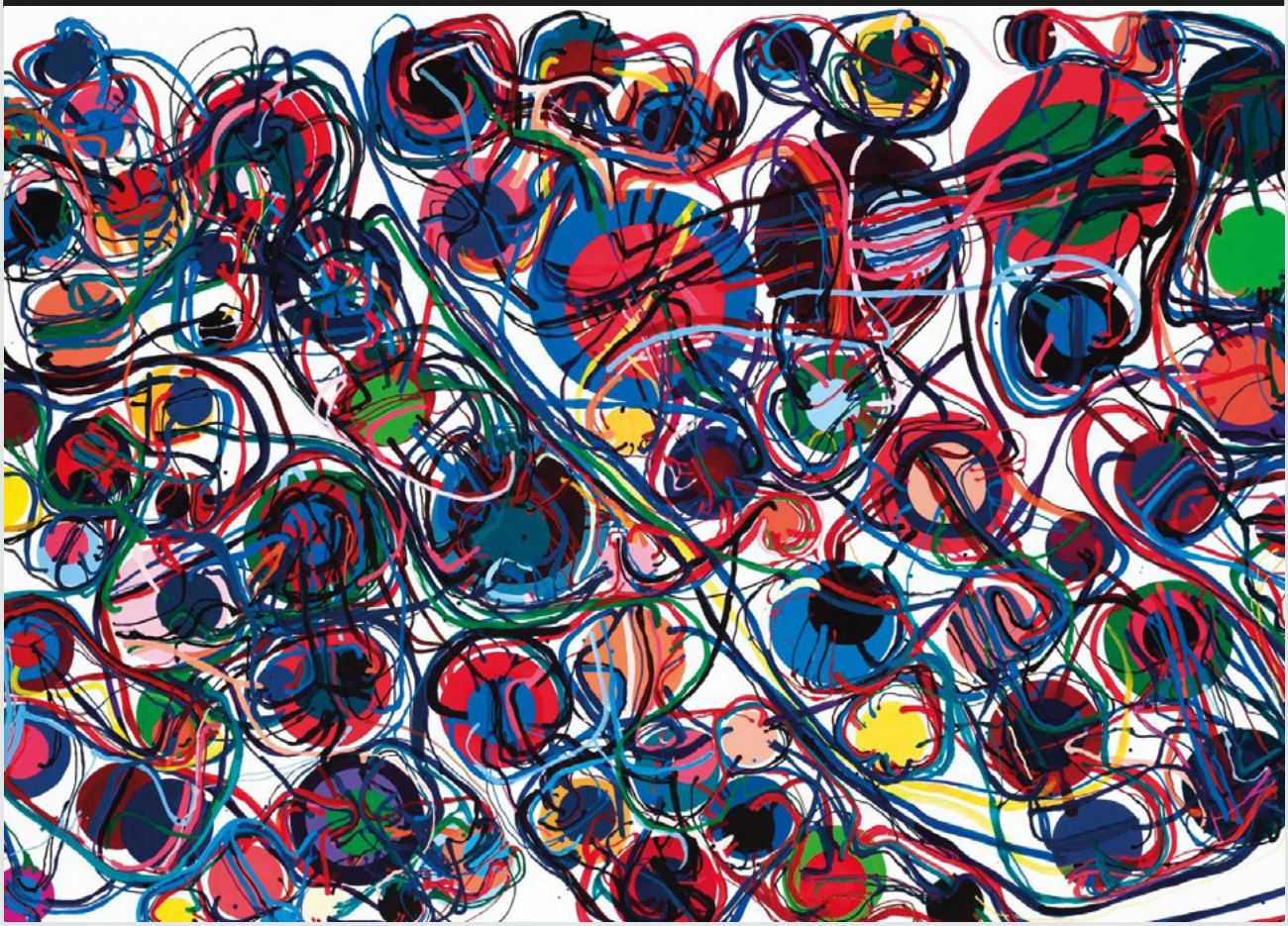
PHARMA BOARDROOM

InFocus

Cell & Gene Therapy



DECEMBER 2020

In collaboration with: NOVARTIS

Contents

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In collaboration with Novartis.

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Preface

As innovative pharma continues to invest heavily in high-risk frontier research involving stem cells and the harnessing of a patient's own immune system to attack the onset of a disease, a brave new world of potentially curative treatment possibilities is unfolding. This has become most evident in fields like oncology where expensive, yet thoroughly transformative CAR-T therapies are displacing classic treatments and offering newfound hope to patients where previously there was none.

Yet, although cell and gene therapy has already become a powerful new engine of value creation for patients and heralds a paradigm shift in the treatment of some of the world's most devastating and intractable illnesses, widespread uptake of these game changing technologies remains, thus far, elusive. Through the comments of top regulators, HTA bodies, and leading industry executives, this e-book strives to look in detail at some of the outstanding bottlenecks and challenges to adoption, while considering potential solutions.

US FDA APPROVED CELL & GENE THERAPY PRODUCTS

ALLOCORD (HPC, CORD BLOOD)
SSM Cardinal Glennon Children's Medical Center

CLEVECORD (HPC CORD BLOOD)
Cleveland Cord Blood Center

DUCORD, HPC CORD BLOOD
Duke University School of Medicine

GINTUIT (ALLOGENEIC CULTURED KERATINOCYTES AND FIBROBLASTS IN BOVINE COLLAGEN)
Organogenesis Incorporated

HEMACORD (HPC, CORD BLOOD)
New York Blood Center

HPC, CORD BLOOD
Clinimmune Labs, University of Colorado Cord Blood Bank

HPC, CORD BLOOD - MD ANDERSON CORD BLOOD BANK
MD Anderson Cord Blood Bank

HPC, CORD BLOOD - LIFESOUTH
LifeSouth Community Blood Centers, Inc.

HPC, CORD BLOOD - BLOODWORKS
Bloodworks

IMLYGIC (TALIMOGENE LAHERPAREPVEC)
BioVex, Inc., a subsidiary of Amgen Inc.

KYMRIAH (TISAGENLECLEUCEL)
Novartis Pharmaceuticals Corporation

LAVIV (AZFICEL-T)
Fibrocall Technologies

LUXTURNA
Spark Therapeutics, Inc.

MACI (AUTOLOGOUS CULTURED CHONDROCYTES ON A PORCINE COLLAGEN MEMBRANE)
Vericel Corp.

PROVENGE (SIPULEUCEL-T)
Dendreon Corp.

TECARTUS (BREXUCABTAGENE AUTOLEUCEL)
Kite Pharma, Inc.

YESCARTA (AXICABTAGENE CILOLEUCEL)
Kite Pharma, Incorporated

ZOLGENSMA (ONASEMNOGENE ABEPARVOVEC-XIOI)
AveXis, Inc.

Source: FDA

JAPAN PMDA APPROVED REGENERATIVE MEDICINE PRODUCTS

BRAND NAME	GENERIC NAME	APPROVED
Collategene	beperminogene perplasmid	March 2019
HeartSheet	human (autologous) skeletal myoblast-derived cell sheet	September 2015
JACC	human autologous tissue for transplantation	July 2012
JACE* Initial Approval	human (autologous) epidermal cell sheet	October 2007
JACE Partial Change Approval	human (autologous) epidermal cell sheet	September 2016
JACE Partial Change Approval	human (autologous) epidermal cell sheet	December 2018
Kymriah	tisagenlecleucel	March 2019
Nepic	human (autologous) corneal limbus-derived corneal epithelial cell sheet	March 2020
Stemirac	human (autologous) bone marrow-derived mesenchymal stem cells	December 2018
Temcell	human (allogeneic) bone marrow-derived mesenchymal stem cells	September 2015
Zolgensma	onasemnogene abeparvovec	March 2020

* This product was approved as a medical device under the previous regulatory framework.

EMA APPROVED ADVANCED THERAPY MEDICINAL PRODUCTS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NAME	DEVELOPER	INDICATION	APPROVAL DATE	STATUS
Zynteglo	Bluebird bio	Beta-thalassemia	June 2019	Conditional approval
Luxturna	Spark Therapeutics	Retinal dystrophy	September 2018	Approved
Yescarta	Kite Pharma	Blood cancer	August 2018	Approved
Kymriah	Novartis	Blood cancer	August 2018	Approved
Alofisel	TiGenix	Perianal fistulas in Crohn's disease	March 2018	Approved
Spherox	CO.DON	Cartilage defects in the knee	May 2017	Approved
Zalmoxis	MolMed	Stem cell transplantation in high-risk blood cancer	June 2016	Approved
Strimvelis	GSK	ADA-SCID	April 2016	Approved
Imlygic	Amgen	Melanoma	October 2015	Approved
Holoclar	Chiesi	Severe limbal stem cell deficiency in the eyes	March 2015	Approved
Provenge	Dendreon	Metastatics prostate cancer	October 2013	Withdrawn in 2015
MACI	Vericel	Cartilage defects in the knee	July 2013	Withdrawn in 2014
Glybera	uniQure	Lipoprotein lipase deficiency (LPLD)	November 2012	Withdrawn in 2017
Chondrocelect	TiGenix	Cartilage defects	November 2009	Withdrawn in 2016

Source: Labiotech.eu

EMA: RETHINKING THE SYSTEM

EMA's Head of Advanced Therapies Dr Ana Hidalgo-Simon outlines Europe's evolving regulatory framework for regenerative medicines and touches on ethical and pricing challenges

Dr Ana Hidalgo-Simon
head of Advanced Therapies, EMA

In the US, the work on regenerative medicines has really been driven by the 21st Century Cures Act, which outlined a clear direction for the US FDA. What are for Europe the guiding principles of your work at the Office for Advanced Therapies?

ANA HIDALGO-SIMON (AHS): As you alluded to, the systems in the US and Europe are completely different, to the point that even the definitions for these therapies are different: regenerative therapies versus advanced therapies. Our legislations are also different.

The basic principle is that we want these medicines to be used by the patients, not merely available in the market. That is quite a departure from the traditional approach where regulators would not worry about the commercial viability of a product. However, for advanced therapies, market approval is not the end of the journey, and we really want to reach the final destination, which is having patients benefit from these therapies. Access is fundamental.

The other aspect of advanced therapies is that we realized that we need to engage and work with academics a lot more because many of the ideas and initial research actually come from that community, who have not traditionally been commercial drug developers. Therefore, they are less familiar with the regulatory and clinical development processes, the post-authorization requirements, large-scale clinical trials, etc. At the same time, because patients are more involved in the development, there is a seminal role for them to play as well. Even before the formation of the Office for Advanced Therapies, EMA's Committee for Advanced Therapies (CAT) included patient and healthcare professional representatives as full members, with full voting rights.

At EMA, among other incentives and support tools for developers, we have the PRIME scheme, which is intended to enhance the support for the development of medicines that target an unmet medical need, including but not limited to advanced therapies. However, due to the revolutionary nature of advanced therapies, we have noticed that around half of all PRIME products are now advanced therapies, and this is because the scheme works very well for these advanced therapies, facilitating early dialogue and scientific advice, with numerous benefits for sponsors. For instance, we appoint a rapporteur from the Committee on Advanced Therapies to provide continuous support, and we also provide scientific advice at key development milestones.

What are some of the main ethical challenges your office has faced in regulating advanced therapies?

AHS: One of the main issues is how to deal with out-of-specification therapies, i.e., when an advanced therapy presents one or more parameters that fall outside the authorized specifications. This is not an uncommon occurrence. The ethical dilemma is that you have a product that falls outside established parameters, but has been produced using the

patient's own material, and sometimes the patient's condition is so severe that they are running out of time. The argument is whether the product should be used on the patient anyway? This is a very difficult choice, and it requires a dialogue between the patient and their doctor, certainly. From our side, we are always trying to avoid this scenario, and we work with sponsors closely to ensure that we define the best product specifications. We cannot have specifications so tight that products fall out of them frequently and materials are wasted but we also need to ensure that we have efficacious and safe therapies. At the end of the day, we need to set some parameters – and to do that well, we have to work very, very closely with all the stakeholders.

With how new this field is and how quickly it is advancing, how does EMA stay on top of all the new developments?

AHS: Firstly, we draw upon all the national experts that are exploring these areas. Their systems and processes are not uniform, but they are working with their own national experts and academics, and our committees draw representatives from each country to bring all of their expertise together. The work of EMA is very much of coordination, alignment and compensation, and through that, we have insights into the upcoming and ongoing innovations.

For instance, we know that gene therapy is rapidly dominating this space, and we have access to a lot of scientific and academic advice and research. We also see that many new innovations, for instance, like drug-device combinations and health wearables and so on, no longer fall into clear-cut categories of drug, device or other. The field is evolving, and the boundaries are blurring, so we are also preparing for this, partly through the recruitment of experts – though not so much now due to the COVID-19 situation – and partly through our dialogues and exchanges with national regulators, who are themselves exploring these areas.

There are many players in these new areas, from Big Pharma companies to small- and medium-sized enterprises, many of whom are spin-offs from academic and research institutions, so in that context, working with academics and other experts also helps us avoid duplicating research or reinventing the wheel. Through all these efforts, we have become much better at outlining and anticipating the regulatory science for these new areas. We also have our regulatory strategy to 2025, at EMA level and soon at EU level, overarching all national agencies.

You highlighted that access is fundamental for the Office when it comes to advanced therapies- to avoid approving therapies that then never reach patients. Since in Europe it comes down to the national health systems and payers when it comes to pricing and reimbursement, is there any means of coordination regarding access to approved therapies?

AHS: Access and affordability are fundamental worries for patients. The new Executive Director of EMA, Emer Cooke, has made it clear in her initial weeks that these are our main concerns. Traditionally, indeed, pricing and reimbursement are not responsibilities of EMA because these are set by national authorities. But we have started to have conversations with various stakeholders, including HTAs and payers at the EU level. Actually, this work began a few years ago. The idea is that the systems in these countries are already quite scattered, but we can help in certain ways. For instance, we spoke to the European Network for Health Technology Assessment (EUnetHTA) about the kind of information they need to make their decisions, so we could discuss how we could align our requirements. This would help drug developers and sponsors collect and arrange their data in an efficient way that would still meet all of our needs at the same time. We cannot just think about ourselves in isolation, we are pieces of a larger puzzle.

> "We need to rethink the system to ensure not only that a medicine is approved but also that it stays on the market."

We need to rethink the system to ensure not only that a medicine is approved but also that it stays on the market. There have been cases of advanced therapies, approved ten years ago, that were no longer available because the manufacturer considered them no longer commercially viable. We have to work harder to ensure that these therapies ultimately reach the patients.

THE BUILDING BLOCKS OF GENE THERAPY

Dr Peter Marks, director of the US FDA's Center for Biologics Evaluation and Research (CBER) examines the successes of the Regenerative Medicine Advanced Therapy (RMAT) designation since its introduction in 2016 and outlines the importance of a regulatory & scientific infrastructure for gene therapy manufacturing.

Dr Peter Marks
director, Center for Biologics Evaluation and Research (CBER), US FDA

On what the RMAT Designation is...

The RMAT designation is very much like the Breakthrough Therapy designation but with certain features targeted for regenerative medicine products. The first is that, as opposed to the criterion for Breakthrough Therapy designation that requires the product be better than an existing standard of care, for the RMAT designation, the company simply has to show evidence of activity against the disease in question, instead of showing that the therapy is better than a standard of care. The second is that, should a therapy with RMAT designation be approved under an accelerated approval pathway, which would then require a confirmatory trial, there is an extended array of ways of fulfilling that post-approval commitment. Under standard rules, one cannot simply follow the same patients in the registrational trial for a longer period of time. But for RMAT designated therapies, that is an option.

To illustrate, imagine a hypothetical therapy in which replacement bladders are made by seeding cells on scaffolds. If the therapy receives RMAT designation and a clinical trial is performed, after six months of appropriate replacement bladder functioning, we could grant it accelerated approval but we might want to see how the bladders would continue to function after a year or two, so we would be able to simply ask the sponsor to return in six months or another year with more data on that same group of patients.

On reduced approval numbers compared to exorbitant amount of applications...

We have received a large number of applications, especially in the area of cell-based regenerative medicine, but many were requested early on in the development process. It takes time for these products to work their way through, and it is a young field as well, which tends to have more products that do not make it through the entire product development process. We know the statistics of product development: only about 10 percent of the therapies that make it into Phase 1 trials will ever see the light of day. Cell therapies are not all that different at this point. I am sure we will see some in the near future, but it is taking a little longer than might have been thought.

On developing a regulatory & scientific infrastructure for gene therapy manufacturing...

We are very interested in helping to move the field forward by looking at how one can develop gene therapies for small patient populations and also how to do that in what would ultimately be a commercially viable manner. Right now, gene therapy populations that include fewer than 100 patients treated per year are important targets for development. However, due to the expenditures involved in R&D, approval and commercialization, these therapies are not seen as commercially viable targets for companies. On the other hand, if regulatory frameworks and science could be developed for the manufacture of gene therapies, such as reusing certain vectors and changing out inserts, or the use of common manufacturing protocols and techniques, manufacturing costs could be reduced sufficiently to interest more companies into working on gene therapies for patient populations of 50 or 100 people. That could make a big difference in people's lives.

EUnetHTA: SEPARATING THE CHALLENGES

Niklas Hedberg outlines how EUnetHTA has adapted to cell and gene therapies, squaring the affordability circle, and why discussions about value assessment, cost effectiveness, payment, and financing models are all separate discussions to be resolved.

When confronted with paradigm-shifting cell and gene therapies, what questions has EUnetHTA had to ask itself and its peers?

NIKLAS HEDBERG (NH): We have had to relate to new kinds of evidence which are structured in new ways. For example, there has been a need to handle umbrella, basket, and single-arm trials as grounds for medical approval; meaning that the clinical trial paradigm has been turned upside down.

Over the past five to ten years, we are, on national and regional level, increasingly being asked to grant reimbursement for products where the data is based on Phase I studies, even though, traditionally these studies only included healthy volunteers. This is especially true of new products in oncology, orphan drugs and precision medicine.

Niklas Hedberg
chair of the Executive Board, EUnetHTA

This is of course challenging but we must not forget the basic tools with which we start every assessment. In the national setting at TLV we had our first experiences with CAR-T about two years ago. Then we realised that many of the challenges we were facing were also those facing us in assessing traditional products. The difference is that these uncertainties were multiplied by a larger number for cell and gene therapies.

After that, since medical approval had already been granted, we had to focus on follow-up data and evidence generation and how we were able to make wise decisions now that are still meaningful for the downstream decision maker. We must maintain the triangle of relevance, predictability, and flexibility.

If the HTA always says that more research is needed and that the data is too weak to draw any conclusions, then downstream stakeholders like regions, individual clinics, and clinicians will have to meet the patient and make decisions without us. Therefore, TLV has preferred to say that an assessment result is very uncertain and that it is of utmost importance to follow-up and generate further data. Clinicians should know that they have a responsibility, if they want to use an expensive new drug, to make sure that we can follow up the results.

How do you foresee the evolution of these therapies impacting your work and how are you planning to square the affordability circle?

NH: I need to look into the pipeline more and update my horizon scanning a bit, but we will probably be having this same discussion for the upcoming three to five years. There will be an ever-increasing number of products and an increas-

ing number of patients, but ultimately, they will still serve only fairly small patient groups.

In the longer run of the next eight to ten years there needs to be a shift, as even the wealthier nations are challenged on affordability. I cannot see how, in general, we will be able to afford all these interventions with the prices that they come with today.

That is a tremendously difficult discussion. Right now, we can still afford the discussion that perhaps we haven't put all the value components into the equation. Perhaps we need to rethink how we do the analysis. But in the long run, for equitable care, more and more people are starting to talk about national responsibility for these therapies rather than the responsibility lying with individual hospitals.

I am not going to judge whether that is a positive or negative development, but the national money also needs to come from somewhere. National budgets will also have their limits. I am seriously worried about the affordability of precision medicines if we don't start talking about a shift to something more sustainable for developers, patients, assessors, and payers

What would you like developers, regulators, and other stakeholders to keep in mind about cell and gene therapies moving forward?

NH: We are trying to formulate that there are different and separate challenges. The first challenge is a just assessment of the value of a product. There are a number of difficulties there, including the assessment of new kinds of evidence or putting a value on a product that may be given in combination with another.

Then there needs to be a discussion and an agreement on how to evaluate cost effectiveness. Although not all countries work with cost effectiveness, there are questions around how calculations and analysis is done and what can be brought in from the value and costing discussions.

The third challenge is different payment models, whether they are made based on assumptions or results and how they are discussed.

Finally, there also needs to be a discussion about financing models; how is the money going to be paid, when, for what kinds of results, and where is it going to come from?

It is useful not to mix these discussions, but to realise and clearly state that these are different kinds of discussions. We must try to solve them all. Just going in very fiercely to the discussion about value and cost effectiveness does not solve the financing issue.

The Future of EUnetHTA

"Three years ago, the EC produced the first proposal on the future model for HTA. After the political decision-making that is still ongoing in the Council of the European Union after a number of different presidencies, it seems that during the end of the German presidency (July-December 2020) and the beginning of the Portuguese presidency (January-June 2021), an agreement will be struck and a decision made about which HTA regulation Europe will adopt in the future.

"That means that the project base and the joint action base might eventually come to an end. But hopefully the network will remain, where we have a pool of participating agencies, communication and information exchange, interaction, and mutual learning.

"It is not possible to entirely say [if there be a mandated law about HTA assessment across Europe] because discussions among member states in the Ministerial Council are still ongoing, but it will not be a fixed entity like the European Medicines Agency (EMA); it will not be a new EU agency. It will probably be a Secretariat, under the Commission, but we will have to wait and see. However, we can say that there will be more explicit regulation on how the network partners from different Member States act and work."

TRULY TRANSFORMATIVE

Stefan Hendriks, Global Head of Novartis Oncology's Cell & Gene division outlines the company's progression to becoming the global leader in cell and gene therapies, the strategy he has outlined for the business, and the key issues of manufacturing and access.

Stefan Hendriks
Global Head, Cell & Gene, Novartis Oncology

Novartis Oncology is the global leader in cell and gene therapies. What do you see as the major milestones of Novartis Oncology's journey within this space?

STEFAN HENDRIKS (SH): Cell and gene therapies are truly transformative. With CAR-T therapies, we are entrusted to work with a patient's own living T-cells. That is a huge responsibility as we have to know where the cells came from and monitor them carefully every step of the way. Within the pharma industry, companies always try to be patient-oriented but with cell and gene therapies, that has to be a part of our DNA because we are working with the patient's own living cells! That sense of purposefulness and responsibility is truly amazing and inspiring, and it does not end with the extraction and manufacturing process, it also carries forward to the distribution, to the services we provide, and to our partnerships with hospitals, all of which are essential if patients are to benefit from these transformative therapies.

There have been many defining moments for us. We have seen so many firsts: our therapy was the first CAR-T to reach the market, it was the first CAR-T to be approved for two indications, and it was the first CAR-T to reach global markets, with initial approvals after the US and Europe in Canada, Australia, Japan and a couple of other Asian markets – and more coming. Today, this therapy is reimbursed in 27 markets globally and we have onboarded, qualified and trained over 285 hospitals in the world. I am very proud of that.

Being the first mover in these markets, our teams had to partner with local healthcare systems and payers to explain the value of CAR-T and to find innovative ways to create access for patients. Healthcare systems are not built for one-time, potentially curative, treatments so there was a period of acclimatization. Value is also defined differently in each market so it was essential to listen and understand our partners in order to create a common understanding of the value that CAR-T therapies can deliver, and then to develop and offer innovative models to support access.

Another significant achievement is that we have now built the largest and most comprehensive manufacturing platform for cell and gene therapies in the world. We currently have five – soon to be six – active manufacturing sites across four continents.

What strategy have you outlined for the business moving forward?

SH: From all my previous roles, I have learnt that it is essential to define clear and strategic focus areas for any business, to ensure that cross-functional teams are working seamlessly together. Once the teams know their North Star, they can be empowered to work towards it.

We have identified three strategic pillars for the business. The first is the commercialization of CAR-T therapies, which means ensuring that we bring them to as many patients as we can, across different areas. We are currently running six CAR-T clinical trials and we are looking to add a couple more indications.

The second is ensuring that our manufacturing is competitive in terms of process robustness and capacity, which is why, as I mentioned, we have established a number of sites, this year in France, Switzerland and Japan, and we expect the sixth to be open in Australia in the coming months.

The third is creating an exciting pipeline. Even as we focus on commercialization of approved CAR-Ts, we also need to dedicate resources to build our portfolio. We are working on a next-generation manufacturing platform that has the potential for higher efficiencies, shorter turnaround times and hopefully better outcomes. It will also allow us to preserve a different subtype of T-cells that we believe will have a positive impact on durability of efficacy. Using this platform, we are developing a portfolio of novel CAR-Ts, addressing multiple antigen targets across different malignancies.

We are also constantly scanning the business landscape and speaking with other players to identify interesting areas for partnership, for instance, in solid tumors or in allogeneic CAR-T therapies. We are definitely willing to invest if we see the right opportunities.

We are also looking to partner on the data front. We have generated a lot of manufacturing and clinical data, as well as real world evidence (RWE), so we have started to partner with IT players such as Microsoft on AI, as well as Carnegie Mellon University (CMU) to develop advanced analytical models. All these efforts are intended to further improve the cell and gene development and manufacturing processes so that we can provide better outcomes for patients.

When we spoke to the FDA and EMA regulators on cell and gene therapy, both emphasized the importance of manufacturing and close collaboration with industry on this topic. What is your perspective on this?

SH: I agree with them. As I alluded to, since we were the first to launch a CAR-T therapy, we were also the first to build a great collaborative partnership with regulators across the world. We had the opportunity to learn together, and there is still a lot to learn regarding what it takes to deliver safe and high-quality products to patients. We have made significant progress on this over the past few years, and I am particularly proud that we have been able to open and qualify multiple manufacturing sites even through the global pandemic. We are also generating and analyzing manufacturing data to identify opportunities to make the manufacturing process even more robust, again in collaboration with the regulators.

One of the learnings we have gained is that we should have a nice mix of in-house manufacturing capabilities and external partnerships. We need the former because we need to build that manufacturing expertise ourselves, but we also need to enrich and complement those in-house capabilities, which is why we have formed collaborations with, for instance, Fraunhofer-Institut for Cell Therapy and Immunology in Germany, the Foundation for Biomedical Research and Innovation (FBRI) in Japan, Cell Therapies in Australia, and Cellular BioMedicine Group (CBMG) in China. When it comes to these partnerships, geography is not as important as the expertise and experience of our partners. We are looking for companies and institutions with the same value and quality standards that Novartis holds.

It is also important for us to develop an extensive manufacturing network globally - that is part of our mission to deliver these transformative therapies to more patients around the world. We went as broadly and as quickly as we could to build our global capacity in a balanced manner.

Novartis Oncology has been working to expand access to CAR-T therapies globally. One of the initial concerns in the US and Europe when CAR-T therapies reached the market, was their price Are you seeing similar concerns in other regions?

SH: Not particularly. It comes down to the quality of dialogue we build over value. The total value of CAR-T therapies as a one-off treatment that is potentially curative, that could eliminate the need for any future therapies and health services, that would allow patients to return to normal lives, is transformative. We have been able to leverage our experience of commercializing and launching CAR-T therapies in the US and Europe. We bring those learnings to other markets when it comes to engaging with payers and regulators. It is about building that dialogue about what value means to them, understanding their challenges, and then finding innovative solutions and models.

> “Since we were the first to launch a CAR-T therapy, we were also the first to build a great collaborative partnership with regulators across the world”

As long as we focus on patients and finding solutions to help them, we can go a long way. If you think about how fast we have entered the 27 markets where patients can now access approved CAR-T therapies, that is about as fast as – or even faster than – normal oncology products. But different countries have different needs, and of course, not all countries have the necessary level of technical advancement to implement cell and gene therapies either.

In general, we have seen a lot of excitement around our CAR-T therapies. Regulatory authorities globally have been very collaborative and responsive. There is a lot of enthusiasm.

A WIN-WIN CAR-T COALITION?

Professor Nicolaus Kröger, president of the European Society for Blood and Marrow Transplantation (EBMT) introduces the multi-stakeholder GoCART Coalition and the impact that it stands to have on the cell and gene therapy field in Europe.

Prof Nicolaus Kröger
president, European Society for Blood and Marrow Transplantation (EBMT)

Can you share more about the mission of EBMT and the motivation for establishing this Coalition?

NICOLAUS KRÖGER (NK): EBMT was formed in 1974, when stem cell transplantation was still a very new technology. It had been developed by academics and was a very complex and potentially dangerous treatment. A number of small centres in Europe were administering this treatment but because they only saw around ten to 15 patients, they decided it was better to work together. As a society, we then also created a registry to collect all the data. This allowed us to perform more clinical studies and deliver more results to the community about the results of this therapy for different indications.

EBMT has grown over the years to include over 500 centres around the world, with over 600,000 stem cell transplants within our registry.

In terms of cell and gene therapy, we had also done a lot of research on this, and we had received permission from health authorities to advance our research, but nothing was actually approved by regulators. The tipping point came when Drs Joseph Murray and Donnall Thomas jointly won the Nobel Prize for Medicine in 1990 for discoveries relating to organ and cell transplantation. However, it was recognized that such cells could have therapeutic effects but also that they might have side effects, so researchers started to work on developing or modulating cells, and this sparked the beginning of genome editing and the manipulation of T-cells. For the first time, the industry took an interest, and Novartis was the first company to really commercialize a product in this therapeutic modality. That acted as some sort of starting signal for the industry, and now many companies are working on CAR-T therapies, and cell and gene therapies in general. For the first time ever, cell therapies have become commercial.

Cell therapies are also very interesting because they are a type of living drugs, since the cells are alive within the patient, unlike conventional medicines, which are metabolized by the body. As a result, they are also potentially curative in nature, so they are a great treatment option.

But we also recognize there is a big hype surrounding them, so we thought it would be great to advance the field by establishing a CAR-T registry across Europe. This was also important because there are so many stakeholders involved in cell and gene therapy. We have disease-specific groups, medical groups, industry

> “We understand that different stakeholders have different interests. The idea is to generate some consensus that can benefit everybody”

groups, regulatory authorities, payers, hospitals and so on. A CAR-T registry could be of interest to all of them, so we decided to establish the GoCART Coalition.

How challenging is it to bring all these different stakeholders together within the Coalition?

NK: For us, it was critical to build a coalition that is win-win for everyone. It is challenging because there is so much competition in the field, within the industry but also within the academic community, since we compete on publications, impact factors and so on. Therefore, we wanted to be careful about how we approached this. The first thing we did was to reach out to the European Hematology Association (EHA), which had always been a competitor of sorts. The idea was to show that, if two major scientific societies for hematology and stem cell transplantation in Europe could work together, other competing groups across academia, industry and elsewhere would also work together.

We understand that different stakeholders have different interests. The idea is to generate some consensus that can benefit everybody – and especially patients, who are the most important stakeholders at the end of the day. We are still at the beginning and there is still some uncertainty and reluctance, but we can only succeed if we work together. Nobody will win by doing it alone.

In terms of the structure, we have ownership of the registry, but we allow each centre to take their own data from the registry and analyse it. Through the registry, we can also offer services like benchmarking, quality systems, certification and so on. For instance, if a centre comes to us with their own data, we can also provide them with the other data we have so they can compare their own performance and outcomes and identify potential areas for improvement.

What do you envision as the initial impact of this coalition over the next few years?

NK: I expect Europe to become the third player in cell and gene therapy in the world, after the US and China. I hope this will happen but I think we need something like the GoCART Coalition to bring everyone together. In the US, yes, there are different universities and states but at the end of the day, it is still a country with a federal system. China has a more unified system as well, whereas in Europe we have different nations, cultures and different regulations as already mentioned above, it is a question of finding consensus.

Our idea is therefore to bring all the stakeholders together – payers, regulators, industry, academics, patient groups, healthcare practitioners and so on – where they have access to data, and then hopefully based on that we can harmonize our approach to cell and gene therapy, and then in the longer run, we hope to be able to harmonize this with other regions, especially the US and Asia.

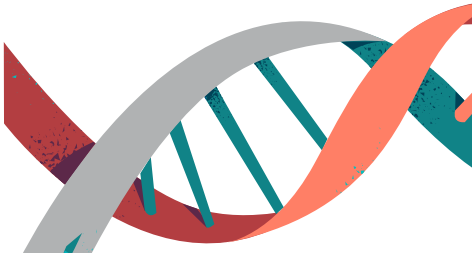
This is also important because medical centres and hospitals have to be trained to administer cell and gene therapies. Currently, each company has their own process. Imagine if you have ten approved products from ten manufacturers, the hospitals have to undergo ten different training programs, which is a little impractical. We need to have a qualification or accreditation system to certify hospitals in a standard way of administering such therapies.

We have created different working groups within the Coalition and one of the aims is to develop a common educational program. Once we do this, we can reach out to regulators to see if it can be approved. This would make things much easier for hospitals and healthcare practitioners.

We are still at the beginning of our journey and we expect to grow further.

Thomas D. Szucs, European Center of Pharmaceutical Medicine at the University of Basel; Hirslanden Private Hospital, Switzerland; Chairman, Helsana Group

HOSPITALS: KEY TO THE EVOLUTION OF GENOMIC MEDICINE



Genomic medicine expert Professor Thomas D. Szucs examines how payers and authorities are adapting to the strain on resources that genomic medicine can contribute to and whether a truly sustainable system can be forged.

Genomic medicine requires a lot of resources and expertise throughout the healthcare system. How are payers and hospital systems adapting to this?

THOMAS D. SZUCS (TS): This is a broad question. Certainly, the evolution of genomic medicine needs to be accompanied by the willingness of the hospital system – and to some extent, the payer system as well – to embrace these new technologies. Speaking for the hospital group where I work, we are investing heavily in this space. For instance, we have decided to establish our own genetic testing lab and develop our own sequencing capabilities. This means we will have faster turnaround times and quicker results.

We also want to involve many clinicians across the 17 hospitals that are part of the group. We are really accelerating our efforts to adopt the use of precision medicine. That being said, we cannot accomplish this from one day to the other, a lot of education and training is required to upskill our clinicians because while precision medicine is becoming more mainstream, it is still a new science. We need to communicate with our clinicians, so they understand how to use and are comfortable with using these new technologies.

Can you give any examples of this?

TS: For instance, with CAR-T therapies and some of the gene therapies that are emerging, one of the most important aspects is that we have the buy-in of clinicians. This means understanding the technology, understanding the patient need, but also adapting to more interdisciplinary discussions. Increasingly, I think we will be discussing the question of whether the patient should receive a specific therapy in dedicated tumor boards that will be much more molecularly driven. We have seen some great results from CAR-T therapies, and some are definitely breakthrough treatments, but we still have to see whether they are best used as first-line, second-line or third-line therapies.

I currently run the genomic board at the Hirslanden hospital where I work, looking partially at genomics in both oncology and non-oncology areas. CAR-T therapies are so far concentrated in the oncology space but we know that there is a possibility that such therapies could also work in the non-oncology areas, so ultimately it is important to take an interdisciplinary approach when it comes to identifying the best treatment for each patient.

Certainly, the administration of such therapies will be confined to hospitals that are equipped and able to understand the entire patient pathway. They would need to have the capabilities to manage patients in advanced disease stages.

Prof Thomas D. Szucs
European Center of Pharmaceutical Medicine at the University of Basel; Hirslanden Private Hospital, Switzerland; Chairman, Helsana Group

Thomas D. Szucs, European Center of Pharmaceutical Medicine at the University of Basel; Hirslanden Private Hospital, Switzerland; Chairman, Helsana Group

Many academics and stakeholders have argued that healthcare systems might be able to afford a couple of these but certainly not thousands CAR-T therapies with price tags of that can reach the USD 1 million each. If we are moving towards an environment of increasingly personalized therapies, is this sustainable? What are your views on this?

TS: I can share the current Swiss approach. CAR-T therapies are currently being reimbursed based on a contractual approach directly with the manufacturers. It is not as straightforward as simply having the CAR-T therapies on the reimbursement list and the reimbursement being automatic. The process is actually strictly regulated, and it is a contractual agreement between the payer and the manufacturer, where the price is agreed upon and so on.

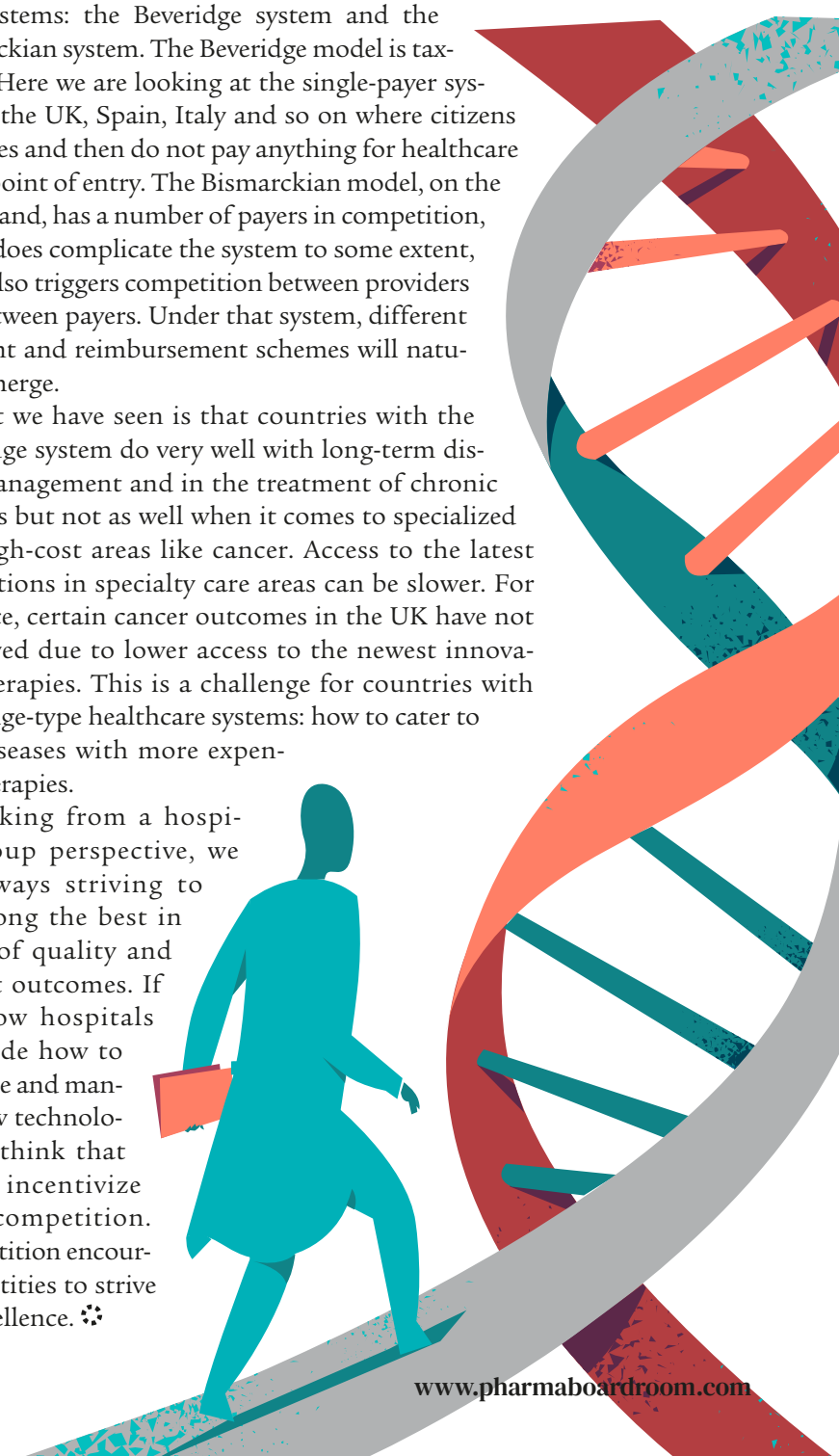
The fundamental question is whether the current provision model is sustainable for large volumes. It is not too futuristic to imagine that the engineering of the T-cells could eventually be done closer to the patient in the hospitals. With autologous CAR-T therapies, where the patient's own T-cells are extracted, this may be more challenging because of time and space constraints, since hospitals are not equipped to manufacture hundreds of CAR-T doses, but this may be feasible with allogeneic CAR-T therapies, because the doses could be pre-manufactured and there may be more economies of scale. We can look at it as 'off-the-shelf' CAR-T therapies that can perhaps be shipped more easily and across longer distances.

Ultimately, every hospital and health system will have its own approach to the adoption of new technologies and innovations. I think this is positive because that is also how different entities compete to offer the best services. The playing ground also varies from country to country, and even from hospital to hospital.

The classical view is that there are two types of healthcare systems: the Beveridge system and the Bismarckian system. The Beveridge model is tax-based. Here we are looking at the single-payer system in the UK, Spain, Italy and so on where citizens pay taxes and then do not pay anything for healthcare at the point of entry. The Bismarckian model, on the other hand, has a number of payers in competition, which does complicate the system to some extent, but it also triggers competition between providers and between payers. Under that system, different payment and reimbursement schemes will naturally emerge.

What we have seen is that countries with the Beveridge system do very well with long-term disease management and in the treatment of chronic diseases but not as well when it comes to specialized and high-cost areas like cancer. Access to the latest innovations in specialty care areas can be slower. For instance, certain cancer outcomes in the UK have not improved due to lower access to the newest innovative therapies. This is a challenge for countries with Beveridge-type healthcare systems: how to cater to rare diseases with more expensive therapies.

Speaking from a hospital group perspective, we are always striving to be among the best in terms of quality and patient outcomes. If we allow hospitals to decide how to embrace and manage new technologies, I think that would incentivize more competition. Competition encourages entities to strive for excellence.



THE VIEW FROM CEE

Bridging the East-West Gap in Romania

Professor Marius Geanta, co-founder and president of the Center for Innovation in Medicine, Romania looks at how cell and gene therapies may increase the gap between Western and Eastern Europe in cancer care and why there needs to be a more holistic appraisal of their value.

In terms of cell and gene therapies, which are very disruptive innovations bringing a new dimension of personalization, I am afraid that they, and other related technologies like genomic medicine, will only increase the gap between Western and Eastern Europe. I think this needs to be a critical part of the conversation about Europe's Beating Cancer Plan, because innovation should be a factor for cohesion between East and West, not a factor of division.

It is not just the money perspective. There are many sources of European funding, like Europe's Beating Cancer Plan, Horizon Europe and so on, and in Romania, we have a number of national programs too. But we have to be careful in the way we use these funds, we need to maximize the value we can generate. For me, it is incredibly important that we pay for value, and that we have the right tools to monitor and control the way we use these funds so that the money follows the patient and their needs. It is not about how many CT machines or how many oncology institutions we set up. It is about how we address the real needs of the patients.

Data is another aspect, in terms of infrastructure and so on. We have seen discussions regarding the establishment of a new European Cancer Data Center, and we are strong supporters of this. I think it is positive if patients and citizens across Europe have the option to access such resources at the pan-European level if they are unable to access them at the national level, whether it is because the national health system lacks the necessary capabilities or capacity, for instance, to organize or handle national health registries. But in order for this to work, we have to create a pan-European model based on transparency and trust. We need to make it clear to every citizen and patient who has access to their data and what their data will be used for.

Medical education is key too. Many doctors are not yet trained to use Big Data and other digital tools. We need to help them understand the importance and value of such data.

The engagement around cell and gene therapies began in Romania two years ago. It is clear that we

Prof Marius Geanta
co-founder and president, Center for Innovation in Medicine, Romania

cannot achieve the potential of these incredible therapies if we focus solely on the therapy and its reimbursement. We have to work on education, on diagnosis, and so on. Patients need to know where they can access such therapies.

The Novartis CAR-T therapy has received recommendations for unconditional reimbursement for both its approved indications. It is expected to be included on the reimbursement list in a couple of weeks. For the moment, the therapy is not yet being administered in Romania.

The reimbursement decision was made through the conventional health technology assessment (HTA) process but the country is now also working on a different HTA process for advanced therapies. I think we have to differentiate traditional and advanced therapies. With cell and gene therapies, we are looking at potential cures: the therapy is administered just once and all that needs to be done after is to monitor the patient for a number of years after. This is very different from conventional therapies that payers have to pay for each year. We are also talking about very small patient populations.

Creating a Pathway in the Czech Republic

Czech patients were among the first in Europe to be able to receive CAR-T treatments after the EMA granted market authorisation in 2018. The first Czech patient received Gilead's CAR-T immunotherapy, for free, on December 2nd, 2019 at the University Hospital in Brno and in September 2019 a memorandum was signed between VZP, the largest health insurance fund in the Czech Republic, and the Czech Society of Hematology, granting funding to this therapy for the next twelve months. However, there is still currently no regular pathway for breakthrough cell and gene therapies to gain access to reimbursement. Pavel Brezina, MD for Gilead Sciences Czech Republic & Slovakia explains how he is advocating for the creation of such a pathway.

Pavel Brezina
MD, Gilead Sciences Czech Republic & Slovakia

There is currently a gap in legislation, as these orphan treatments and advance therapy medicines are not addressed by the law. As a result, companies do not know how to submit an application for regular reimbursement. The law is designed for standard drugs requiring the applicant to prove cost-efficiency, which is not possible in cases of such costly and innovative therapies.

We are happy that Ministry of Health is currently preparing an amendment to the Act on Public Health Insurance to address orphan drugs. They plan to introduce so-called soft criteria and create an advisory committee composed not only of payers and representatives of the Ministry but also scientific associations and patient groups. All these stakeholders will be assessing these orphan drugs against soft criteria, which should in my opinion take into consideration the impact on the quality of life of patients and their families, as well as indirect socioeconomic outcomes on disability costs, tax income, and other factors which are not taken into account for regular drugs. In fact, I wish these factors would be taken into consideration for regular prescription drugs as well.

Right now, the healthcare budget and social budget are managed separately. Nevertheless, treating a patient in serious conditions with an innovative therapy, although more expensive than the standard of care, can reduce disability costs and increase tax income when the patient is able to return to work. All these factors should be accounted for in the calculation of budgets so that society can decide if investing in an innovative therapy pays off not only from a healthcare perspective but also socially and economically. I am optimistic that in the future the health and social budgets will be managed in sync.

Launching CAR-T in CEE

Predrag Tanasijevic looks at how market access for Novartis' CAR-T product has played out in Central, Southern and Eastern Europe so far, what lessons he has been able to draw from this process, and the major challenges has the company faced so far, especially in terms of innovation and market access.

Predrag Tanasijevic
head of Cell & Gene Therapy for Central, Southern & Eastern Europe, Novartis Oncology

Our plan is to secure commercial availability of our CAR-T therapy in 11 countries in Central, Southern and Eastern Europe, by the end of 2021. In every country we aim to create a tailor-made approach, designed to offer long-term predictability and flexibility for payers, and sustainable equitable access for patients.

To achieve this, we nurture unreserved partnership and a continuous open dialogue with payers and stakeholders. They have taught us three important lessons:

1. The worst distance between two people is misunderstanding: People perceive the value of innovation differently. Innovation, like beauty, is in the eye of the beholder - what is logical and evident for one person may not necessarily be acceptable or feasible for the other. My team and I had to learn to "speak the same language" and make sure we understood and addressed the toughest challenges first

2. The greatest innovation comes from being uncomfortable: We have to be open to the unconventional, and experiment with different concepts, ideas and solutions that may not have been used yesterday, but have the power to change tomorrow

3. Authorities expect us to deliver ideas & potential solutions, and co-create the future together: We shouldn't only bring a challenge to the discussion table – authorities have enough of them. We should aim to bring solutions, and help transform systems and regulations to accommodate for the future

By far the biggest challenge we have faced so far is that existing local legislative and regulatory frameworks have not been designed to accommodate the specificities and complexities of CAR-T therapies. This applies not just to the finished product, but also to the initial stage of the manufacturing process.

In some countries, the procedure for placing cell and gene therapies on the reimbursement list is not well defined (is it a medicinal product or a therapy?), or simply doesn't allow much flexibility. In other countries, existing distribution and supply chain models do not foresee the possibility of so-called direct distribution.

There were also countries where the initial step in our manufacturing process - procurement and exportation of the patient's own cells (the starting for commercial manufacturing) - simply wasn't recognized by the local regulation and legislation in place. This created a huge obstacle for bringing the product to market.

Existing EU regulatory frameworks only set the stage to a certain extent, providing clear recommendations and guidance, but the actual transposition into local rules or simple recommendations were often missing. At the beginning, this clearly created a number of roadblocks, but at the same time offered us an opportunity to partner with authorities in co-designing new solutions for the future.

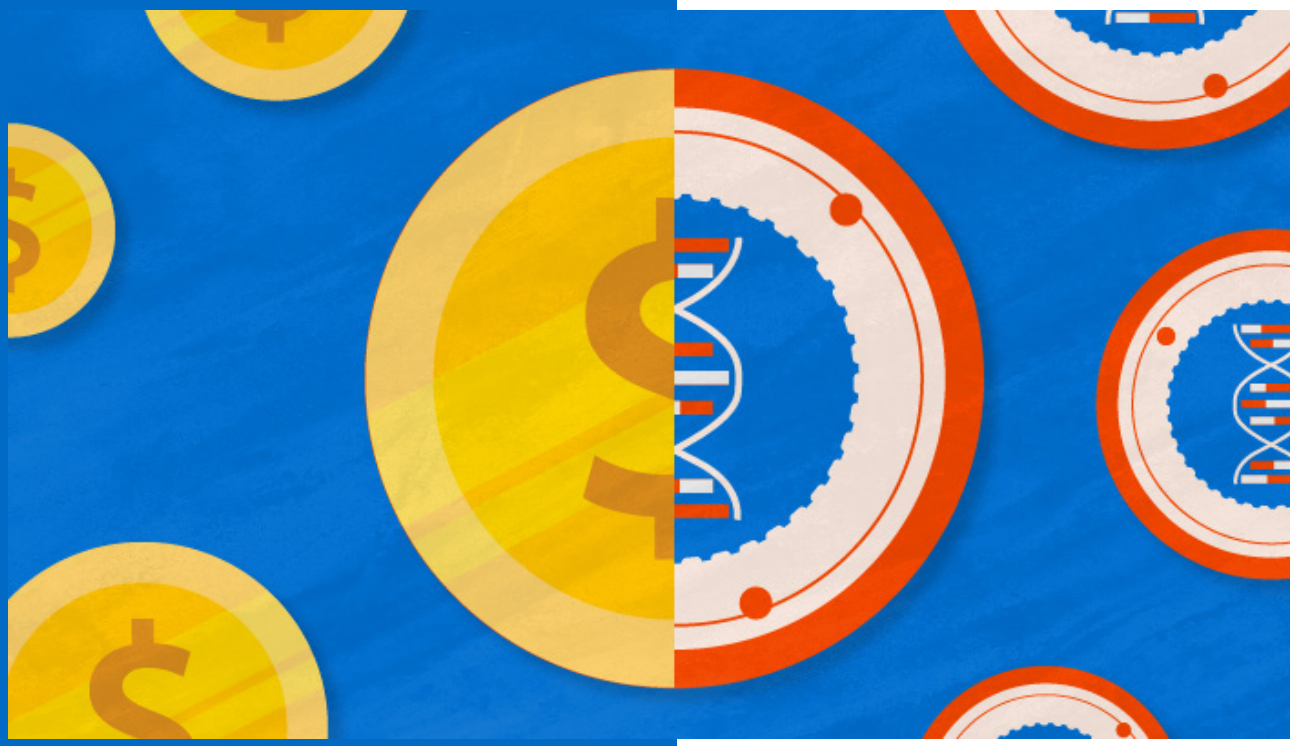
CAN WE AFFORD TO PAY FOR FUTURE CURES?

Pharmaceutical innovation is racing ahead of the US health system's ability to adjust payment models, but innovative concepts are finally emerging. We will have to move beyond siloed thinking to establish them for the sake of getting patients sustainable access to a new wave of transformative cures, argues Certara's Ulrich Neumann.

A look at recent drug approvals reveals the truly fascinating juncture in human health we find ourselves at. Pharma, for long accused of preferring the de-risked advancement of so-called 'me-too therapies' has produced remarkable innovations in genetic and cellular therapies in recent years, providing extraordinary benefits to patients.

The US Food and Drug Administration (FDA) approved four gene therapies in the past three years, while investment in transformative drug research exceeded $13 billion in 2018. Many more treatments are now in the development pipeline with an estimated 40-60 new products that could reach the market by 2030.

It is widely believed that we will find cures for inherited genetic diseases such as in muscular dystrophy, a set of rare disorders whose muscle-weakening and wasting conditions see patients progressively worsening, and often dying due to heart and breathing complications.



A lifetime of value, injected once

As exciting as it is from a medical point of view, the advent of a wave of transformative and gene therapies has amplified affordability concerns among payers, providers and patients.

While much has changed in the evolution of the science, very little has changed in the evolution of thinking about how to pay for and deliver such innovation. Consider Zolgensma, the first gene therapy approved in May 2019 to cure young children with spinal muscular atrophy (SMA), a rare genetic disease.

While recent investigations have exposed data manipulations in Zolgensma's pre-clinical research, the FDA highlighted that human clinical trial data support its efficacy and justify its place in the market. It is priced by Novartis/ AveXis at over $2 million, an injection administered once, while the therapy value accrues over a patients' lifetime.

The disconnect between payment and outcomes reveals a fundamental challenge to the current 'pay-as-you-go' funding approach in the heterogenous US payer system. As is the case for most curative therapies, the lifetime savings potential is exceptional in terms of reducing the burden of mortality, disability and overall treatment costs.

But collapsing decades worth of potential cost-offsets into the single, one-time administration of a drug produces extra-ordinary up-front budget pressure on payers. The cumulative effect of curative therapies across multiple conditions is likely going to put increasing strain on the current structure.

Another compounding challenge for health systems' value determination is the lack of long-term durability data at launch, performance outcomes which clinical trial research can't capture. In view of the evidence, are we right to assess these therapies under the same criteria we established decades ago to manage the much more predictable cost of chronic conditions?

In the case of Zolgensma, the US Institute for Clinical and Economics Review (ICER) estimated a value-based price to be between $1.2 million and $2.1 million as my colleague Oliver Leatham has pointed out here, looking at the question of value. Once we move beyond value assessment to corresponding reimbursement models, are our health systems even equipped to afford the value-based prices of these novel technologies?

US payer risks around transformative therapies

Rising patient copays, increased coinsurances and at times perverse rebate incentives already reveal the inadequacies of a US reimbursement system under pressure to pay for today's therapies.

There's little doubt that both funding and delivery systems are wholly inadequate to deal with a wave of future cures. As the recent FDA commissioner, Scott Gottlieb, said in no uncertain terms, "without innovation in financial engineering and financial arrangements to overcome the chasm between current patient need and available cash flow, the U.S. will not be able to reap the full benefits of genomic technologies".

With respect to gene therapies, different US payer types are variably exposed to three core risks:

- **Actuarial uncertainty** (how many eligible patients will be in our insurance pool?)
- **Therapeutic performance** (how do we assess long-term real-world effectiveness of treatments?)
- **Payment timing** (how do we administer payment given plan switching and beneficiary migration?)

Broadly speaking, smaller beneficiary numbers result in higher financial exposure of gene treatments on a per-patient cost basis, and comparatively greater operational challenges given the need for highly specialized treatment knowledge. Overall, small commercial payers, self-insured employers, MA Advantage and Medicaid can be expected to see a higher impact than larger commercial payers and Medicare Fee-for-Service.

These insurance risks also vary across therapy modalities for the different target populations in question. Multiple payment solutions are thus required to mitigate the impact of a proliferation in novel high-cost therapies.

A few collaborative efforts have lately put the development of so-called 'precision financing' schemes for precision cures on the public policy agenda. One of the most prominent multi-stakeholder initiatives in the US was launched at the Massachusetts Institute of Technology (MIT). Their Financing and

Reimbursement of Cures (FoCUS) project has recently presented a set of alternative reimbursement models based on "Design Lab" workshops, primary research, financial modeling and case study analyses. The aim is to advance a practical toolkit that helps drive early adoption and enables payers to guarantee patient access to novel therapies. Below is my assessment of the most promising models to come out of these early deliberations.

Precision financing and innovative access, some US options

Milestone based performance contracts involve an upfront payment and reception of refunds over either the short-term (<1 year) or long-term (e.g. five years). These contracts can help to reduce the risk around a variability in response and limit treatment costs.

Developers may rebate based on non-response rates in individual patients, pay a discount based on performance within a population, or pay for additional treatment costs associated with suboptimal response to therapy.

One of the major challenges with such outcomes-based agreements is the need for third-party adjudication services and a data and analytics infrastructure to track patients over time (across payers and providers). These steps, in turn, add again to the already costly administration and legal complexity. Equally importantly, you have to be able to agree to a set of measurable outcomes which can be challenging depending on the disease state.

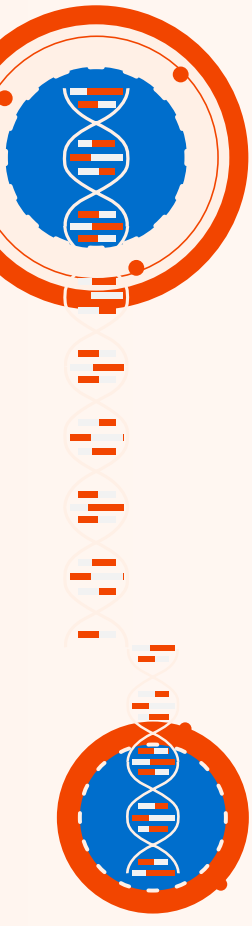
The current types of outcomes agreements have seen limited scale, payers in the US are not very optimistic about expanding the deals beyond pilots, with the exception of Integrated Delivery Networks (IDNs) which is usually the most bullish US payer archetype to be somewhat likely to double down on launching them with pharma partners. Early adopters are generally not opposed to renewing existing agreements that provide value for money, but are cautious about crossing the chasm to wider adoption, frequently cite lack of resources and lack of manufacturer' commitment to more meaningful areas of implementation.

Annuities payments (with or without performance guarantees) spread the cost of a therapy over a fixed time frame, thus smoothing the scheduling of financing. The model would help tackle the immediate budget pressures in the first year faced by smaller insurance pools, and partially mitigate the actuarial risk around patient backlogs and individual high-cost cases. Given the multi-year contract horizon, open questions around patient tracking, pricing regulation and accounting issues persist.

Reinsurance (e.g. purchased by payers) and stop-loss insurance (e.g. purchased by self-funded employer organizations) is currently employed to manage the actuarial risk of single plan-year contracts. For example, payers pay the third-party insurer per member per month (PMPM) to assume the risk for unexpected events above a certain cost threshold. Applied to gene therapies the approach could [work well in incident populations, but faces challenges in multi-year agreements since high-cost claimants will have to be disclosed to re-insurers and are often "lasered out" of policies since these focus specifically on unknown and unexpected financial risk. When imagining the future state of gene therapy commercialization, the colleagues at MIT also suggest that novel provider-administrator entities might emerge to support and administer novel financing models.

These intermediaries, so-called Gene Therapy Administrators or Orphan Reinsurer and Benefits Managers (ORBM), could combine the risk-bearing of reinsurers with the therapy contracting capabilities of PBMs, the provider network building, and medical management capabilities of insurers. While no such dedicated vendor exists today, third parties are already providing these services.

Except for the specialization on orphan diseases, it's actually not such a novel idea, "it builds on existing concepts in the marketplace – think about behavioral or organ transplant carve-outs", tells me Mike Cierametaro, Research Director at the National Pharmaceutical Council. Additional capabilities such as specialty pharmacy distribution could, hypothetically, be added as well. However, the specific confines of the business model behind the ORBM are yet to be fully fleshed out. An MIT initiative called FoCUS is currently endeavoring to conceptualize the promise of an inter-mediating entity.



Outlook for developers

Despite heightened excitement around innovative financing models, payers in the US see comparatively little use overall. Realistically, there are only few immediate opportunities for the adoption among private insurers in the US today. This is partially due beneficiary switching at the end of the plan year that does not allow for the continuity in the treatment population that the approaches require, while unit-level reporting requirements are legal and administrative barriers.

Propositions relevant for Medicaid payers, such as licensing models ("Netflix"), have unquestionable public health value as long as no further treatment innovation is to be expected in the category. By nature, this limits the model to indications and categories where continued R&D can be sacrificed for budget surety, such as curative therapies. While some tactical benefits may sound appealing to manufacturers at first sight – e.g. annual recurring revenue and cashflow certainty, reduced COGS etc – the shift may be indicated for a limited set of competitive scenarios, e.g. for a hold on a patient pool that is diminishing when competitive differentiation is unable to open the funnel.

While commercial stakeholders in the biopharma industry are trying to embark on advancing possible adoption of novel financing models, regulatory clarity would serve as a key enabler. The Center for Medicare and Medicaid Services (CMS) should provide reasonable accommodation for best-price and other government price reporting, the Office of the Health and Human Service Department's Inspector General (OIG) advance anti-kickback statues to define explicit safe harbours, and FDA could further specify communication guidelines to enable appropriate communication between payers and developers. There have been encouraging proposals by the OIG and CMS for new AKS and Stark protections for value-based agreements on the provider site, currently pending at OMB, but such arrangements explicitly exclude manufacturers of drugs, medical equipment, prosthetics, orthotics or supplies.

Policymakers have hitherto made little commitment to developing an infrastructure for annuity financing or to enabling long-term, value-based pharmaceutical reimbursement. However, the public discussion around the sustainability of paying for therapies such as Zolgensma may have shifted the mindset on Capitol Hill lately.

Notably, the current bi-partisan legislation from the Senate Finance Committee would enable Medicaid plans to amortize the cost of delivering curative gene therapy over time. The drug bill may be a mixed bag for pharma, but it is the only one supported by the Trump White House.

In the meantime, for any non-traditional pricing agreement, successful developers are well-advised to rely on strategic external support to identify and simulate real world effectiveness in populations of interest, pressure-test program designs with their customers, and then adequately provision for monitoring and adjudication systems. Internally, those at the frontlines of pioneering payment innovation empower multi-disciplinary pricing steering committees and make sure the effort is championed by executive commitment. A critical question for all stakeholders around the future of innovative contracting is whether any of the negotiated financial benefits between manufacturer and payer will ultimately ever reach the patients. We will need a lot more innovative, out-of-the-box approaches to operationalize such concepts, thinking in horizons of collaborative change beyond the status quo. Given how entrenched the parameters of any solution are, and will ever be, within legal and operational constraints, this type of innovation will have to be shared and open, to be sustainable.

THE JAPANESE MODEL

Dr Ken-ichiro Hata, representative director and chairperson of Japan's Forum for Innovative Regenerative Medicine (FIRM) outlines how Japan has been able to cultivate one of the world's most mature regenerative medicine ecosystems focusing on autologous rather than allogenous regenerative therapies, and highlights key challenges including regulatory misalignment across Asia and the need for better manufacturing and commercialisation models.

Dr Ken-ichiro Hata
representative director and chairperson, FIRM

Japan is one of the countries with one of the most mature regenerative medicine ecosystems in the world, and FIRM has been a pioneer in this space. How do you evaluate the progress that has been made so far?

KEN-ICHIRO HATA (KH): We are very pleased with the support that the Japanese government and the Japanese regulator, PMDA, have given to the area of regenerative medicine, particularly following the awarding of the Nobel Prize in Physiology or Medicine to Dr Shinya Yamanaka and his colleagues at Kyoto University for their research in induced pluripotent stem (iPS) cells in 2012. This brought a lot of attention to the important work being done in this space in Japan, both within Japan and internationally.

In 2014, the Ministry of Health, Labor and Welfare (MHLW) implemented the 'Strategy of SAKIGAKE', as one of the action plans to implement "Healthcare and Medical Strategies" adopted in 2013, consisting of the following two key measures:

– SAKIGAKE Designation System: promoting R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines.

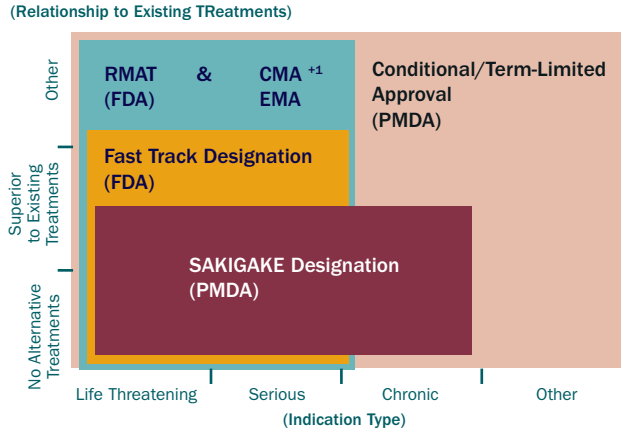
– Scheme for Rapid Authorization of Unapproved Drugs: accelerating the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved Western countries if it satisfies certain conditions and by improving the environment for companies to undertake the development of such drugs.

This strategy has been quite effective. In 2014, two important pieces of legislation relating to regenerative medicine were also enacted: the Act on the Safety of Regenerative Medicine (ASRM) and the revised Pharmaceutical Affairs Act (PMD Act). In particular, the revised PMD Act implemented the conditional and time-limited marketing authorization system for regenerative medicine products, if they meet a number of conditions, including the lack of any major safety concerns and the "suggestive" findings of efficacy, can be sold on the market for up to seven years. This means that we no longer need to recruit large numbers of patients for clinical trials, which can be very challenging. Following this conditional and time-limited approval, the safety and efficacy of the product need to be confirmed continuously in conjunction with post-marketing safety measures.

These measures position the Japanese ecosystem for regenerative medicine ahead of international competition. Today, Japan has nine regenerative medicine products on the market, and

> "Moving forward, we would like to focus on strengthening our collaborations with other entities within the Asia-Pacific region."

COMPARISON OF VARIOUS PROGRAMS ACROSS THE US, EUROPE AND JAPAN



Reference: FDA, EMA, PMDA websites
+1: Can also be obtained if intended to be used in emergency situations or if deisgnated as an orphan medicine

three of them are conditionally approved, which is very positive.

However, in terms of areas for improvement, from the regulator standpoint, we would like to see more flexibility in the evaluations of regenerative medicine therapies, particularly when it comes to 'efficacy'. Our experience through the various regulatory approval processes has indicated that demonstrating the safety of these therapies in clinical trials is feasible but demonstrating a standardized or consistent level of efficacy across patients is not necessarily possible, due to the heterogeneous nature of the therapies. We hope to work with the regulator to address the topic of 'efficacy' through other approaches.

Ultimately, we would like to increase the available therapeutic indications for both existing and also upcoming products. The market size of these products is currently still rather limited. In order to cater to larger patient populations and address the significant unmet medical needs that still exist, we need to expand the reach of regenerative medicine products. From the industry standpoint, this also means we need to invest in more clinical trials.

Looking at cell and gene therapies, there are two major barriers to widespread adoption and utilization: manufacturing scale-up and commercialization models. What is your perspective on these two challenges?

KH: These are both very important topics for the industry. In Japan, the regenerative medicine industry has developed around the concept of autologous regenerative therapy, i.e. using stem cells taken from the patient's own body, as opposed to allogeneic regenerative therapy, i.e. using stem cells from donors. The approval pathways are perhaps faster for autologous therapies but the manufacturing, supply chain and commercial models are different.

The single-payer system in Japan has not resulted into a large market structure thus far but I am not sure how a multiple-payer approach will improve the way regenerative medicine therapies can be developed and brought to market, especially with regard to pricing.

Other Asian countries, especially South Korea and China, are also advancing in the field of regenerative medicine but there is a clear regulatory misalignment between various Asian countries that hinders regional collaborations. How can this be better addressed?

KH: We must admit that we have not sufficiently promoted awareness of our achievements in the regenerative medicine space on the global scale but moving forward, we would like to focus on strengthening our collaborations with other entities within the Asia-Pacific region. This is not always straightforward because other countries also have their own agendas and priorities. Regulatory alignment is also a complex endeavor. However, we are happy to see that foreign companies have found many opportunities and channels to come to Japan with work with our academics, researchers and industry members, which demonstrates that Japan is a leader in regenerative medicine.

What can we look forward to from FIRM and the Japanese regenerative medicine industry in the next couple of years?

KH: Moving forward, we want to expand the range of therapeutic indications and launch more products successfully on the market, as well as improve the industrialization and manufacturing of such therapeutics, to support these therapies becoming more mainstream solutions for patients in Japan and globally. We will also strive to form more fruitful collaborations with relevant stakeholders within Japan and internationally. We are confident that 2020 and 2021 will be very relevant years for regenerative medicine in Japan.

Jon Amund Kyte, Department of Experimental Cancer Treatment, OUH Comprehensive Cancer Center, Oslo University Hospital, Norway

NORWAY: ALL THE FUNDAMENTALS FOR CAR-T CLINICAL TRIALS

Oncologist Jon Amund Kyte, whose work encompasses developing new CAR-T cells for cancer therapy and combining immune checkpoint inhibitors with standard therapies, talks up what Norway and the Oslo University Hospital has to offer for advanced cancer therapy clinical trials.

One of the most important factors [in attracting clinical trials to Norway] is our ability to do long-term follow-ups. If you start a trial in the US, you have to recruit considerably more patients than you are actually aiming to get the data from. In Norway, you will get the data and the follow up for almost all participants. The reason for that is the strong national healthcare system with no private alternative. Even if people move around Norway, they will still be within the national healthcare system, so we do not lose patients. Our registries, including the Norwegian cancer registry, could also be useful for companies looking to extract real world data on patients.

Here in Norway, we can enrol patients from across the country in clinical trials, because the government pays travel expenses for patients to visit study sites. Yesterday, I got an email about a patient living in a town on the Russian border. I will probably get this patient into my clinical trial, even though they live the same distance from Oslo as Oslo is from southern Italy. They connect with three flights, paid for by the regional government.

Another key factor is Norway's highly educated population that speaks good English, which is useful for international studies, as they are able to understand and closely follow instructions, including the reporting of side effects etc.

At our site we are strong in some very specific areas, one of which is immuno-oncology, and we also have the largest academic cell therapy facility in northern Europe, meaning that we have strong milieus for CAR-T cell research, checkpoint inhibitor research, and other aspects of oncology.

We are now also focusing on investigator-initiated trials, where we get free drugs from companies. Through collaborating with companies, we allow them to test their drugs in promising patient populations, and in return we are able to carry out important research. The added benefit of these trials is that we put Norway on the map for clinical research.

In summary, even though Norway is a very small country, our hospital is actually a very big cancer hospital. In two years, we will also get a proton therapy centre thanks to a very big investment from the government. Our centre is also accredited by the Organisation of European Cancer Institutes (OECI) as a Comprehensive Cancer Centre due to the fact we carry out both translational and basic cancer research activities, as well as clinical activity. I, for example, spend 50 percent of my time in the research lab, and the other part of my time in the hospital seeing patients and doing clinical trials. I can carry out both tasks in the same location because the Cancer Research Institute is co-localized with the hospital. That co-localization is extremely valuable because it means people like me can have direct contact with researchers.

Jon Amund Kyte
head, Department of Experimental Cancer Treatment, OUH Comprehensive Cancer Center, Oslo University Hospital, Norway

Photo: Sofia Linden / Oslo Cancer Cluster

COST-EFFECTIVE CAR-T IN BELGIUM

Miguel Forte, CEO of Bone Therapeutics, outlines the Belgian biotech's 'off-the-shelf' CAR-T therapy's journey to market and why Belgium represents a conducive ecosystem for these technologies.

Miguel Forte
CEO, Bone Therapeutics

One of the Bone Therapeutics' key assets is the protein solution, JTA-004, that has documented advantages over existing treatment for knee osteoarthritis, which is a very prevalent condition, and we also developed a cell therapy platform, ALLOB, which is allogenic and off-the-shelf. This is particularly relevant for the cell therapy's value proposition because it takes advantage of the innovation of using the cell's function through the ability of cells to form the bone: we produce it in a cost-effective way, it comes from a healthy donor and being cryopreserved is ready-to-use.

This technology is about to go into the next clinical studies. We already got the approval to conduct the Phase 3 study with JTA-004, so we are close to the marketing of the product which is a very exciting time for us! Our Phase 2b trial with ALLOB will confirm the previously generated data before we get to the next step. Over the next two years, these two studies will really be about taking the company to the next level and the resulting documented and controlled clinical data will take us there. This excitement really is my main motivation and what gets me up in the morning.

As a company, we are very proud to contribute to the Belgian ecosystem. I am a foreigner and moved to Belgium especially because of the biotech environment was very interesting and rapidly evolving. The Belgian healthcare system is well advanced, providing an essential service and has a great background for innovative activities, clinical trials, industrialization and commercialization as well. I really appreciate that the regulators have strong experience and that they implemented a fast-acting regulatory environment. The regulators in Belgium are integrated into the European regulatory system and they provide very useful guidance and precious pieces of advice when needed and especially to companies in development.

Within the member states, the regulators are fast decision-takers and enable a fast access to the clinical trial decision. As you know, Belgium is the country with the highest number of clinical trials per capita. One of the elements that led Belgium to this leading position is the regulatory environment and the other is the academic environment. The country has developed a lot of academic and scientific innovation and the clinical sites are motivated, ready and competent to realize the trial. The government and institutions like the SFPI, SRIW (Walloon Society of Regional Investments) and Sambrinvest that support and promote the industrialization enable local companies, especially biotech companies, and let them create the opportunity to go from an idea generated in the university to the establishment of a company, taking their product through clinical trials and delivering it through the industrialization to patients.

> "The biotech environment in Belgium is conscious of cell therapy's potential"

The biotech environment in Belgium is conscious of cell therapy's potential and it is really involved and promoting these opportunities. I believe cell therapy is at the forefront of innovation, bringing enormous value to patients, not only in immune-oncology but also for situations that requires a regenerative approach dealing with significant morbidity that will have an important impact on the Belgian healthcare.

We speak directly with healthcare leaders and pharmaceutical executives globally.

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