

Interview with Egbert Flory on the authorization of cell therapies

“Stem cells need flexible rules”

Anyone seeking to manufacture stem cell-based medicinal products are obliged to fulfil the authorities' regulatory requirements when moving into clinical application. It is important to retain an understanding of this situation. If stem cells undergo additional engineering on their way to becoming a finished product, they are classified as Advanced Therapy Medicinal Products (ATMP) within the EU. They will then require a centralized marketing authorization from the European Medicines Agency (EMA).

Egbert Flory, a virologist at the Paul Ehrlich Institute (PEI) in Langen, is one of Germany's leading experts in ATMP regulations. He made major contributions to preparing the EU regulation that came into force at the end of 2008, and continues to serve on the EMA committee responsible for decision-making on ATMPs. At PEI, Flory is the deputy head of the Medical Biotechnology Division. In addition to managing the regulatory work there, he also runs his own laboratory that performs research into stem cells.

Mr. Flory, what are the current major developments in the field of stem cell-based medicinal products in Europe and in Germany?

Ever since the ATMP regulation entered into force in 2008, we have been experiencing a sharp rise in clinical developments and applications for stem cell therapies – particularly those that are based on adult stem cells, such as mesenchymal stem cells (MSCs). Surveys show that just below 200 European clinical studies are focusing on stem cells. I'd estimate that Germany has about 35 such studies. So far, there are no clinical trials or approved ATMPs based on iPS cells in Europe. However, developers have been seeking out scientific advice for this area – including in Germany. Several EU member states currently also host a number of clinical studies that are using human embryonic stem cells as their starting materials.

Why are stem cell-based products such a big challenge from a regulatory point of view?

Stem cells are extremely diverse, so it is difficult to characterize them. Furthermore, the different types of cells have very different risk profiles. This presents major challenges for regulators and the applicants them-

selves. Even the starting material is highly heterogeneous: there are pluripotent stem cells, adult stem cells, and a variety of “precursor cells.” The manufacturing processes are usually very complex, and biological assays are often not established and validated in a pharmaceutical sense. In some cases, only a few relevant animal models are available for the non-clinical development phase. Besides, the individual characteristics of patients also makes things complicated.

In your view, what functions should a regulatory framework for stem cell-based therapies fulfill?

As is the case with conventional medicinal products, it is primarily a question of quality, safety, and efficacy. However, for years my mantra has been that we desperately need a flexible regulatory framework for stem cell-based medicinal products. They have to be considered individually, on a case-by-case basis. To achieve this, we need a close, multidisciplinary collaboration between scientists, expert organizations, and regulators. Regulatory decisions regarding stem cell products must be based on scientific knowledge and must take into account the specific risk profile of the cells.

The regulatory authorities call stem cell-based products ATMPs. This means they fall within a European legal framework. What are the key points of the EU's ATMP rules?

The EU regulation on ATMPs entered into force in December 2008. This created a harmonized, EU-wide process for the highly complex and innovative cell-based therapies.

Essentially, this means that these types of products cannot be placed on the European market without having received approval centralized marketing authorization. The European Medicines Agency is responsible for granting the latter, and reaches its decisions in London. A special EMA committee was also set up – the Committee for Advanced Therapies (CAT) – to take charge of ATMPs as a special group of medicinal products..

What exactly is the CAT's role?

The CAT is the body that reviews all the data on a product. Thus, for ATMPs in Europe, it is the supreme committee for preparing a decision on an authorization via



Egbert Flory



providing developers with scientific advice, and providing expertise during inspections. The state authorities carry out the pharmaceutical monitoring, including the inspections. They also grant the manufacturing authorizations for ATMPs, based on the European Good Manufacturing Practice guidelines. The state authorities also categorize medicines in accordance with pharmaceutical legislation – they perform the classification, which is legally binding in Germany.

Have there been any notable changes to the ATMP rules in recent years?

The regulations are based on the EMA's Guideline on Human Cell-based Medicinal Products from 2007. This is the parent guideline for all cell-based therapies, and it was a global pioneer. Even back then, the aim was to remain open and flexible. In 2010, the CAT published the world's first stem cell guideline, which also has a great deal of influence outside Europe. In recent years, the CAT has also focused extensively on the classification of cell-based medicinal products. Stem cell-based products are not only considered as ATMPs when they have been "substantially manipulated" using biotechnological processes; cell products are also classified as ATMPs if they are applied in a "non-homologous" manner – in other words, if the cells have different functions in the donor and the recipient. The CAT published classification recommendations relating to these aspects last year. The observations contained in this "reflection paper" are especially helpful with regard to stem cell products.

the European Commission. Every member state appoints two experts to the committee. My PEI colleague Dr Martina Schüssler-Lenz and I are currently the members for Germany. The CAT makes the decisions, provides scientific advice, and assigns the cell products according to their properties, i.e. performs the so-called classifications. The committee considers future developments in the ATMP field. We meet at least once a month. The CAT also includes members who represent patients and clinicians. This diversity is rare at the EMA and underscores the committee's very multidisciplinary approach.

What are the tasks of the Paul Ehrlich Institute (PEI) and the state authorities here in Germany?

As a federal authority and national licensing authority for biomedicines, the PEI is legally responsible for all processes relevant to ATMPs – i.e. for authorizing clinical studies,

How many ATMPs have been approved in the EU to date?

Six products have been approved in the EU so far, and the process is underway for four others.

That is rather a low output.

Photo: MDC

Chair Tissue Engineering and Regenerative Medicine (TERM)

Artificial Vascularized Tissues

Implants with autologous cells are engineered by Tissue Engineering methods which minimize the body's own implant rejection. The hereby activated self-healing mechanisms result in tissue regeneration (Regenerative Medicine).

We develop human test systems as alternative tissue models to animal trials. Tissue specific bioreactors providing culture conditions of the cell's natural microenvironment in the body are created to ensure *in vitro* functionality of the used cells. A biological vascularized scaffold, the BioVaSc, is applied to generate vascularized

tissue *in vitro*. Tissue models as well as models for cancer or (infectious) diseases have successfully been set up.

Chair Tissue Engineering and Regenerative Medicine (TERM)

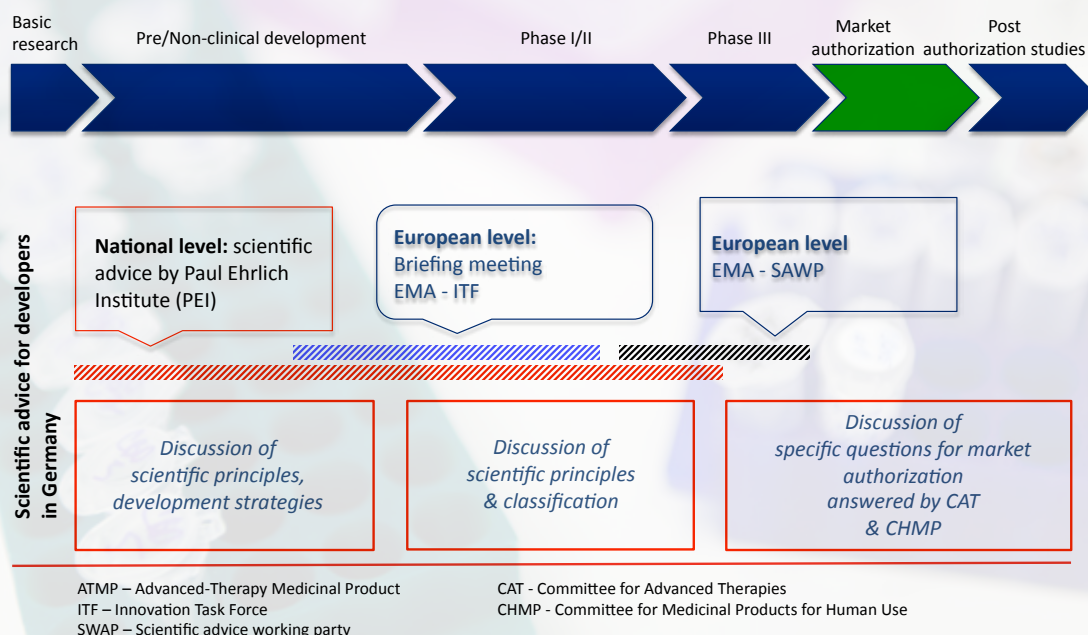
Universitätsklinikum Würzburg
Röntgenring 11
97070 Würzburg
www.term.ukw.de

Universitätsklinikum Würzburg UK
Lehrstuhl für Tissue Engineering und Regenerative Medizin



Tissue-specific bioreactors and incubators.

Stem cell-based ATMPs: The regulatory path to the European market



I don't see it that way. The number is appropriate for a field that is still in its infancy. It is important to remember that we are dealing with very complex, innovative, and scientifically oriented products. Not so many of those exist. And the number of applications is rising steadily. Authorizations in this field are just as rare in the U.S. and Japan as they are here in Europe.

There was of course an important premiere in April 2015, when Holoclar became the first stem cell therapy to be granted a marketing authorization in the EU. How does this product work?

Holoclar is a stem cell treatment used in the eye. It is intended for patients who have suffered damage to the surface of the cornea, for instance as a result of physical or chemical burns. Limbal stem cells are removed from the edge of the patient's cornea, cultivated in the laboratory, and then re-transplanted into the damaged areas. An Italian company manufactures the product. The clinical

data were convincing, with many patients experiencing improvements to their eyesight. The product was granted what is known as a conditional authorization. This means that additional confirmatory clinical studies are being run in several centers, including in Germany. The developers thus have to submit further data on the efficacy of the medicinal product.

What went well with Holoclar? What can future developers learn from it?

It was the fastest ATMP process that my team and I have handled so far. Once the application had been submitted, it took just one year to reach a decision. The manufacturer in Italy was very well connected and organized. Another plus point was that the scientific development work, which had lasted many years, was extremely good and transparent. Overall, that is the ideal basis for our regulatory work. It means we can still work if there are only limited data from non-clinical studies or if no randomized clinical trials have

Fraunhofer Research Institution for Marine Biotechnology EMB

Innovative research & development at the new institute building of the Fraunhofer EMB in Lübeck



For one year the Fraunhofer EMB is working now in the new institute building on the Lübeck Bio-MedTec Science Campus. The newly constructed building has got modernly equipped laboratories, aquaculture facilities, a food technology center and biobanks with fully automated state-of-the-art technology covering a total area of 8 292 m² (BGF). The technical re-equipment includes a X-ray microscope, a non-invasive small animal MRI as well as several 3D printer of the latest generation, which are used for the development of novel laboratory appliances.

"With these excellent research capacities we look forward to strengthening the life science expertise of the Fraunhofer-Gesellschaft. The new research building gives us the opportunity to explore promising topics for applied research and to promote existing business areas with the most modern equipment" concludes Prof. Charli Kruse, director of the Fraunhofer EMB. The Fraunhofer EMB works on industry-related research topics with focus on life sciences. Here, novel technologies, procedures and instruments for cell isolation and exploitation were developed. Moreover, the scientists from the

EMB work on innovative aquaculture systems and on the utilization of aquatic raw materials for food engineering. With the "Cryo-Brehm" the EMB maintains one of the largest archives for cell cultures from wild animals.

Fraunhofer-Einrichtung für
Marine Biotechnologie EMB
Mönkhofer Weg 239a
23562 Lübeck
www.emb.fraunhofer.de



been carried out. We are gaining many valuable experiences from the first approved stem cell product. This will certainly facilitate the process for subsequent applicants.

When it comes to developing a stem cell-based medicinal product, how important is the classification?

Classification first involves defining which medicinal track companies or universities are involved in their product. I think it is important that developers know this at an early stage. Seeking a recommendation for a classification is often the first contact that an applicant has with the relevant authority. However, an EMA classification – which takes about six weeks – is not a legally binding scientific recommendation. In Germany, the state authorities are responsible for legally classifying medicinal products. It is not an official task of the PEI, but since we obviously have specialist expertise in the field, the state authorities generally ask us for advice.

At the Paul Ehrlich Institute, you offer scientific advice to medicinal product developers. How does this work?

Since 2009, the PEI Innovation Office has been providing interested parties with advice on ATMP development at any time. Fortunately, many developers have shed their initial hesitance to make contact. We conduct about 50 advisory sessions a year. These might be intensive consultations similar to those held at the EMA, or they could be orientation discussions, which involve an informal chat without any major documentation. Seeking advice makes particular sense in the early phase of product development and in the run-up to clinical studies, as it can help developers avoid potential errors that will require a lot of extra work and money at a later stage. The costs are also attractive: the hourly rate per expert is just € 68.

After a marketing authorization has been granted, companies have to start grappling with the problem of cost reimbursement at a national level.

Unlike the authorizations, cost reimbursement is not organized centrally in Europe. Each country therefore decides how the costs of a therapy are to be reimbursed and who is responsible for it. We have comparatively generous reimbursements for cell-based therapies here in Germany. The situation is very different in other EU countries. That

can be frustrating for manufacturers. Take, for instance, Provenge, a tumor vaccine for prostate cancer that was authorized as an ATMP in 2013. The manufacturers of this immunotherapy have since withdrawn the EU marketing authorization because the future reimbursement situation in Europe was unresolved. Germany was the only EU country where health insurance providers reimbursed the costs. The EMA and PEI are now working very hard to include reimbursers in the scientific advisory sessions at an early stage – i.e. before the authorization process begins.

What does the term “hospital exemption” mean? How does the rule affect developers of stem cell-based therapies in Germany?

The exemption, which is anchored in the ATMP regulation, exists because a great deal of innovation happens in hospitals, and because local production and application are very common. The European Commission formulated the exemption in order to allow these non-routine applications to be used in hospitals in a very limited way. EU countries have taken quite different approaches to implementing it. Germany has implemented it in a very interesting manner, I think: once innovative products receive PEI authorization, hospitals can use them on patients to a limited extent. The manufacturing and processing can be done by a toll manufacturer.



Photo: MDC

The Collaborative Research Center SFB 873

Maintenance and Differentiation of Stem Cells

The Collaborative Research Center SFB 873 “Maintenance and Differentiation of Stem Cells in Development and Disease” at Heidelberg University works towards defining the regulatory principles underlying the balance between maintenance, expansion and differentiation of stem cells in diverse systems on a mechanistic level. To this end the SFB873 studies a wide spectrum of experimental models ranging from plants to human to elucidate the inherent properties of specific stem cell systems, but also to uncover common and divergent principles behind regulatory regimes and molecular signatures.

Our consortium brings together internationally recognized researchers, with unique scientific strengths in cell biology, biophysics, developmental biology, molecular medicine or modeling. With our research we hope to advance our understanding of principles underlying stem cell function and lay the foundation for translational approaches.

Centre for Organismal Studies (COS)

Im Neuenheimer Feld 230
69120 Heidelberg
www.sfb873.de





The manufacturer has to be in Germany but does not have to be located in the hospital. This creates interesting possibilities for specialized companies. In Germany, seven developers have so far been granted a national exemption under Section 4b of the country's Drug Law. Nevertheless, our feeling is that the hospital exemption is a step along the way toward a central marketing authorization – and should remain an exception.

Interview: Philipp Graf

Suggested reading

Egbert Flory, Paolo Gasparini et al. (2015), "Regulatory viewpoints on the development of advanced stem cell-based medicinal products in light of the first EU-approved stem cell product", *Cell & Gene Therapy Insights*, DOI:10.18609.cgti.2015.010

What are ATMPs?

Cell-based medicinal products that contain living or non-living cells and were engineered during manufacturing are legally classified as Advanced Therapy Medicinal Products (ATMP) in the EU. The European Medicines Agency (EMA) is responsible for the marketing authorization of these products. ATMPs are divided into different classes: gene-therapy medicines, tissue-engineered products, somatic-cell-therapy medicines, and combinations thereof. Six products have been granted a marketing authorization in the EU since the ATMP regulation entered into force:

Product name	Manufacturer	Year of EU marketing authorization
ChondroCelect	TiGenix	2009
Glybera	UniQure	2012
Provenge	Dendreon	2013 ¹
MACI	Genzyme	2013 ²
Holoclar	Holostem Advanced Therapies	2015
Imlygic	Amgen	2016

¹ Since withdrawn at manufacturer's request

² Suspended due to manufacturing stoppage

Disclaimer: Please take notice, that the online version of the interview is slightly different to the printed version due to further editing.



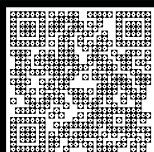
DISTRIBUTED IN AUSTRIA, GERMANY AND SWITZERLAND BY PELOBIOTECH GMBH.



ReproCELL Stemgent® microRNA Technology for Enhanced mRNA Reprogramming

Enhances, and simplifies mRNA reprogramming for fast, efficient iPS cell line generation from difficult to reprogram cell lines.

- Improved efficacy on hard-to-reprogram or refractory cell types
- Cost-effective, fast reprogramming kinetics
- Streamlined protocol



REPROCELL GROUP COMPANIES



bioserve



stemgent



reinnervate