive 2001/83/EC and Regulation (EC) No. 726/2004. The prerequisite to start clinical studies is approval on the national level by the PEI (Section 4b of the AMG (Special Provisions for ATMPs), Sections 40, 41, 42 [clinical trial]). The PEI Innovation Office provides scientific and procedural advice to small and medium-sized companies on the permission of clinical trials of ATMPs, therapy concepts, the manufacturing process, non-clinical development as well as national and central approvals. The PEI's Innovation Office provides scientific and procedural advice to small and medium-sized companies on the approval of clinical studies of ATMPs, but also on therapeutic concepts, the manufacturing process, the non-clinical development and the national and central approvals. The Innovation Office was founded in 2009 with a focus on ATMPs to promptly support their development and market approval in Germany.

For gene therapies in Germany, the basic legal framework conditions of biotechnological drugs apply

Since gene therapy drugs represent a new class of drugs that are continually evolving, regulatory guidelines normally only provide general guidance. The existing legal framework conditions for the group of biotechnological drugs are initially adequate for gene therapies. In addition, decisions on studies for proving the quality, safety, and efficacy of an administered gene transfer drug usually need to be made on a case-by-case basis since the fields of application, mechanisms of action, and product classes are often of a different nature.

In Germany, there is the “German Registry for Somatic Gene Transfer Studies” (Deutsche Register für somatische Gentransferstudien, DeReG). This registry was established in 2001 at the instigation of the German Society for Gene Therapy (Deutsche Gesellschaft für Gentherapie, DG-GT) and the Commission for Somatic Gene Therapy in Freiburg and is supported by the Federal Ministry for

Education and Research (Bundesministerium für Bildung und Forschung, BMBF). The registry appears to be useful for achieving an increase in **the transparency of gene therapies**. The DFG therefore requires registration of the gene therapy study in the DeReG before approving clinical research projects. Registering phase I and II gene transfer studies in a central registry has proven successful so far, which is why registration shall continue to be a prerequisite to receive support from the DFG.

The assessment of the added benefit of gene therapies is made using the AMNOG procedure

In addition to the PEI, the BfArM, and the DFG, other relevant stakeholders of the German healthcare system are intensively working on gene therapy approaches and dealing with the associated challenges with respect to the regulatory aspects and the reimbursement problem. For example, it wasn't until February 2018 that the G-BA (Federal Joint Committee) got together with a few companies and the PEI to discuss various aspects of this. On April 1, 2020, the amendment to the Fair Health Insurance Competition Act (Fairer-Kassenwettbewerb-Gesetz, GKV-FKG) came into force, stipulating that ATMPs must undergo a benefit assessment according to Section 35a SGB V instead of the assessment of investigation and treatment methods according to Sections 135, 137c or 137h. In general, the **AMNOG procedure** (Figure 7) **is definitely relevant for ATMPs as well** and therefore relevant for gene therapies. That means that pharmaceutical companies are obligated to submit a benefit dossier, whereupon the subsequent price negotiations with the umbrella organization of statutory health insurance (GKV-SV) takes place (for more information on the AMNOG procedure, please see: "White Paper: Orphan Drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implication").

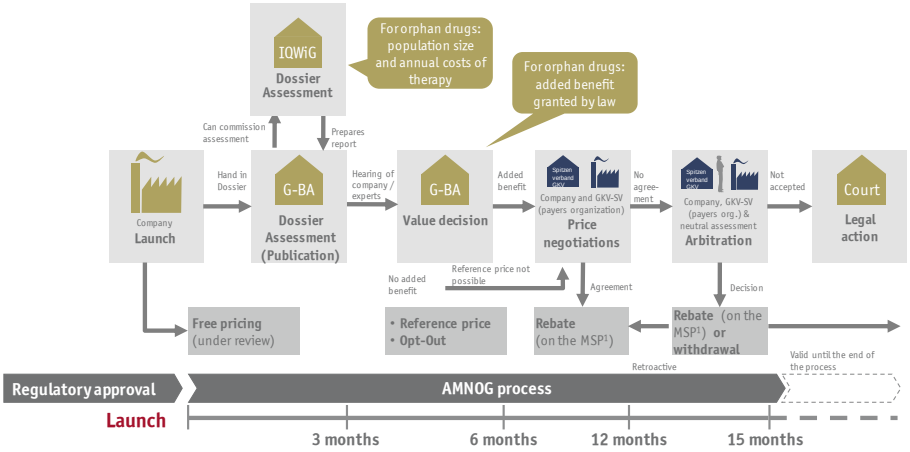

Figure 7: Overview of the early benefit assessment process according to § 35a SGB V Drug Market Reorganization Act ("AMNOG", from the law that introduced it). Key-player during the process are the G-BA, the Institute for Quality and Efficacy in Healthcare (IQWiG) and the pharmaceutical company, as well as the national association of statutory health insurance funds (GKV-SV). Source: G-BA, SKC-Analysis

The only exception in this setting is the exemption from the benefit assessment due to insignificance (Section 35a, Para. 1a of the Social Security Code, Volume V in conjunction with Section 15 of the Code of Procedure). The prerequisite for this exception is that the expected costs for statutory health insurers are less than €1 million within 12 calendar months in the inpatient as well as outpatient sector. This is a reform from the Pharmaceutical Care Strengthening Act (Arzneimittelversorgungsstärkungsgesetz, AMVSG), according to which it was decided that the reimbursement amount also applies to the inpatient sector as a maximum price and as a consequence, the insignificance threshold also refers to the costs from the outpatient and inpatient sector. To date, for the the benefit assessment, the same requirements apply as to "normal" drugs, i.e., by implication, gene therapies with only orphan drug designation receive the advantages of the benefit assessment associated with this – such as the added value determined by law, even without comparison against a purposeful comparator and a shortened version of the dossier. With respect to a potentially limited body of evidence, as is often the case with orphan drugs, the G-BA indicates that regardless of indication, treatment option, and supply reality, a randomized controlled trial represents the gold standard of evidence, however, **registry data** can be used as additional evidence. Yet in the scope of the AMNOG, there is hardly any practical experience. In August 2019, with the Act for more Safety in Drug Supply (Gesetz für mehr Sicherheit in der Arzneimittelversorgung, GSAV), the legislator granted the G-BA the possibility to collect data accompanying the application of orphan drugs or drugs whose approval is based on low evidence for a benefit assessment. So far, only five medicinal products have been granted a registration by the G-BA (Asfotase alfa and Sebelipase alfa, Idebenone (EMA requirement), Afamelatonide and Cerliponase alfa), which led to a conditional decision. Since most gene therapies were approved on the basis of little evidence and long-term effects of these therapies could not be clearly assessed at the time of the benefit assessment, it can be assumed that in future, creating a registry will become the rule rather than the exception for gene therapy. Based on the precedents, the following **requirements from the G-BA for registries** can be derived. These are of particular importance in the field of gene therapies:

- It is recommended that registries are set up **prior to the planned market access**;
- **Evidence of alternative treatment options** must also be collected, either by incorporating a control group or by making the registry indication-specific and thus also recording data from patients receiving alternative treatment;

- If there are **EU-wide registries**, these data (complemented by **data from the German cohort**) must also be submitted;
- **Data regarding the disease symptoms** and the **health-related quality of life** must always be generated;
- Data regarding **patient-relevant endpoints** that are representative of the German care context must be collected;
- Registries should be representative samples of the target population, for (very) rare diseases, the aim should be the inclusion of the complete population;
- **Compatibility** with existing registers should be checked in order to avoid duplications.

Analysis of precedents – status 2020

Gene therapies are often administered only once or over a short period of time. After the administration, the hope is that it results in a permanent improvement for the severe disease or perhaps even a cure. Below is a brief overview of the underlying evidence of gene therapies that are already on the market and a look at how long-term follow-up plans are being implemented.

Glybera®

GLYBERA

Chiesi

The case of Glybera®, formerly marketed by UniQure and most recently by Chiesi GmbH, has shown that approval does not simultaneously guarantee the product's success per se. After the CHMP had previously decided against the product, the orphan drug Glybera® then received EMA approval in 2012 as an *in vivo* AAV-based gene therapy for the treatment of adults who have been diagnosed with familial lipoprotein lipase deficiency (LPLD), and in which severe or multiple pancreatitis flare-ups have occurred despite a low-fat diet. Its launch in the individual European countries, however, did not take place until a few months or years after receiving approval. The assessment of its clinical efficacy and safety, as well as the approval took place in 2012 on the basis of a total of 27 patients from three interventional, open-label, non-placebo-controlled phase III studies (CT-AMT-010-01, -011-01 NCT01109498, and -011-02 NCT00891306). The clinical efficacy of Glybera® was primarily determined based on the reduction of blood lipid levels (reduction in the level of triglycerides in plasma) after a single intramuscular injection of the gene therapy (one treatment contains approximately 60 individual injections). Further efficacy analyses were carried out in a retrospective long-term analysis with a median follow-up duration of 5.6 years among 19 of the study participants. Findings from this study indicate a reduction in the frequency and severity of pancreatitis flare-ups and a reduction in hospital admissions as well as admissions to

intensive care units. Despite the limited body of evidence, Glybera® was approved in "exceptional circumstances" due to the rarity of the disease and the difficulties associated with collecting additional data. In addition, based on the available data for the patients examined, the benefit of the gene therapy outweighed the associated risks. The company was required to subsequently provide additional data from the studies and to establish a patient registry (NCT03293810) in which information on the epidemiology of the disease and the demographic data, safety, and efficacy of the patients treated could be documented in order to monitor patients over the long term.

In Germany, Glybera® was not launched until November 2014. It was only then that the basis of the first benefit assessment pursuant to AMNOG for a single-use gene therapy was established. The result of the assessment by the G-BA showed a non-quantifiable benefit. For a product to have a chance of success on the international market, it not only needs a clear body of evidence and the regulatory framework conditions, it also needs a well-thought-out marketing strategy. In the case of Glybera®, the "annual therapy costs" of just under €1 million per treatment, the treatment of only one single patient, and the lack of a confirmed efficacy in the end were the main reasons that the therapy was withdrawn from the market just five years after it received approval.

Strimvelis®

STRIMVELIS

Orchard Therapeutics

Strimvelis®, formerly marketed by the GlaxoSmithKline (GSK) pharmaceutical company and most recently by Orchard Therapeutics, likewise received orphan drug status for the treatment of patients with severe combined immunodeficiency due to ADA-SCID for which no suitable human leukocyte antigen (HLA)-compatible stem cell donor is available in the family. The approval of the second gene therapy introduced in Europe was based on an open-label pivotal phase I/II study (NCT00598481, n=18) in children with ADA-SCID who did not have an HLA-compatible sibling as a stem cell donor and who did not respond satisfactorily to PEG-ADA and/or did not tolerate this therapy (6 months – 6 years). In this study, an optimal survival rate of 100% after four years was able to be achieved. The median follow-up duration is 7 years, in which the survival rate was consistently 100% and the majority of patients have demonstrated a lasting gene correction in their T-lymphocytes. Despite a few side effects, which include fever and autoimmune reactions, Strimvelis® is considered well-tolerated. Normally the disease will result in death in the first 1 to 2 years without adequate treatment. After a successful administration of the one-time therapy, the majority of patients did not require any additional long-term interventions (≥3 months) such as the administration of PEG-ADA or stem cell transplants. In addition, the rate of severe infections among patients treated

in the pivotal study decreased throughout the entire follow-up period. The 20-minute intravenous gene therapy infusion needs to be performed at what is currently the only dedicated transplant center in Milan by an experienced physician. In addition, the patients are subsequently added to a patient registry in order to monitor potential long-term consequences and efficacy. Likewise, the basis for recording the long-term safety and efficacy of the Strimvelis® therapy is a retrospective, non-interventional long-term follow-up study (NCT03478670), which the company is obligated to carry out and whose results must be presented to the EMA. Due to the very low number of patients in this case as well, it is not possible to make complete statements about the safety of Strimvelis®. Furthermore, additional long-term observations are required in order to be able to assess its benefit-risk profile. By using a retroviral vector, there is a potential risk of developing cancer and autoimmune diseases, although no such cases of this have occurred to date. To assess and minimize this risk, the pharmaceutical company has already started a study (NCT03232203). A further study (NCT03311074) is planned for the beginning of June 2020. The aim of the studies will be to evaluate the potential effects of the introduction of Strimvelis®, such as the activation of oncogenes by a new technique.

Kymriah®

The CAR-T cell therapy Kymriah® from the pharmaceutical company Novartis was approved by the FDA for the first area of indication based on the ELIANA study (NCT02435849), an open-label, single-arm, multi-center phase II study to determine the efficacy and safety of CTL019 administered intravenously to children and young adults (ages 3 to 25) with relapsed or refractory B-cell ALL (n = 63). Relevant endpoints included overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The primary endpoint was represented by the overall remission rate (ORR) over a three-month period after administration. Thanks to the therapy, an 83% ORR was able to be demonstrated in a patient group in which probably fewer than 10% would have survived the first 5 years after diagnosis. In addition, no minimal residual disease (MRD, a blood marker that can predict a potential relapse) was able to be detected. Despite impressive scores, therapy was not effective in eleven patients and 29 patients suffered a relapse after six months. The median follow-up duration was 4.8 months, after which the expected median duration of response had not yet been reached. An analysis of the blood and bone marrow was able to demonstrate that Kymriah® was still present two years after treatment. Treatment with Kymriah® demonstrated severe side effects, such as the formation of an immune deficiency and the occurrence the cytokine release syndrome (CRS), in the majority of patients only eight weeks

KYMRIAH

Novartis

after treatment (79%). However, in contrast to the Yescarta® studies (see below), no patients have died because of the serious treatment-related side effects to date. Both CRS as well as other neurological events can be life-threatening. Approximately 84% of the patients (full analysis set, n = 68) were still alive at the last data cut-off. Overall though, according to the regulatory authorities of the United States, the benefits outweigh the risks. Novartis Pharmaceuticals is sponsoring a CD19 CAR-T cell long-term follow-up (LTFU) study with the goal of following all patients treated with CD19 CAR-T cells over a period of 15 years in order to ascertain the long-term efficacy and safety. In addition, the retention of the lentiviral vector in the body will be analyzed.

FDA approval of Kymriah® for the second indication in adults with relapsed or refractory diffuse B-cell lymphoma (DLBCL), a non-Hodgkin's lymphoma (NHL), after two or more systemic lines of treatment (who are not eligible for an autologous stem cell transplant) has been granted (May 2018). In particular, DLBCL is a form of NHL for which there are only a few treatment options following non-response to other drugs and a relapse and the patients have an average survival of approximately six months. The approval after priority review was based on the multi-center pivotal phase II JULIET study (NCT02445248, n=106), in which patients were treated with Kymriah® in both outpatient and inpatient settings and the efficacy and safety were analyzed. This study was able to demonstrate a 50% ORR – the primary endpoint of the study, a complete response in 32% of the enrolled patients, and a partial response to therapy in 18%. Because Kymriah® caused severe side effects in this study as well, such as CRS in 74% of patients treated with r/r DLBCL and neurological toxicity, the treatment is only available in a limited fashion for both indications as part of a Risk Evaluation Mitigation Strategy (REMS) program in order to detect and counteract side effects as quickly as possible.

After the FDA, the EMA assesses Kymriah® in an accelerated approval procedure for both indications. The CHMP adopted a positive opinion on 28 June 2018, recommending the granting of a marketing authorization for Kymriah®. The EU approval of Kymriah® for both indications was granted in August 2018 followed by the launch in Germany the same year. Besides the ELIANA study, the market authorization within the German health care context for the first indication was also based on the ENSIGN study (NCT02228096), an open-label, single-arm, phase II study to evaluate the efficacy and safety of CTL0919 therapy in patients aged 3 to 21 years. In both cases, the G-BA has awarded a non-quantifiable added benefit. The annual therapy costs per patient in Germany amount to €320,00.00 and are therefore expensive considering the serious adverse events associated with the infusion. Since the benefit assessments resulted in conditional authorizations until 15 March 2020, new assessments

started after the deadline. A decision on the G-BA procedures is expected at the beginning of September 2020.

Yescarta®

YESCARTA

Gilead

Yescarta® from Kite Pharma and Gilead has received "priority review" "breakthrough therapy," as well as "orphan drug" status from the FDA. Orphan drug approval is based on the ZUMA-1 phase II study (NCT02348216, n=108 for phase I + II, n=101 for phase II only), with the primary endpoint of complete remission. In the study, 72% of patients demonstrated a significant response (Objective Response Rate, ORR) and 51% of patients demonstrated a complete remission of cancer after a single intravenous infusion of Yescarta®. After a median follow-up period of 15.4 months after the administration of Yescarta®, 42% of patients remained in remission with 40% of patients in complete remission. The durability of Yescarta® was determined using an updated analysis of the ZUMA-1 study patients (n=108). However, as a CAR-T cell therapy like Kymriah®, Yescarta® also carries high risks such as the onset of severe side effects, e.g., CRS and neurological toxicity, both of which can be life-threatening or fatal. Three patients died during clinical trials due to the severe side effects. Yescarta® is therefore only available through a limited program as part of a risk assessment and mitigation strategy, whereby, according to the FDA, hospital staff need to be specially trained and certified in administering treatment with Yescarta®. Similar to other approved gene therapies, the G-BA has awarded a non-quantifiable additional benefit for patients with diffuse large B-cell lymphoma (DLBCL) and patients with primary mediastinal large B-cell lymphoma (PMBCL) with a conditional approval until May 15, 2022.Currently, Yescarta® can be administered at roughly 15 centers, whereby the long-term goal is 70 to 90 centers. In order to make statements regarding long-term safety, the FDA additionally requires that the company conduct a post-marketing observational study on patients who are treated with Yescarta®.

Luxturna®

LUXTURNA

Spark

Luxturna® from Spark Therapeutics, which was given a priority review designation, has been granted orphan drug, breakthrough therapy, and rare pediatric disease status by the FDA. Luxturna® also received orphan drug status from the EMA. The approval was based on the open-label, randomized, and controlled phase III study (NCT00999609) to determine the efficacy and safety (n=31 currently included) in children and adults ages 4 to 44 with biallelic RPE65 mutation-associated retinal dystrophy and sufficiently viable retina cells. Two phase I/II open-label dose-finding studies for determining the efficacy and safety (n=12 and n=11) took place in advance. After one year, the phase III study showed significant differences between the results of the primary endpoint of

multi-luminance mobility testing (MLMT) score changes in the intervention and the control group. In addition, the full-field light sensitivity threshold (FST) and the mobility test change score for the first eye treated in the group receiving treatment at baseline improved significantly compared to the control group. The three-year follow-up data from the ongoing phase III study show that the effect of Luxturna® is still present even after this time. In addition, no other new side effects have occurred. The follow-up studies thus provide important information on the efficacy, safety and durability of the gene therapy, which is why a patient registry was set up (NCT03597399) to determine the long-term safety of Luxturna® 5 years after treatment. In addition, a further post-marketing observational study of patients treated with Luxturna® is planned. After Luxturna® from Spark was approved by the FDA in December 2017, the first patient, a 13-year-old boy from New Jersey, started treatment on 03/20/2018. However, there are currently no findings regarding a repeated administration of gene therapy within an eye that would enable additional statements to be made regarding the advantages/disadvantages of a repeated administration. Spark Therapeutics has limited the administration of Luxturna® to its excellency cluster (Ocular Gene Therapy Treatment Centers), where trained personnel are available in order to ensure adequate patient care. Luxturna® was approved in Germany in April 2019. With a considerable additional benefit, Luxturna® represents the first benefit assessment procedure for gene therapies in which a higher benefit category was granted by the G-BA.

Zynteglo™

ZYNTEGLO

bluebird bio

Zynteglo™ is the first gene therapy for the treatment of transfusion-dependent patients with ß-thalassemia (TDT). The gene therapy approved by the EMA is the most expensive drug in Europe to date and has been available on the market by the pharmaceutical company bluebird bio since May 2019. The EMA approval was granted in a record time through the Priority Medicines (PRIME) scheme. Additionally, Zynteglo™ has received an orphan drug designation. Zynteglo™ is indicated for the treatment of patients 12 years and older with TDT who do not have a ß0/ß0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. Clinical efficacy and safety were assessed based on open, single-arm phase I/II studies (HGB-204, NCT01745120 and HGB-205, NCT02151526) and the ongoing phase III studies (HGB-207, NCT02906202 and HGB-212, NCT03207009). These studies (HGB-207, n=16; HGB-205, n=4; HGB-204, n=11; HGB-212, n=4) in patients with ß-thalassemia who required regular blood transfusions have shown that Zynteglo™ effectively reduces the need for blood transfusions. The primary endpoint was transfusion independence (TI) by the 24th month, defined as the

weighted average hemoglobin (Hb) value of ≥ 9 g/dl without red blood cell transfusions for a continuous period of ≥ 12 months at any time during the study after infusion of Zynteglo™. A total of 20 (HGB-207, n=9; HGB-205, n=3; HGB-204, n=8) of the 24 patients (83.3%) with a non-ß0/ß0 genotype achieved a TI by the 24th month. The median follow-up duration was 31.20 months, after which all patients remained alive at the last follow-up. The only serious adverse event associated with Zynteglo™ was thrombocytopenia.

Since this promising therapy has only received a conditional approval from the EMA, the results of the ongoing studies (HGB-207 and HGB-212) must subsequently be submitted for further evaluation of efficacy and safety. The decision of the benefit assessment, granted a non-quantifiable added benefit to Zynteglo™ until May 2025 due to the limited evidence. To be awarded a full market authorization, study results requested by the EMA must also be submitted to the G-BA.

Zolgensma®

ZOLGENSMA

AveXis

Zolgensma® was developed by AveXis, a subsidiary of Novartis, and has been on the US market since May 2019. In addition to the orphan drug designation granted by the FDA, Zolgensma® has also received fast track, priority review and breakthrough therapy designations. Zolgensma® is a recombinant adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than two years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. SMA is currently the most common hereditary, fatal disease in infants and leads to muscle weakness. The FDA approval was based on the pivotal phase III study ("STRIVE-US", NCT03306277) and further studies (AVXS-101-CL-101, NCT02122952 and "START", NCT03421977). "STRIVE-US" is an open-label, single-arm, multicenter, ongoing study to determine the efficacy and safety of onasemnogene abeparvovec-xioi in children of less than six months of age with SMA (n=21). To evaluate the efficacy, the pivotal study defined two primary endpoints including overall survival at 14 months of age and the proportion of children able to sit independently for ≥ 30 seconds by 18 months of age. As of the data cut off (March 8, 2019), one of the 21 patients aged 7.8 months had died due to disease progression. Another patient withdrew from the study at the age of 11.9 months and the 19 remaining children between 9.4 and 18.5 months of age lived without permanent ventilation. After a single administration of the therapy, 48% of children were able to sit independently for 30 seconds at 18 months of age. The treatment with Zolgensma® seemed to be well tolerated, as the adverse events were similar to those of the disease and patients could be treated with a suitable therapy. Based on these safety results,

the initiation of a Risk Evaluation Mitigation Strategy (REMS) program or a safety study in accordance with the post-marketing requirements was not deemed by the FDA as necessary.

At the end of May 2020, Zolgensma® was approved in the EU for the treatment of patients with 5q (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. To further evaluate the efficacy and long-term safety of Zolgensma®, two additional studies (NCT03837184, NCT03461289) were added to the clinical portfolio of Zolgensma®.

Imlygic®

IMLYGIC

Amgen

Unlike other gene therapies, the treatment with Imlygic® is not based on a single administration, but rather a continuous one over at least 6 months. Imlygic® (Talimogene laherparepvec) is marketed by Amgen and is an attenuated herpes simplex virus type-1 (HSV-1) genetically modified to destroy tumor cells. It was launched in the US in October 2015 and in Europe two months later. Furthermore, Imlygic® is the first oncolytic immunotherapy to be approved in Europe. As a novel gene therapy (ATMP), Imlygic® is indicated for the treatment of adults with unresectable that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. The approval was based on the open-label, multicenter, phase III clinical trial (n=436, NCT00769704) with the primary endpoint of durable response rate. In this study, 295 patients were treated with Imlygic® and 141 patients with human granulocyte-macrophage colony stimulating factor (GM-CSF). It was shown that 25% of patients treated with Imlygic® achieved a durable response. Despite the positive efficacy in the treatment with Imlygic®, there were concerns about virus transmission from treated individuals to others. Consequently, the company was asked to conduct a post-marketing observational study (NCT02910557) with patients who had previously received Imlygic®.

Imlygic® was launched on the German market in June 2016 for the same indication. The evaluation of the added benefit of Imlygic® was evaluated based on the above-mentioned evidences. However, an added benefit was not granted by the G-BA due to a direct comparison study considered unsuitable compared to the appropriate comparative therapy.

Based on this underlying evidence of the respective therapeutic options, the assessment was carried out and approval was granted by the US and European regulatory authorities. The approval process is regulated with time limits by

both the FDA and the EMA, and support opportunities throughout the entire process, e.g. in the form of new or revised guidelines, consulting services, honorariums, and other assistance from the authorities for the pharmaceutical companies and entities involved are currently being developed or expanded. But even after approval (post-launch), pharmaceutical companies that launch gene therapies and likewise want to receive reimbursement for the treatments will face new challenges. Here, previous pricing models that are used for the reimbursement of "normal medications" are only partially applicable for innovative therapies, such as single-administration gene therapies, as these therapies follow a completely new logic.

3. Pricing and reimbursement

Development of pricing strategies - the reimbursement dilemma

The development of a pricing strategy in the medicinal products market is subject to specific challenges, such as high research and development (R&D) expenses

A **pricing strategy** is largely based on two elements: the objectives of the company and the characteristics of the consumers. Other factors such as the type of market (from competitive to monopoly market), regulatory requirements, product characteristics (such as the degree of innovation), regional price differences, etc. also have an influence on the pricing strategy. The medicinal products market is particularly characterized by its strict regulatory framework and the associated requirements as well as by the characteristics of the respective patients. The external influences on the price differ considerably depending on the country in which the medicinal product is launched or for which indication the drug is used. Although the general rule is that the price consists of the cost coverage component and the profit component, there is a particular challenge in the pharmaceutical field: covering the **extremely high research and development costs** of the new medicinal product. Most products require decades of research and development, and then there is the time and expense of clinical phases on top of that. However, a distinction must also be made here according to the different investors in the development phase of a drug. To a certain extent, basic research is carried out in public institutions, and the knowledge gained can be outsourced and subsequently brought to market maturity by pharmaceutical companies. If basic research takes place in public institutions, the patented research results are remunerated, e.g. through licensing agreements between the pharmaceutical company and public institutions (e.g. universities). Often, an outsourcing of basic research is still used by the public as an opportunity to critically question the price of drugs again, especially when very high prices are raised. The second component is also of particular relevance in the pharmaceutical sector: the **ethical or moral component** has a profound impact on the entire development and market access process

of a new medicinal product in the healthcare sector since it is essentially about the most valuable possession that people have - their health. For this reason, pharmaceutical companies are often viewed with particular criticism when it comes to the publication of the price of a new product. As such, a pricing report can quickly become a controversial discussion where the price can be torned by both the public and the patient representatives. Investors, however, can just as easily become vocal due to a supposedly low price or, in the worst case, both sides can get involved. The **internal and external management of expectations** plays another crucial role in the run-up to the publication of the initial launch price. Due to the few precedents and the sometimes very different indication areas as well as the rarity of the diseases, the publication of prices is followed closely by the different interest groups and the public, especially for gene therapies. This is because, with the announcement of the generally high annual treatment costs, the health systems and the payers in the individual countries must face the challenge of reimbursement. Access to innovative therapies is offset by the high costs. Considering the large pipeline of gene therapy treatments in particular, this may be a crucial challenge in the future, since in addition to the previous aspects, the special feature of gene therapy - the one-time treatment - has to be taken into account. This new logic of the gene therapy paradigm challenges payers in particular with the task of designing an adequate reimbursement of gene therapy options, which is unlikely to be counteracted by traditional cost-containment and reimbursement systems. The following therefore explains the gene therapy inherent **reimbursement obstacles** and discusses **possible solutions** at the national and international level. The objective is to present options on how gene therapy approaches can be reimbursed, taking into account the different interests involved. The basis for this is the paradigm shift to a curative approach and the associated cost logic: in the future in this field, the approach will move away from a chronic, often lifelong treatment with relatively clear and largely constant fixed costs, to an extremely high one-time expense, which, in the best case, leads to a lifelong cure with no additional costs. The existing health insurance algorithms, both in private and public health insurance, have not been applicable with regard to this completely different logic of value creation up until now, so new actuarial approaches need to be developed and possibly fixed in care contracts.

The gene therapy paradigm in particular involves the payers in the decision about adequate reimbursement

Introduction to the previous refund logic in Germany

The previous reimbursement models seem to show their limitations for the reimbursement of gene therapies, especially gene therapies where a single administration of vectors is sufficient. The existing reimbursement system for new medicinal products in Germany is generally separate for the outpatient and inpatient sectors. While the **benefit assessment of medicinal products** is

The German reimbursement system is not designed for one-time, cost-intensive treatment options

determined by law (§35a SGB V [Sozialgesetzbuch V (Volume V of the Social Insurance Code)]) in the outpatient sector, where the pharmaceutical companies must submit a dossier to the G-BA in which they demonstrate the added value of the new drug compared with the existing therapies, reimbursement is possible for inpatient care without the need for any benefit assessment within the existing DRG (diagnosis related group) system. However, the amount of the DRG is not calculated based on the drug costs, but instead is determined by the diagnoses and the operations and procedures performed. To achieve a higher reimbursement, a request for an extra-budgetary allowance can be made by the hospitals within the DRG system using the **NUB procedure** (neue Untersuchungs- und Behandlungsmethoden [new examination and treatment methods]), which acts as bridge financing until the DRG system adequately reflects the additional costs. In this case, the respective hospital negotiates with the payer regarding the amount of the additional compensation and the expected number of cases. In the outpatient sector, the price can be set by the pharmaceutical company within the first 12 months (free pricing episode). This year, the benefit assessment is carried out by the G-BA as part of the AMNOG procedure, which forms the basis for the subsequent price negotiations between the pharmaceutical company and the GKV-SV. From the thirteenth month onwards, the reimbursement amount negotiated between the two parties or determined by the arbitration panel, if applicable, shall apply.

Up to now, the reimbursement is based on an upfront payment system

The potential cure of diseases through gene therapy in the current model would be based on a one-time reimbursement of the drug (at the time of administration) - **upfront payment**. The respective health insurance pays the full amount of the negotiated reimbursement amount to the pharmaceutical company at this time, although the effectiveness and safety of the drugs only becomes apparent in the later course of the treatment. This is associated with a high risk for the payer. This is a potential challenge in the system of upfront payments that does not occur for conventional treatment options. The reimbursement of a long-term or limited-term treatment has the advantage that patients may discontinue the treatment and, if necessary, switch to another active substance if the efficacy diminishes, side effects are experienced, or the authorization of more effective options occurs. Reimbursement therefore only takes place in this clearly defined period, in which the patient experiences a benefit from the therapy. An upfront payment, such as for a one-off use of gene therapy, means that the health insurance companies must refund the full amount before and not during the treatment, even though the **cost-effectiveness** usually has still **not been evaluated conclusively**. Potential cost savings or amortization as a result of further treatment being unnecessary are sometimes only achieved years after the actual treatment. This leads to a belated and uncertain

The unclear cost effectiveness leads to high uncertainty in this model

break-even for the health insurance companies. In addition, the free choice of the insured in choosing a health insurer does not guarantee that the financing health insurer can post the counter-financing or amortization effect as well, since the patient can also switch to another payer after the therapy has been completed now that they are "healed". There is currently no compensation mechanism for the imbalance of costs and benefits between the different payers. However, the Fair Health Insurance Competition Act (GKV-FKG) which expired in February provides the reintroduction of a risk pool until 2021, from which health insurance companies are to receive 80 percent of the expenditures for each service exceeding €100,000 per year. This is expected to lead to fair competition between health insurance companies, in particular for high price drug therapies. The upfront payment leads to controversy especially in the inpatient sector, since the lifelong benefit is compared to an annual budget negotiation. In addition, the uncertainty among the health insurance companies about the efficacy and safety of the treatment due to the lack of precedents and long-term observations is very high, so from a payer perspective, the high prices of the medicinal products may appear unjustified.

The (potentially) lifelong efficacy is offset by annual budget negotiations in the inpatient sector

This dilemma between the price expectations of the pharmaceutical company, which must cover its anticipated costs for research and development and its revenue through the one-off sale of the product, and the concerns of the respective health insurance companies, which are uncertain about the long-term efficacy and possible (later) side effects of the treatment and also the possibility of amortizing the high costs, have to be counteracted by the development of innovative reimbursement models, not only in Germany.

International view - How are the current gene therapies reimbursed?

Glybera®

Glybera® was approved by the EMA at the end of 2012 as the first gene therapy, but the market launch in Germany did not take place until November 2014. At the same time, the only AMNOG procedure to date for the evaluation of the additional benefit as well as the later price negotiation with the GKV-SV and the associated reimbursement in the outpatient sector in the field of single-use gene therapies began. In the inpatient sector, the NUB process for an appropriatereimbursement of the innovative method was also initiated at the time of launch. While a non-quantifiable additional benefit was assessed in the AMNOG procedure and the negotiated price from the negotiations with the GKV-SV was not published, a reimbursement was possible via the **NUB payment** in the inpatient field. The reimbursement amount is determined by individual negotiations between the respective hospital and the health insurer. Since then,

GLYBERA

Chiesi

an individual additional fee of €900,000 has been negotiated for the only patient in Germany so far. In October 2017, Glybera® was withdrawn from the market due to low patient numbers, previously unquantifiable efficacy and high treatment costs, while the five-year EMA approval expired at the same time.

Strimvelis®

Strimvelis®, the second approved gene therapy in Europe (approved in May 2016), estimates treatment costs of €594,000, making it one of the most expensive single-use therapies in the world. In all of Europe, only about 15 children are born each year who have ADA-SCID and only four patients have been treated with Strimvelis® outside the clinical trials, which corresponds to a very small patient population. The first patient was treated in March 2017 at the only treatment center in Europe, in Milan. It took about one year from approval to negotiation and reimbursement of the first treatment, which became a patient-specific **pay-for-performance (P4P) approach,** negotiated in the form of an **installment payment** of the reimbursement amount by the payer, coupled with a **refund** by the pharmaceutical company, GlaxoSmithKline, in the event of failure. Approval in the UK finally took place in January 2018 by the NICE (National Institute for Health and Care Excellence), with a cost-effectiveness threshold of €594,000. Although Strimvelis® is associated with immense costs, the cost of alternative therapies, such as substitution of the ADA enzyme, is around €400,000 per year, which far exceeds the cost of the single dose of Strimvelis® in the long run. In March 2018 GSK sold Strimvelis® to the Orchard Therapeutics.

STRIMVELIS

Orchard Therapeutics

Kymriah®

The launch price for Kymriah® are estimated at approximately $475,000 in the United States. The argument in justification of the price was that the development costs (about $1 billion, according to Novartis) would have to be allocated to a relatively small number of an estimated 600 patients in the US and also an extremely complex patient-specific production, which is calculated at about $50,000 per patient. Another influencing factor in the further pricing is the competing product in the field of CAR-T cell therapies – Yescarta®, which became a direct competitor in May 2018 with the extension of the indication DLBCL from Kymriah®. There were already some challenges in pricing in the pipeline as investors reckoned with a higher and patient representatives with a lower price. In addition, the development of the treatment was not fully funded by the pharmaceutical companies, but funded by tax revenues (up to $200 million) at the beginning. However, there is no question of the benefits

KYMRIAH

Novartis

of Kymriah®, at least for the FDA, since the study data, such as the overall survival (OS) was convincing. Novartis's pricing system is based on a **"money back guarantee"** or a **value-based pricing approach**, which means that a reimbursement based on an agreement with CMS (Centers for Medicare and Medicaid) are only payable if the patient responds to treatment within the first 30 days of treatment. However, critics object that an effect can always be seen initially for CAR-T cell therapies, but lasting results can only be determined after 6 to 12 months at the earliest. The potentially severe side effects occurred in Kymriah® after a median duration of only 3 days (maximum 21 days) after administration, but also allow only limited conclusions about the actual efficacy of the treatment. This could also be a reason why Kymriah® sales fell short of expectations by at least $12 million, at least in the first quarter of 2018. However, sales have increased significantly ($278 million in 2019) in the meanwhile. Novartis attributed production bottlenecks to the main reason for the rather sluggish market entry, which is why a new plant for the processing of Kymriah® was opened in Switzerland in November 2019. Another plant in France is currently being expanded. In August 2018, Kymriah® was also approved in Europe. For the first year after entering the German market, Novartis signed an agreement with the Society for Economy and Quality in Health Insurance (Gesellschaft für Wirtschaftlichkeit und Qualität bei Krankenkassen, GWQ) and the Association of Health Insurance Funds (Verband der Ersatzkassen, VDEK) on an outcome-based reimbursement model. In this pricing model, it was agreed that, upon death of a patient after the administration of Kymriah®, part of the treatment costs will be reimbursed to health insurance companies. An AMNOG procedure was also started in September 2018 for both indications. Although Kymriah® obtained an orphan drug designation, already demonstrating an added benefit of the product, it was only granted a non-quantifiable additional benefit due to low evidence from ongoing single-arm studies. The subsequent approval was conditional and limited to one year. In March 2020, two further AMNOG procedures started for both indications for re-evaluation after the deadline expired, and decisions are expected in September 2020. According to the G-BA, there are approximately 490 to 765 patients in both indication of Kymriah® in Germany. Currently, Kymriah® is only administered in an inpatient setting in Germany and is currently listed in the Lauer Taxe with an hospital purchase price (Klinik-Einkaufspreis) of €275,000. This price already decreased significantly compared to the German launch price of €320,000 in 2018. The hospitals can obtain a reimbursement for expensive therapies via the NUB procedure. However, to benefit of this service, every hospital would first have to submit an application form by October 31 to the Institute for the Hospital Remuneration System (Institut für das Entgeltsystem im Krankenhaus, InEK) to register a new NUB procedure for the following year. In 2019,

107 hospitals submitted a NUB application for the "administration of CAR-T cells for the treatment of hematological diseases". These applications were granted a NUB status 1 by the InEK, meaning that the criteria for a NUB agreement were met and reimbursement fees can be agreed for the requested services.

Yescarta®

YESCARTA

Gilead

The second CAR-T cell therapy approved in the US after Kymriah® is the gene therapy Yescarta®, which is available since October 2017 from Kite Pharma or Gilead. The launch price was $373,000, more than $100,000 below the price of Kymriah®. Again, the manufacturing cost per patient is about $50,000. Overall, sales of $264 million were achieved in the US alone in 2018. In 2019, sales of Yescarta® increased significantly to $456 million. Following the EMA approval of Yescarta® in August 2018, Gilead also agreed a pay-for-performance reimbursement with the VDEK in June 2019, under which Gilead will reimburse part of the therapy costs currently amounting to €282,000 (hospital purchase price, Taxe-Klinik-Einkaufspreis) if the therapy does not work. This contract is valid for two years. In addition, two AMNOG procedures for the two indications of Yescarta® started in November 2018. According to the G-BA, 440 to 700 patients in Germany are eligible for treatment with Yescarta®. Similar to Kymriah®, Yescarta® has only been granted a non-quantifiable additional benefit in both indications despite orphan drug status. In addition, the market authorization was conditional until May 15, 2022 due to uncertainties regarding the long-term effects of the therapy. Like Kymriah®, Yescarta® is only administered in an inpatient setting. For Yescarta®, hospitals can also submit a NUB application for the "administration of CAR-T cells for the treatment of hematological diseases", which can be used to cover additional costs.

Luxturna®

LUXTURNA

Spark

The cost of one-time treatment with Luxturna® in the US is currently $425,000 per eye, therefore Luxturna® is considered having the highest list price to date. To counteract reimbursement issues, Spark works closely with patient representatives, clinicians and public and private groups to implement innovative access arrangements. As an example, **results-oriented reimbursement approaches** have been discussed among other things. An **outcome-based rebate agreement** has been negotiated with the company Harvard Pilgrim Health Care, for example, which was based on the efficacy of Luxturna®. It assesses the efficacy of the short-term treatment (after 30 to 90 days) and long-term treatment (after 30 months). Spark has also signed an exclusive contract with Express Script. As a result, additional fees of hospital pharmacies of six percent for treatment are no longer applicable, leading to significant cost savings for

the expensive therapy. This innovative contract model aims at guaranteeing that treatment centers are protected from treating patients without being reimbursed by the patient's health insurance company. Prior to the European approval in November 2018, Novartis purcharsed the license for Luxturna® in all countries outside the US at the end of January 2018. In Germany, Luxturna® is only administered as an inpatient treatment and, like Kymriah® and Yescarta®, can be reimbursed via a NUB procedure (NUB status 1). In 2019, 21 hospitals submitted a NUB application for the administration of Luxturna®. Besides, the therapy has already been evaluated in the AMNOG procedure. According to the decision of the G-BA in October 2019, a considerable additional benefit was granted to Luxturna®. However, since the study data presented did not allow for conclusions to be drawn about the long-term effect of the therapy, the decision was conditional until December 31, 2021. According to the G-BA, between 100 to 530 patients in Germany are eligible for treatment with Luxturna®. Based on the Lauer Taxe, the hospital purchase price (Klinik-Einkaufspreis) is currently €295,000 (May 2020) per eye, which is €50,000 less than the launch price of €345,000.

Zynteglo™

ZYNTEGLO

bluebird bio

Following EMA approval in May 2019, Zynteglo™ was launched on the German market in January 2020. To date, Germany is the first country to market the therapy. Bluebird bio expects to treat the first patients in the first half of this year. With a launch price of €1,575,000, Zynteglo™ is currently the most expensive drug on the European market. Bluebird bio already came to an agreement with payers prior to approval and settled on a pay-for-performance reimbursement model. The AOK Rhineland/Hamburg was the first health insurance company to agree to the pay-for-performance approach. Meanwhile, other health insurance companies have followed this lead. According to this approach, payment is to be staggered over four years: 20 percent of the total costs are to be paid upon treatment administration, another 20 percent a year later, but only if the the patient does not require transfusions. Subsequently, the transfusion independence, which was the primary endpoint in clincal studies, will be monitored every 12 months. The third, fourth and fifth installments will only be paid if the treatment is successful. In September 2019, the AMNOG procedure for Zynteglo™ also started. In its decision of May 14, 2020, the G-BA awarded a non-quantifiable added benefit to Zynteglo™ due to the high potential for bias in the open, single-arm study design. In addition, because of the small number of patients included in the studies, the G-BA is uncertain about the proportion of patients who could truly benefit from treatment with Zynteglo™. According to the G-BA, approximately 50 patients in Germany are eli-

gible for treatment with Zynteglo™. Since at the time of the benefit assessment, no final data from the two ongoing studies and no data from the follow-up study evaluating the long-term efficacy and safety were available, the G-BA granted a conditional authorization until May 15, 2025. As requirements for the re-evaluation, the G-BA requested the submission of final data from two ongoing studies and the 5-year data from the follow-up study. In addition, a registry is to be created including data on the long-term safety and efficacy of Zynteglo™, in accordance with the requirements of the EMA.

Zolgensma®

ZOLGENSMA

AveXis

With a price of $2.1 million, the gene therapy Zolgensma®, approved in the US since May 2019, is the most expensive drug in the world. AveXis, a subsidiary of Novartis, has agreed with the payers over a five-year installment for the therapy costs. Part of the costs will be paid at the time of injection and the remaining installments will only be made based on the success of the therapy. Hence, the payers will not have to reimburse the full price if the treatment fails. In the EU, Zolgensma® initially received a positive opinion from the CHMP in March 2020 and was finally approved by the EMA at the end of May 2020. In Germany, GWQ and AveXis signed a contract on a reimbursement model based on the success of therapy prior to approval. In contrast to previous contracts with a similar innovative reimbursement model, this model takes into account several patient-relevant outcomes, whereby AveXis risk reimbursing up to 100% of the costs in installments. It is assumed that the price in Germany will be €1.9 million. The expensive price of Zolgensma®, adds great pressure on health insurance companies. Already after the approval in the US, parents of affected children and patient representatives in Germany have been campaigning in the media for German health insurance companies to also pay for the drug. However, the regional social court of North Rhine-Westphalia ruled in March of this year that the insurance companies do not have to pay for Zolgensma®. However the discussions around Zolgensma® are far from being ended since Novartis announced at the end of 2019 that it would be giving away 100 treatments for free to affected children. The initiative was received with great criticism as such a lottery was considered unethical by many.

Imlygic®

IMLYGIC

Amgen

Imlygic®, the first oncolytic immunotherapy approved in Europe, was estimated at a launch price of €234,770 per patient in Germany. The evaluation of the G-BA did not attribute any added benefit to Imlygic®. This led to a decision on the reimbursement be setteld by the arbitration board. After the price negotiations, the price of Imlygic® with current annual therapy costs of

€119,467[2] per patient decreased significantly. This represents a net rebate of 52.11%. Imlygic® is therefore the first gene therapy product with a reimbursement settled by the arbitration board. Since treatment with Imlygic® is to be carried out by medical professionals and risks of transmission and complications due to herpes may arise, Imlygic® can only be administered in an inpatient setting. Due to the mode of application (continuous administration), the therapeutic costs of Imlygic® cannot be compared with other gene therapies. The reimbursement of therapy costs with Imlygic® is possible via the NUB procedure. In addition, Imlygic® has been granted a NUB status 1 by the InEK for 2019. In total, 235 hospitals have applied for the NUB status in 2019. To date, there are no information on the hospitals that are already offering a treatment with Imlygic®. It is estimated that about 65 melanoma centres in Germany are offering the treatment. According to the G-BA and depending on the patient subset, there would be approximately between 35 to 450 patients in Germany who could benefit from treatment with Imlygic®.

Initial national and international reactions of the regulatory authorities

The development of individual price systems is already focused in the field of gene therapies by the pioneers and the majority of pharmaceutical companies have shown themselves open to new reimbursement models, at least where the general public are concerned, and even payers are coming up with some individual solutions. However, it is already apparent that these new treatment options must deal with challenges that affect not only regulatory requirements but also reimbursement issues. This often comes with a lot of paperwork and discussion potential for those affected and makes clear the need for **sound strategic preparation** to respond to any unforeseen situations.

Kymriah® and Yescarta® were considered cost effective in an initial evaluation of the ICER

There has already been some initial feedback on the reimbursement issue from the **US**. The **ICER** has confirmed that despite the high price, both Car-T cell therapies (Kymriah® and Yescarta®), are cost-effective compared to the current SoC (standard of care), chemotherapies, because the price of the treatment is justified by the clinical value. In contrast, the treatment costs of Luxturna® were rated as too high by the ICER. A 50% - 70% discount would therefore be needed for the treatment to be considered cost effective. According to ICER, this is because, despite the novelty of the therapy and the pioneering role in the field of gene therapies, the **cost-effectiveness** cannot be achieved on the assumption of an efficacy lasting 10 to 20 years. Following an expert discussion

[2] Lauer Taxe, as of May 2020

with the various stakeholders, ICER recommends that, in addition to examining the cost-effectiveness:

- For treatments that have a major impact on treatment, current treatment standards or on the cost of care, the manufacturers, insurers, and providers should meet with the FDA prior to market approval to clarify the **role of the drug in the actual medical care situation,** to define the target population and to discuss pricing parameters and possible reimbursement models. This could avoid possible delays after market launch, as the uncertainties on the payer side would be addressed early in the process.
- In the case of **limited data** one of the following options can be chosen: A low launch price, which will be raised once the long-term data confirm efficacy and safety, or a high launch price, with discounts or refunds if the "real world evidence" does not confirm expectations.
- Value-based pricing approaches must also be viewed in connection with the **affordability** of the therapy for payers or insurers, where affordability should be assessed based on the size of the target population.
- **Register** in which all treated patients are included to ensure the long-term follow-up.

The general suitability of the previous method for evaluating gene therapies was determined in a mock study in the UK

The NICE in the UK has responded based on the evaluation system for the regulatory requirements along with the reimbursement issue for gene therapies. In collaboration with York University, NICE has created a mock CAR-T Cell Therapy study to determine the appropriateness of the current methodology for evaluating new gene therapies. The focus here was whether the clinical efficacy was sufficiently proven and a reasonable calculation of the costs of treatment could be made despite the limited data available. The study was based on the three challenges specifically associated with regenerative medicine and cell therapies for the NICE method evaluation – high costs per patient, poor evidence, and potentially significant health benefits. The conclusion of the final report is that the current methods are well suited to assess novel treatments such as gene therapies. Safety, efficacy and cost-effectiveness requirements should generally remain in place, however **specific regulations regarding potential payment models** and other parameters, such as the discount rate, should be addressed in more detail. With regard to the discount rate, it was proposed that, due to the uncertainty about the actual budget impact of such treatment options, the current **discount rate** could be reduced from 3.5% to 1.5%, for example. When assessing gene therapy approaches, the uncertainty aspect should also be taken into account as an important feature in the assessment and cost calculation. **Innovative payment methods** should be taken into consideration, especially in areas where a potentially significant patient benefit is achieved. In this way, access to therapies for patients can be secured,

but the risk is shared between payers and pharmaceutical companies. A particular challenge is the financing of gene therapies in the inpatient sector, as the current mechanisms are not yet able to guarantee the reimbursement of such innovative but costly therapies. A cost-effective treatment for curative therapy was estimated at £528,000, assuming 10 QALYs (quality-adjusted life years) would be achieved under the therapy. However, this is only a sample calculation, so that for other therapies lower annual therapy costs could be considered cost effective, especially considering the possibly high hospitalization costs combined with lower patient benefit.

At the **pan-European level** however, no statements have been made on reimbursement methodologies or general cost-effectiveness limits, but this can be attributed to the fact that the reimbursement is regulated individually within each European country due to the different health care systems, making it difficult to enforce centralized approaches. The specific requirements for the potential reimbursement models of gene therapies can therefore differ greatly depending on the country. In analogy with the UK, in **Germany** only the statement that the previous methods (such as the AMNOG procedure including price negotiation with the GKV-SV in the outpatient sector) shall apply to gene therapies has been made thus far. Nevertheless, it seems sensible to take a closer look at the options for the reimbursement of gene therapy approaches based on the sometimes innovative approaches of previous precedents in this area. The individual contracts signed between some insurance companies and pharmaceutical companies show that the German health care system is also open to new reimbursement models.

Summary of reimbursement options of gene therapies

There are numerous options for innovative reimbursement models

In some of the previous methods and procedures of various regulatory authorities, the **cost-effectiveness** is calculated for the evaluation of new medicinal products to be able to determine a maximum price or maximum cost based on this (see, for example, NICE and ICER). These models are based on initial hypothetical assumptions about the actual efficacy and safety of the product and are therefore subject to uncertainty. In Germany, the reimbursement amount is the original price set by the pharmaceutical company less a discount (§130b and §130a of SGB V). The **official price anchors**, which serves as a basis for the calculation or negotiation of the reimbursement amount, are the additional benefit determined by the G-BA, the costs of comparable medicinal products and the purchasing power-adjusted and sales-weighted European price level of the medicinal product. The price is negotiated between the pharmaceutical company and the GKV-SV in a 6-month price negotiation, taking into account

other aspects, such as the budget impact and the negotiating skills of the parties, and the discount is set. Overall, both the model and the procedures of NICE and ICER are broadly concerned with **valuation-based models based on the pre-launch evidence** of the pharmaceutical company, which is used as the basis for determining adequate reimbursement. In addition, almost all systems are currently based on the concept of **upfront payment**.

For annuity-based models, costs are spread over a defined period of time

One way to reimburse gene therapies is to develop **annuity-based models**. The idea of an annuity-based reimbursement model is to spread the costs over a defined period of time. This means that the reimbursement amount will not be reimbursed in full at the time of treatment, instead the payment will be divided proportionately over several years (**installment payment plans**). The determination of an adequate reimbursement amount can be made based on methodically-developed health economics models, which make it possible to quantify and evaluate the (lifelong) benefit and efficacy. Therefore, a long-term or lifelong effect should be assumed in the modeling, the monetized benefit of which is discounted at the time of the intervention. It is also possible to link the reimbursement to the treatment outcome or the individual "performance" of the treatments in terms of long-term efficacy and safety (**outcome-based approach, such as the pay-for-performance approach, P4P**). The advantage here is that the risk or uncertainty of the efficacy of gene therapy is shared between the pharmaceutical companies and the respective payer. There are, however, some obvious challenges here: For one, the **measurement of the efficacy**. Patient-relevant endpoints could be used for this, but these are often not adequately validated or recognized, especially for rare diseases. In addition, they must always be determined individually for each treatment. The number of endpoints that are considered to be patient-relevant must also be defined. When choosing multiple points, it should also be determined which endpoints need to be significant to what extent and at what time. The **amount of the partial payments** can also be structured as variable. Depending on the data situation or treatment, it may be useful to reimburse higher amounts at the beginning or end of the treatment, or to set a constant amount for the entire period. This can be done depending on the predicted onset of efficacy or any potential long-term damage that may occur. Another version of the model would be to reimburse the entire amount at the beginning and, depending on the efficacy, to arrange a reimbursement from the pharmaceutical company to the payer (**refund**). Again, however, the issues raised must be defined and agreed in advance. In general, this approach seems feasible at first, but relies on very customized solutions. To do this, general criteria would have to be set for establishing the model, thereby creating a formal framework. This enables a flexible yet standardized solution.

The installment payments of an annuity-based model can be determined using a results-based approach

Another possibility is not to link the results-based approach to an installment payment, i.e. not to combine it with an annuity-based model, but instead to redesign the pricing system based on the **post-launch evidence**. In this sense, by establishing common standards for the generation of follow-up data, one or more time periods could be determined in which the treatment is re-evaluated, for example, based on "real world evidence" or phase IV studies. Depending on whether the results of the clinical trials are confirmed, or a better or worse efficacy is determined, the annual treatment costs at the time of reassessment could remain the same or be increased or decreased. There are various options, in particular with regard to the responsibility for the reassessment; for example, a central reassessment (simplified process) or country-specific assessments by the regulatory authorities or payers is conceivable in Europe. One of the challenges of this approach is the design of the re-evaluation. This can range from a comprehensive and once again time-consuming evaluation to renewed country-specific price negotiations based on a short evaluation of registry data by the payers. On the other hand, this approach may mean that, at the time of re-evaluation a large proportion of patients had already been treated, and the budget impact would be relatively low as a result of the new price negotiations, especially for gene therapies for rare or ultra-rare diseases. The exact timing of a reassessment is therefore of immense importance, since the balance between sufficient evidence for the assessment and the size of the patient population must be found. This leads to the assumption that a generally valid definition of the time period would not be necessary, but rather a product-specific one.

The systematic integration of post-launch evidence offers a possibility of counteracting the payer's uncertainty

Another problem that cannot solve either the benefit assessment-based determination of the reimbursement amount or the allocation of costs over a longer period of time, is the problem of the lack of amortization of the expense paid if the insured switches between the SHIs. This can only be carried out using a **collectivization of the expense**. In the US in particular, the focus is on a reimbursement of the short-term benefit of the drug by the payers. This model is a result of the fact that the insured change insurance on average every three years. An example in the German system for a possible collectivization would be an adaptation of the morbidity-oriented risk structure compensation (Morbi-RSA), for example via a reintroduction of the so-called high-risk pool, which could cover the specific gene therapy interventions. However, fund solutions could also be organized privately in the sense of an intermediate company, the coverage risk of which is cushioned by reinsurance. As a result, the initial costs incurred would be collectivized and covered by insurance, so that the ability of the insured to choose a SHI does not need to be limited, and the fund or pool balances the expense and the amortization. Likewise, if treatment

The objective of the fund solutions is to collectivize the expense and thus to split the risk on a societal level

fails, i.e. if the promise of lifelong recovery is not met, the fund could cover additional treatment accordingly. In the following, the different reimbursement options of gene therapies differentiated according to the extent of risk splitting (low to high) and the type and/or level of post-launch evidence is summarized (Figure 8).

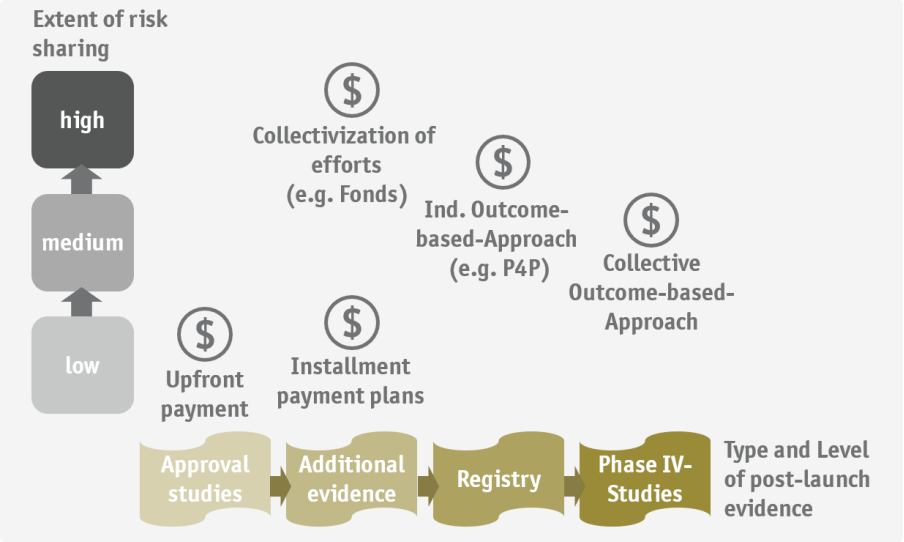

Figure 8: Potential reimbursement models differentiated by the extent of risk sharing and the type and level of post-launch evidence. In general, 5 different models can be differentiated. The status quo is represented by the upfront payment. The pricing is based on the available evidence at the time of approval, no more data has to be presented indicating a low extent of risk sharing as longterm efficacy and safety can only be assessed hypothetically. Installment payment plans can be evaluated equally, as they are not necessarily based on additional evidence. In the generation of post-launch evidence, on the other hand, the extent of risk sharing between the insurance providers and the pharmaceutical companies' increases, as can be seen in the individual and collective outcome-based approaches. Despite a low level of post-launch evidence, a high degree of risk sharing at the societal level can only be achieved by collectivizing the effort. Source: SKC-Analysis

4. Conclusion

Based on the precedents, it is clear that pharmaceutical companies currently testing the **opportunities of gene therapies on the market**. It is also possible that the initial precedents have been used for rare diseases for this reason too. However, growth and also advancement into disease areas with higher prevalence numbers will certainly not be far behind. Gene therapies such as the CAR-T cell therapies Kymriah® and Yescarta®, the autologous HSC-based therapy Strimvelis® or the *in vivo* applied treatment Luxturna®, are all new options for the treatment of severe rare diseases of genetic origin, where previous thera-

pies were absent, failed or did not provide a long-term solution for the treatment of the disease and the patient. The five gene therapy products listed here differ in their respective study design and thus the data collected. It is evident that it is not necessarily only efficacy that plays a role in pricing. For example, Glybera®, priced at almost €1 million, is priced almost twice as high as the four other treatments. At the same time, treatments such as Strimvelis® or Luxturna® have been able to show a somewhat clearer efficacy to date than that of Glybera®. Figure 9 offers a concise **integration and comparison** of the previous **evidence** and the currently used **reimbursement models** for the gene therapies approved by the EMA and FDA.

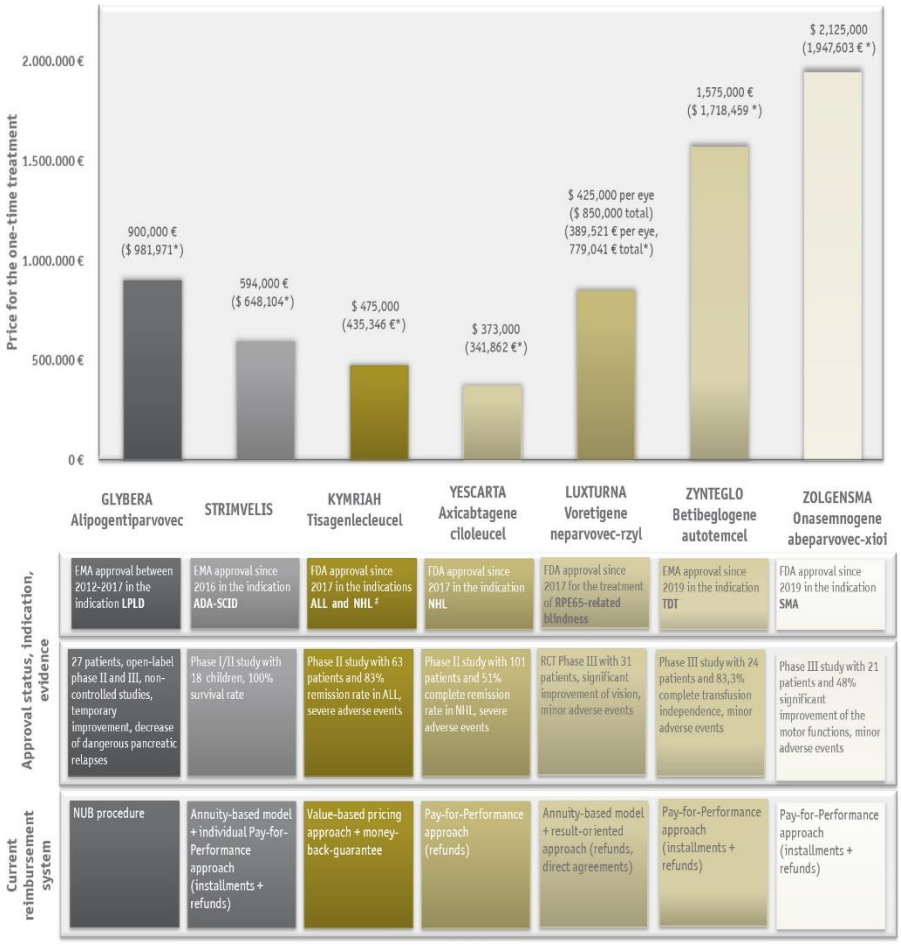

Figure 9: Overview of previously approved gene therapies by the FDA and EMA with regard to their approval backlog and current reimbursement systems of the one-time treatments. *Date of exchange rate 22/05/2020, # second indication (no price available so far). Source: SCK-Analysis. This information is provided without liability.

Over the next few years, the number of gene therapy options will multiply. The pipeline of pharmaceutical companies is well filled, so that many other approvals can be expected in the next few years in the US as well as in Europe in the field of hemophilia, for example. However, adequate measurement of long-

term efficacy and potential long-term side effects acts as a limiting factor in current systems, leading to high uncertainty in assessment and, along with the treatment modality of curative gene therapy, becomes a challenge for a mutually-appropriate reimbursement. The various institutions at the international and national level have in some cases already dealt intensively with the potentially necessary revision of the previous processes, methodologies and requirements and discussed healing options in exchange with pharmaceutical companies, payers, clinicians and patient representatives. For example, the long-standing guidelines that deal with gene therapy have already been or will be partially overhauled, in order not only to meet the theoretical but also the practical varying demands of gene therapies in the licensing and reimbursement process based on recent precedents.

The regulatory requirements for gene therapies are currently being evaluated, some of which are already being updated by the regulatory authorities

The basis for the assessment, however, are the existing evaluation processes at the FDA as well as at the EMA, NICE and the G-BA, which, according to the authorities, already meet the requirements of gene therapies in essence. However, individual aspects need to be adjusted to varying degrees, in particular in order to include the uncertainty aspect of gene therapy treatment options in the assessment. Thus, for example, a **policy concept** is being drafted by the FDA, which includes establishing a brief approval process and should also provide assistance in setting up disease-specific guidelines that reflect the standards for safety and benefit requirements. In addition, the methods for carrying out pre-clinical studies should be defined in the future, and guidelines for assessing the long-term risk and/or generally for the duration of a follow-up will be developed. The EMA is also currently revising some of the guidelines, which include, for example, assessing safety and efficacy. In particular, the focus is on the early identification of any risks in order to minimize or prevent them in the long term.

In the field of reimbursement, no uniform concepts have yet been created

With regard to the establishment of new reimbursement systems, the regulatory authorities have so far been rather cautious. According to NICE, the determination of a cost-effectiveness limit is also possible with the previous methodology, and the G-BA has thus far only advocated that the previous system of price negotiations following the benefit assessment can also be applied to gene therapies in general. However, due to the new logic of the gene therapy paradigm, this can lead to various challenges in conceptualizing adequate reimbursement. It is true that both the pharmaceutical companies and the various payers are open to new reimbursement models, as already shown in the practical implementation of a wide range of models or individual contracts both in the USA and in Europe. However, it is not currently possible to predict whether, and if yes, when, there will be uniform guidelines or adjustments to the reimbursement system at national or international level. Nevertheless, it

is repeatedly emphasized in the various reports and recommendations that the (early) cooperation of the different interest groups is necessary and desirable for this purpose, but so far no supranational working group has been formed or any possible solutions communicated on this specific topic.

Based on the analysis, in addition to the general recommendations of different authorities and institutions, **specific aspects** have emerged, which could play an important role in the **approval process and for the reimbursement issue.** These are presented in an overview below:

Realiy of care

The role of the drug in the **reality of care** should be evaluated, especially if the treatment has a major impact on current treatment standards as well as on care costs.

Generation of follow-up data

The provision of **follow-up data** plays an essential role, especially with regard to the uncertainty aspect of the treatments. Both the EMA and the FDA recommend a follow-up period of approximately 15 years, although this period may change depending on the treatment or disease. The collection of additional post-authorization data may take the form of extension studies, additional phase IV studies, or registry data, but this should be incorporated into the process early on, so that seamless follow-up can be ensured after approval. The objective of the follow-up is to capture the dynamics of the efficacy of the treatment, i.e. the question of whether and, if yes, when it is necessary to repeat the treatment as well as the evaluation of the product-specific risk.

Target population of the treatment

Special attention should be paid to the determination of the **target population** since the estimation of the healthcare percentage is based on the logic that in a first step based on epidemiological parameters, all patients in this indication who are generally suitable for the treatment

are determined (generally suitable patients), but the proportion of the patients who cannot be treated due in part to their individual characteristics or who do not want to be treated or who are not treatable (individual suitability of patients) must be deducted from this. The target population is therefore based on the estimate of patients in need of and willing to have treatment, whereby this percentage can be determined depending on the indication (for example, depending on the course of disease determined by the severity of symptoms and progression), the application method, other treatment options and the patient-specific factors of the generally suitable population. The estimated number of patients within the target population is of particular importance for the payers for estimating the budget impact and should be determined and presented in the most valid way possible by the pharmaceutical company.

Differentiated illustration of benefits

Even a **differentiated illustration of benefits** is associated with fewer challenges in defining a more precise target population than a broader but not precisely defined population. This is closely linked to the exact wording of the label, which is initially relevant for the presentation of (additional) benefit but also for price negotiations with the GKV-SV (in the German care context). When selecting the target and study population, it must be ensured that the analysis includes in particular those patients who receive the greatest benefit from gene therapy results from the payer's point of view.

Production method - Patient-specific vs. -independent

Manufacturing represents another factor. Gene therapies differ in this respect to a certain extent, because in the case of CAR-T cell therapy, **patient-specific production** in which the patient's body cells must first be removed, modified and propagated may be required or **patient-independent production** can take place, such as for Luxturna®. This has a big impact on the market uptake curve in particular, because the fewer centers there are and the longer and more complex the manufacture of the product, the fewer patients can be treated each year. This should be noted in advance and strategically considered.

Application-specific aspects including tutorials and training

Furthermore, in addition to the manufacturing process, the type of application and the likelihood of short-term side effects also play an important role. The course of treatment and the aspects to be considered for each treatment have an effect on the extent to which and in what form **tutorials and training** will be necessary for the technical personnel and how specialized the technical personnel must be in order to be able to administer the gene therapy or to recognize side effects and be able to react to them. This also includes determining at which location the treatment takes place, for example on an outpatient or inpatient basis, and at how many locations or specialist centers treatment can take place. The necessary prerequisites and plans can and should be developed and integrated during the approval process.

Development of an overall strategy

On the other hand, the development of an overall strategy is essential for the general reimbursement of gene therapies, especially in Europe, due to the different reimbursement systems in each country. This is because, despite the systems that are actually independent, the respective countries influence reference prices, treatment standards and recommendations, for example, to a considerable extent. In addition to determining the launch sequence and deciding on the amount of country-specific launch prices, an analysis of the different reimbursement options shown can also be valuable in order to achieve optimal positioning in each country. Careful examination of which models make sense should take place in combination with the characteristics of the disease, the size of the (target) population and the available evidence. Thus, depending on the therapy, indication and country, a fund-based model could be very well accepted and implemented by the different stakeholders, whereas with a small number of suitable patients and the possibility of concluding individual contracts with the payers, the option of having an installment payment linked to a P4P approach could make sense.

Mobilization of the market

However, due to the challenges that have yet to be conclusively evaluated, **the interaction** between genetic engineering developers and users of genetic engineering methods, geneticists, ethicists, legislators, public officials, government organizations, and stakeholders appears to be essential to regulate and establish the adoption of novel technologies. From the pharmaceutical company's point of view, this means to invest in resources in the **mobilization of the market** especially at the beginning. Intensive contact and exchange with clinical experts, as

well as the early involvement of potential treatment centers but also communication with payers and regulatory authorities can help to identify and address uncertain aspects of the product at an early stage in order to secure its establishment.

Value story

In this sense, the **development, presentation and integration of the value story** of the product plays a crucial role in the entire process. Based on the medical, economic, scientific and political/public levels of the value story, it is important to optimally emphasize the value of the treatment. With regard to gene therapies for rare diseases, for example, creating awareness of the disease, the precise elaboration of the unmet needs and the innovation of the mechanism of action may play a role.

The market access of gene therapies is shaped by VUCA [volatility, uncertainty, complexity, ambiguity] – strategic expertise and agility are therefore fundamental to the participants

In summary, the first things learned can already be deduced from the precedents, but the gene therapy system is still in its infancy. This makes it all the more important to have a sound strategy to meet the diverse challenges, to allow patients access to innovative therapies, and to ensure adequate reimbursement. The level of innovation of gene therapies is only one of many factors influencing the (commercial) success of the product – other factors, such as early stakeholder management, a collaborative approach, and related development of new reimbursement models with mostly country-specific challenges and requirements as well as the long-term generation of data, such as through registries or long-term follow-up studies, to reduce uncertainty, are at least as important and play a decisive role in the market uptake of the product. Especially now that there are only a few gene therapies on the market, there is a chance that the various stakeholders will work together to develop solutions and advance the healthcare system in the field of gene therapies. Pharmaceutical companies can address this by serving as collaborative partners, allowing them to take a proactive approach. The solutions developed should be a viable compromise for all stakeholders in the system; this means giving priority to reducing uncertainty among payers and continuing to encourage manufacturers to develop innovative treatment options. Overall, the

analysis of the regulatory requirements of the EMA, the FDA, NICE and the German institutions, the different approaches to reimbursement, and the general problems associated with the reimbursement of gene therapy, make it clear that the aspects identified early on should already be included in the approval process and considered in order to achieve the best possible positioning. The success of all these innovative therapies will (have to) be based on strict but highly flexible regulations that are constantly changing and adapting with regard to the VUCA (volatility, uncertainty, complexity, ambiguity) of the growing gene therapy field.

5. Appendix

Table 1: FDA guidance for gene therapies

#	FDA guidance for gene therapies	Published in
1	Draft Guidance for Industry - Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations	2020
2	Guidance for Industry - Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	2020
3	Guidance for Industry - Long Term Follow-up After Administration of Human Gene Therapy Products	2020
4	Guidance for Industry - Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up	2020
5	Guidance for Industry - Human Gene Therapy for Hemophilia	2020
6	Guidance for Industry - Human Gene Therapy for Rare Diseases	2020
7	Guidance for Industry - Human Gene Therapy for Retinal Disorders	2020
8	Guidance for Industry - Evaluation of Devices Used with Regenerative Medicine Advanced Therapies	2019
9	Guidance for Industry - Expedited Programs for Regenerative Medicine Therapies for Serious Conditions	2019
10	Guidance for Industry and FDA Staff - Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use	2017
11	Guidance for Industry - Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception	2017
12	Guidance for Industry - Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271	2017
13	Guidance for Industry – Recommendations for Microbial Vectors Used for Gene Therapy	2016
14	Guidance for Industry – Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products	2015
15	Guidance for Industry - Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products	2015
16	Guidance for Industry - Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products	2015
17	Guidance for Industry - BLA for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System	2014
18	Guidance for Industry and FDA Staff - IND Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for	2014

	Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System	
19	Guidance for Industry – Preclinical Assessment of Investigational Cellular and Gene Therapy Products	2013
20	Guidance for Industry - Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage	2011
21	Guidance for Industry - Clinical Considerations for Therapeutic Cancer Vaccines	2011
22	Guidance for Industry – Potency Tests for Cellular and Gene Therapy Products	2011
23	Guidance for Industry - Cellular Therapy for Cardiac Disease	2010
24	Guidance for Industry - Considerations for Allogeneic Pancreatic Islet Cell Products	2009
25	Guidance for FDA Reviewers and Sponsors – Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)	2008
26	Guidance for Industry - Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products	2007
27	Guidance for Industry - Guidance for Human Somatic Cell Therapy and Gene Therapy	1998
	NIH guideline	**Published in**
	NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules	2016

Table 2: EMA guidelines regarding gene therapies

Designation and status	Guidelines, reflection paper and recommendations	Content	Publications
EC No 1394/2007	Regulation on advanced therapy medicinal products	The regulation is a *lex specialis,* which introduces additional provisions.	10.12.2007
EMA/630043/2008	Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) NO 1394/2007	This document concentrates on the initial evaluation of new ATMPs, but its principles also apply to post-authorisation procedures.	25.01.2018
EMA/CAT/852602/2018	Draft: Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	This guideline provides guidance on the structure and data requirements for a clinical trial application for exploratory and confirmatory trials with advanced therapy investigational medicinal products.	21.02.2019

EMEA/14995/2008	Guideline on safety and efficacy follow -up and risk management of advanced therapy medicinal products	The guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs, as well as some aspects of clinical follow-up of patients treated with such products.	21.11.2008 Revision 1 (Draft): 01.02.2018
EMA/CAT/80183/2014 (Revision 1)	Quality, preclinical and clinical aspects of gene therapy medicinal products	Revision of the Note for Guidance on the Quality, Preclinical and Clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99), published in 2001. It defines scientific principles and provides guidance for the development and evaluation of GTMPs intended for use in humans and presented for MAA. Its focus is on the quality, safety and efficacy requirements of GTMPs.	13.07.2018
EMA/CAT/GTWP/ 67163/2008	Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	This document defines scientific principles and provides guidance for the development and evaluation of medicinal products containing genetically modified cells intended for use in humans and presented for marketing authorisation.	03.05.2012 Revision 1 (Draft): 31.07.2018
CHMP/BWP/2458/2003	Development and manufacture of lentiviral vectors	This guideline describes quality aspects that are relevant for lentiviral vectors (LV). It applies to LV intended for ex vivo or in vivo application.	26.05.2005
EMEA/CHMP/GTWP/ 125459/2006	Non-clinical studies required before first clinical use of gene therapy medicinal products	This document defines scientific principles and provides guidance to applicants developing gene therapy medicinal products (GTMPs). It focuses on the non-clinical studies required before the first use of a GTMPs in human subjects	30.05.2008

EMEA/273974/2005	Non-clinical testing for inadvertent germline transmission of gene transfer vectors	This document provides guidance on non-clinical inadvertent germline transmission testing needed to support clinical development of gene transfer medicinal products consisting of or containing replication-incompetent vectors, genetically modified viruses or so-called naked nucleic acids directly administered to humans.	16.11.2006
CAT/CPWP/ 686637/2011	Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	This document provides guidance on the application of the risk-based approach in the preparation of a marketing authorisation application.	08.03.2013
EMEA/CHMP/GTWP/ 60436/2007	Follow-up of patients administered with gene therapy medicinal products	This document addresses specific aspects of the active clinical follow-up of patients administered with gene therapy medicinal products in order to detect signals of early or delayed adverse reactions, to prevent clinical consequences of such reactions, to ensure timely treatment and to gain information on the long-term safety and efficacy of the intervention.	13.11.2009
EMEA/CHMP/GTWP/ 125491/2006	Scientific requirements for the environmental risk assessment of gene-therapy medicinal products	This document provides guidance on the environmental risk assessment of GMO-containing gene therapy medicinal products, as required for marketing authorization under the centralized procedure. It aims to facilitate the application of the methodology laid down in the Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.	01.11.2008

EMA/CAT/GTWP/ 44236/2009	Design modifications of gene therapy medicinal products during development	This document presents regulatory considerations given for specific gene therapy medicinal products where the characteristics have been changed at various stages during clinical development. It gives some insight into the types of studies that are likely to be required in an application dossier to support the modification in the product design introduced during development.	09.02.2012
EMEA/CHMP/GTWP/ 587488/2007	Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors	This document aims to discuss quality, non-clinical and clinical issues that should be considered during the development of medicinal products derived from adeno-associated viral vectors. It indicates requirements that might be expected at the time of a marketing authorisation application	08.07.2010
EMA/CAT/190186/2012	Management of clinical risks deriving from insertional mutagenesis	This document discusses the factors contributing to genotoxicity of vector integration, the strategies to reduce the risk associated to insertional mutagenesis and the assays to evaluate vector oncogenesis at the pre-clinical and clinical level.	01.08.2013
EMA/CAT/499821/2019	Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP)	This document addresses questions on how to demonstrate comparability for gene and cell-based medicinal products following change to the manufacturing process or due to introduction of additional manufacturing sites.	13.12.2019
EMA/CHMP/GTWP/ 212377/2008	Questions and answers on gene therapy	This document addresses questions on matters related to the development of gene therapy medicinal products. It	13.01.2010

		provides harmonized position on issues that can be subject to different interpretation or require clarification, typically arising from discussions during briefing meetings with stakeholders.	
EMEA/CHMP/ICH/ 449035/2009	ICH Considerations: general principles to address virus and vector shedding	This document provides recommendations for designing non-clinical and clinical virus/vector shedding studies. In particular, it emphasizes the analytical assays used for detection and considerations for the sampling profiles and schedules in both non-clinical and clinical studies. The interpretation of non-clinical data and its use in designing clinical studies is also within the scope of this paper, as well as the interpretation of clinical data in assessing the need for virus/vector transmission studies.	01.07.2009
EMEA/CHMP/ICH/ 607698/2008	ICH Considerations: oncolytic viruses	This document describes the general principles for the manufacturing, characterisation, non-clinical and clinical testing of medicinal products based on oncolytic viruses.	21.10.2009

6. Literature

1. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. Cell stem cell. 2016;19(3):293-7.
2. Aerzteblatt.de. Krankenkasse muss Zolgensma-Therapie für zwei Millionen Euro nicht zahlen. https://www.aerzteblatt.de/nachrichten/111057/Krankenkasse-muss-Zolgensma-Therapie-fuer-zwei-Millionen-Euro-nicht-zahlen
3. Aerzteblatt.de. Spinale Muskelatrophie: Millionenteures Medikament Zolgensma vor Zulassung in Europa. https://www.aerzteblatt.de/nachrichten/111477/Spinale-Muskelatrophie-Millionenteures-Medikament-Zolgensma-vor-Zulassung-in-Europa
4. Aerzteblatt.de. Zolgensma vor Marktstart in Deutschland. https://www.aerzteblatt.de/nachrichten/113060/Zolgensma-vor-Marktstart-in-Deutschland
5. Aerztezeitung.de. Gentherapie: Hersteller bietet Kassen an, nur im Erfolgsfall zu erstatten. https://www.aerztezeitung.de/Wirtschaft/Kassen-muessen-nur-im-Erfolgsfall-fuer-neue-Gentherapie-zahlen-406897.html
6. Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, Cassani B, Callegaro L, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. The New England journal of medicine. 2009;360(5):447-58.
7. Aiuti A, Roncarolo MG, Naldini L. Gene therapy for ADA-SCID, the first marketing approval of an ex vivo gene therapy in Europe: paving the road for the next generation of advanced therapy medicinal products. EMBO molecular medicine. 2017;9(6):737-40.
8. Amgen, Inc. Imlygic - Webpage. https://wwwimlygiccom/. 2018.
9. Araujo A, Araujo M and Swoboda KJ, MD. Vascular perfusion abnormalities in infants with Spinal Muscular Atrophy. The Journal of Pediatrics. 2009; 155(2):292-294.
10. Arznei-News.de. Axicabtagen. https://arznei-newsde/axicabtagen/. 2017.
11. Arznei-News.de. Strimvelis. https://arznei-newsde/strimvelis/. 2016.
12. Arznei-News.de. Talimogen Laherparepvec (Imlygic). https://arznei-newsde/talimogen-laherparepvec-imlygic/. 2017.
13. Arznei-News.de. Trisagenlecleucel. https://arznei-newsde/tisagenlecleucel-t/. 2018.
14. Arznei-News.de. Voretigen Neparvovec (Luxturna). https://arznei-newsde/voretigen-neparvovec/. 2017.
15. Bender E. Regulating the gene-therapy revolution. The medical regulatory authorities ride a wave of clinical studies for gene therapies. Nature. 2018; 564: 20-22.
16. Bleß, H. Anwendungsbegleitende Daten in der Nutzenbewertung – Empfehlungen zur Evidenzgenerierung und -auswertung. Monitor Versorgungsforschung. 2020; 1: 47-54.
17. Brennan TA, Wilson JM. The special case of gene therapy pricing. Nature biotechnology. 2014;32(9):874-6.

18. Bryant LM, Christopher DM, Giles AR, Hinderer C, Rodriguez JL, Smith JB, et al. Lessons learned from the clinical development and market authorization of Glybera. Human gene therapy Clinical development. 2013;24(2):55-64.

19. Bundesinstitut für Arzneimittel und Medizinprodukte https://wwwbfarmde/DE/Home/home_node-html.

20. Bundesministerium der Justiz und für Verbraucherschutz. Embryonenschutzgesetz (ESchG). (https://www.gesetze-im-internet.de/eschg/BJNR027460990.html) 2011

21. Bundesministerium der Justiz und für Verbraucherschutz. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG). https://wwwgesetze-im-internetde/amg_1976/. 2005.

22. Bundesministerium der Justiz und für Verbraucherschutz. Gesetz zur Regelung der Gentechnik (GenTG). (https://www.gesetze-im-internet.de/gentg/)

23. Bundesministerium für Bildung und Forschung. https://wwwbmbfde/.

24. Caffrey M. With Approval of CAR T-Cell Therapy Comes the Next Challenge: Payer Coverage. The American Journal of Managed Care (AJMC); (http://wwwajmccom/journals/evidence-based-oncology/2018/february-2018/with-approval-of-car-tcell-therapy-comes-the-next-challenge-payer-coverage). 2018.

25. Carr DR, Bradshaw SE. Gene therapies: the challenge of super-high-cost treatments and how to pay for them. Regenerative medicine. 2016;11(4):381-93.

26. Cicalese MP, Ferrua F, Castagnaro L, Pajno R, Barzaghi F, Giannelli S, et al. Update on the safety and efficacy of retroviral gene therapy for immunodeficiency due to adenosine deaminase deficiency. Blood. 2016;128(1):45-54.

27. COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) . GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS 2009.

28. COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP). GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS. 2006.

29. Crabb and Stevens. Exploring the assessment and appraisal of regenerative medicines and cell therapy products. 2016.

30. Crabb N, Stevens A. Exploring the assessment and appraisal of regenerative medicines and cell therapy products. 2016.

31. Deutsche-Apotheker-Zeitung.de. Zolgensma in der EU zur Zulassung empfohlen. https://www.deutsche-apotheker-zeitung.de/news/artikel/2020/03/30/zolgensma-in-der-eu-zur-zulassung-empfohlen.

32. Deutsche Forschungsgemeinschaft http://wwwdfgde/.

33. DRG-Broschüre 2019: https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-c.html.

34. Elsanhoury A, Sanzenbacher R, Reinke P, Abou-El-Enein M. Accelerating Patients' Access to Advanced Therapies in the EU. Molecular therapy Methods & clinical development. 2017;7:15-9.

35. European Commission. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. https://eceuropaeu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmpspdf. 2017.

36. European Medicines Agency (EMA). Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe. 2016.

37. European Medicines Agency (EMA). Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe. http://wwwemaeuropaeu/docs/en_GB/document_library/Report/2016/06/WC500208080pdf. 2016.

38. European Medicines Agency (EMA). Gene Therapy Working Party. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/contacts/CAT/people_listing_000015jsp.

39. European Medicines Agency (EMA). Glybera (alipogene tiparvovec). http://wwwemaeuropaeu/ema/indexjsp?curl=pages/medicines/human/medicines/002145/human_med_001480jsp&mid=WC0b01ac058001d124.

40. European Medicines Agency (EMA). Guideline - Follow-up of patients administered with gene therapy medicinal products. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/regulation/general/general_content_001375jsp&mid=WC0b01ac058002958d. 2010.

41. European Medicines Agency (EMA). Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products. 2018.

42. European Medicines Agency (EMA). Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/regulation/md_gene_therapy/general_content_001909jsp&mid=WC0b01ac058002958d. 2013.

43. European Medicines Agency (EMA). Imlygic (talimogene laherparepvec). Imlygic (talimogene laherparepvec).

44. European Medicines Agency (EMA). Multidisciplinary: gene therapy. http://wwwemaeuropaeu/ema/indexjsp?curl=pages/regulation/general/general_content_000410jsp&mid=WC0b01ac058002958d.

45. European Medicines Agency (EMA). Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007. http://wwwemaeuropaeu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/02/WC500242957pdf. 2018.

46. European Medicines Agency (EMA). Strimvelis. 2016.

47. European Medicines Agency (EMA). Zynteglo. https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo.

48. European Medicines Agency and European Commission. European Commission-DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs.

49. FDA. Zolgensma. www.fda.gov/vaccines-blood-biologics/zolgensma.

50. FDA. Imlygic. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/imlygic-talimogene-laherparepvec.

51. FDA News Release. FDA announces comprehensive regenerative medicine policy framework. 2017.

52. Gaudet D, Stroes ES, Methot J, Brisson D, Tremblay K, Bernelot Moens SJ, et al. Long-Term Retrospective Analysis of Gene Therapy with Alipogene Tiparvovec and Its Effect on Lipoprotein Lipase Deficiency-Induced Pancreatitis. Human gene therapy. 2016;27(11):916-25.

53. Gemeinsamer Bundesausschuss (G-BA). Künftig auch für Arzneimittel mit ausschließlich stationärem Anwendungsbereich Nutzenbewertung nach § 35a SGB V https://wwwg-bade/institution/presse/pressemitteilungen/730/. 2018.

54. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Alipogentiparvovec. https://wwwg-bade/informationen/nutzenbewertung/146/. 2015.

55. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Axicabtagen-Ciloleucel (Diffus großzelliges B-Zell-Lymphom). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/408/.

56. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Axicabtagen-Ciloleucel (Primäres mediastinales großzelliges B-Zell-Lymphom). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/406/.

57. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Betibeglogene Autotemcel (autologe CD34+ hämatopoetische Stammzellen). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/506/.

58. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Talimogen laherparepvec. https://wwwg-bade/informationen/nutzenbewertung/243/. 2016.

59. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Tisagenlecleucel (Akute lymphatische B-Zell-Leukämie. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/386/.

60. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Tisagenlecleucel (Diffus großzelliges B-Zell-Lymphom). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/385/.

61. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Tisagenlecleucel (Neubewertung nach Fristablauf: Akute lymphatische B-Zell-Leukämie). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/533/.

62. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Tisagenlecleucel (Neubewertung nach Fristablauf: Diffus großzelliges B-Zell-Lymphom). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/532/.

63. Gemeinsamer Bundesausschuss (G-BA). NutzenNutzenbewertungsverfahren zum Wirkstoff Voretigen Neparvovec (Erbliche Netzhautdystrophie). https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/454/.

64. Gemeinsamer Bundesausschuss (G-BA). Verfahrensordnung des Gemeinsamen Bundesausschusses. https://wwwg-bade/informationen/richtlinien/42/. 2018.

65. Gilead Press Release. . http://wwwgileadcom/news/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refractory-large-bcell-lymphoma-after-two-or-more-lines-of-systemic-therapy. 2017.

66. GWQ-serviceplus.de. Vertragsabschluss zwischen AveXis und der GWQ zur erfolgsorientierten Erstattung von Zolgensma®. https://www.gwq-serviceplus.de/aktuelles/news/vereinbarung-gwq-p4p-vertrag-zu-zolgensma_6050

67. HIGHLIGHTS OF PRESCRIBING INFORMATION - Kymriah. 2018.

68. HIGHLIGHTS OF PRESCRIBING INFORMATION - Luxturna.

69. HIGHLIGHTS OF PRESCRIBING INFORMATION - Yescarta.

70. Hollis A. Sustainable Financing of Innovative Therapies: A Review of Approaches. PharmacoEconomics. 2016;34(10):971-80.

71. Institute for Clinical and Economical Review (ICER). Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. 2018.

72. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. Journal of Market Access & Health Policy. 2020.

73. Jorgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. Journal of market access & health policy. 2015.

74. Kirchmann T, Kielhorn-Schönermark H, Schönermark MP, M.D., Ph.D. Orphan Drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implications. 2017.

75. Kymriah (trsiagenlecleucel) - Webpage. https://wwwuskymriahcom/acute-lymphoblastic-leukemia-children/.

76. Laframboise R. Gene Therapy Regualtion: A Proactive Approach. https://wwwndsuedu/pubweb/~mcclean/plsc431/students/rosshtm. 1996.

77. Lee BY, McGlone SM. Pricing of new vaccines. Human vaccines. 2010;6(8):619-26.

78. Locke FL, Davila ML. Regulatory challenges and considerations for the clinical application of CAR-T cell anti-cancer therapy. Expert opinion on biological therapy. 2017;17(6):659-61.

79. Luxturna (voretigene neparvovec-rzyl) - Webpage. https://luxturnacom/.

80. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in Europe: evidence that regulators must be proactive. Molecular therapy : the journal of the American Society of Gene Therapy. 2012;20(3):479-82.

81. MAP BioPharma. EMA Publishes Outcome of Stakeholder Meeting on Advanced Therapy Medicines (ATMP). https://mapbiopharmacom/blog/news/news-eu/2016/ema-publishes-outcome-of-stakeholder-meeting-on-advanced-therapy-medicines-atmp/.

82. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. The New England journal of medicine. 2018;378(5):439-48.

83. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. The New England journal of medicine. 2017;377(26):2531-44.

84. Nicod E, Berg Brigham K, Durand-Zaleski I, Kanavos P. Dealing with Uncertainty and Accounting for Social Value Judgments in Assessments of Orphan Drugs: Evidence from Four European Countries. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2017;20(7):919-26.

85. NIH, U.S. National Library of Medicine. https://wwwclinicaltrialsgov/.

86. Novartis Press Release. . https://wwwnovartiscom/news/media-releases/kymriahr-tisagenlecleucel-first-class-car-t-therapy-from-novartis-receives-second-fda-approval-treat-appropriate-rr-patients-large-b-cell-lymphoma. 2018.

87. Paul-Ehrlich-Institut https://wwwpeide/DE/home/de-nodehtml.

88. Reich J. Interdisziplinäre Arbeitsgruppe Gentechnologiebericht (IAG) der Berlin-Brandenburgischen Akademie der Wissenschaft (BBAW). Genomchirurgie beim Menschen – Zur verantwortlichen Bewertung einer neuen Technologie. 2015.

89. Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet (London, England). 2017;390(10097):849-60.

90. Schimmer J, Breazzano S. Investor Outlook: Solving Gene Therapy Pricing...with a Cures Voucher? Human gene therapy Clinical development. 2016;27(4):132-6.

91. Schule S, Renner M, Longhurst S, Narayanan G. Regulatory requirements for clinical trial and marketing authorisation application for gene therapy medicinal products. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 2010;53(1):30-7.

92. Scott LJ. Alipogene tiparvovec: a review of its use in adults with familial lipoprotein lipase deficiency. Drugs. 2015;75(2):175-82.

93. SKC Beratungsgesellschaft mbH. Erstattung für Gentherapie geht neue Wege – Spark Therapeutics gibt einen innovativen Preisplan für Luxturna bekannt. http://skc-beratungde/pharmazeutik/erstattung-fuer-gentherapie-geht-neue-wege. 2018.

94. Spark Therapeutics Press Release. . http://irsparktxcom/news-releases/news-release-details/spark-therapeutics-biologics-license-application-investigational. 2018.

95. Summary of Product Characteristics - Glybera.

96. Summary of Product Characteristics - Strimvelis.

97. The National Institute for Health and Care Excellence (NICE). NICE final draft guidance recommends gene therapy for rare 'bubble baby syndrome'. https://wwwniceorguk/news/article/nice-approves-gene-therapy-for-rare-bubble-baby-syndrome. 2018.

98. Touchot N, Flume M. Early Insights from Commercialization of Gene Therapies in Europe. Genes. 2017;8(2).

99. Touchot N, Flume M. The payers' perspective on gene therapies. Nature biotechnology. 2015;33(9):902-4.

100. Transkript.de. Zynteglo im Schnellverfahren zugelassen. https://transkript.de/news/zynteglo-im-schnellverfahren-zugelassen.html.

101. U.S. Food and Drug Administration. Approved Cellular and Gene Therapy Products. https://wwwfdagov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/defaulthtm.

102. U.S. Food and Drug Administration. Cellular & Gene Therapy Guidances. https://wwwfdagov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/defaulthtm.

103. U.S. Food and Drug Administration. Framework for the Regulation of Regenerative Medicine Products. https://wwwfdagov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm585218htm.

104. U.S. Food and Drug Administration. Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2018 https://wwwfdagov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm431409pdf. 2017.

105. U.S. Food and Drug Administration. Guidance for Industry - Expedited Programs for Serious Conditions - Drugs and Biologics. https://wwwfdagov/downloads/Drugs/Guidances/UCM358301pdf. 2014.

106. U.S. Food and Drug Administration. Guidance for Industry - Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events. https://wwwfdagov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719pdf. 2006.

107. U.S. Food and Drug Administration. KYMRIAH (tisagenlecleucel). https://wwwfdagov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706htm.

108. U.S. Food and Drug Administration. LUXTURNA. https://wwwfdagov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm589507htm.

109. U.S. Food and Drug Administration. The Orphan Drug Act and the Development of Products for Rare Diseases https://rarediseasesinfonihgov/files/FDA%20Orphan%20drugspdf.

110. U.S. Food and Drug Administration. YESCARTA (axicabtagene ciloleucel). https://wwwfdagov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm581222htm.

111. uniQure Press Release. uniQure Announces It Will Not Seek Marketing Authorization Renewal for Glybera in Europe. http://wwwuniqurecom/GL_PR_Glybera%20withdrawal_FINAL_PDFpdf. 2017.

112. Verband Forschender Azrneimittelhersteller (vfa). vfa-Positionspapier - Somatische Gentherapie. 2018.

113. wissensschau.de. Kymriah: CAR-T-Zellen bekämpfen Leukämien und Lymphome. https://wwwwissensschaude/krebs_tumor/car-t-zellen_kymriah_leukaemiephp.

114. Wissensschau.de. Yescarta: CAR-T-Zellen bekämpfen B-Zell-Lymphome. https://wwwwissensschaude/krebs_tumor/car-t-zellen_yescarta_b-zell-lymphomphp.

115. Wissensschau.de. Zolgensma - Gentherapie gegen spinale Muskelatrophie. https://www.wissensschau.de/genom/gentherapie_zolgensma_spinale_muskelatrophie.php.

116. Yescarta (axicabtagene ciloleucel) - Webpage. https://wwwyescartacom/.

117. Zellstoff. Erste CAR-T-Zelltherapie: wirksam aber teuer. http://zellstoff-blogde/krebs/erste-car-t-zelltherapie-kymriah-wirksam-aber-teuer/. 2017.

7. SKC – Partners to trust

The SKC Beratungsgesellschaft (following „SKC“) is a management consultancy especially designed for the health sector and has been supporting various companies and organisations in strategic challenges in the health sector for over 13 years as a medium-sized company based in Hanover. The focus is always on the development of valuable solutions that are geared to the individual needs of clients from the pharmaceutical industry, MedTech & biotechnology and statutory health insurance companies.

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Contact

SKC Beratungsgesellschaft mbH

Pelikanplatz 21

30177 Hannover

Deutschland

+49 511/ 6468 14 – 0

www.skc-beratung.de

schoenermark@skc-beratung.de