Advanced THERAPIES

MEDICINE INNOVATION REQUIRES MODERNIZING THE HEALTH SYSTEM

NEW FUNDING MODELS CAN ENSURE SUSTAINABILITY

AN INTELLIGENT USE OF DATA HELPS ANALYZE TREATMENT RESULTS

SOLVING HINDRANCES IN THE REGISTRATION AND PRICING PROCESS FOR NEW DRUGS

Photo: Myke Sena/MS - Flickr: Ministério da Saúde

Marcelo **Queiroga**

"We face a major challenge ahead of us, and the pharmaceutical industry has a major role in it. We would like to partner with you in sharing risks and move forward within public policies in the health sphere."

Mara **Gabrilli**

"Years ago, due to the lack of treatment, most diagnoses of major diseases were fatal. We have made great strides in this respect. We must think urgently on how to accelerate making these resources available to those who need them most."

Lucas **Redecker**

"Incorporating these technologies is a claim that eventually will knock at the door of Parliament. The first step should be creating a national registry of rare illnesses. We must map the incidence of these diseases in Brazil to prepare a budget for them."

Nelson **Mussolini**

"The main thing is to develop a strong, ethical pharmaceutical industry, that generates wealth, knowledge and overall health. We must analyze how to help the Brazilian State so that the population can enjoy the most advanced technology."

In the last few years, scientists and biotechnology labs have been doing their share in developing revolutionary medications that bring hope for the cure of illnesses that were once considered untreatable. It is up to the government, the pharmaceutical industry, and the public and private health systems to find new avenues for this new era to become a reality. And this is attainable, first and foremost, with much dialogue.

With this in mind, Health authorities, members of Parliament, and Brazilian and foreign specialists met during the Advanced Therapies Forum – Generating Value to the Patient and Health System Journey, an online event held on August 31-September 2 this year.

"This forum aims at discussing Sciences in its highest level. We must analyze how we – the private industry – can help the population in Brazin have access to these technologies", stated Sindusfarma's executive president Nelson Mussolini, at the opening event of Advanced Therapies Forum – Generating Value to the Patients and the Health System Journey.

Health minister Marcelo Queiroga recalled Brazil's boldness 33 years ago in creating SUS (the Brazilian Unified Healthcare System), the largest universal health system in the world: "We must ensure that it maintains equity and sustainability".

The need to cover multiple lanes was made clear during the debates which covered topics such as pricing, funding, and other aspects to ensure the mission of offering patients this new page in the history of Medicine.

"We need you [the pharmaceutical industry], and you need us. This two-lane avenue is paramount for us to advance", summed up the Minister of Health.

ADVANCED THERAPIES FORUM
GENERATING VALUE TO THE PATIENTS AND THE HEALTH SYSTEM JOURNEY

August 31 to September 2, 2021 [online]

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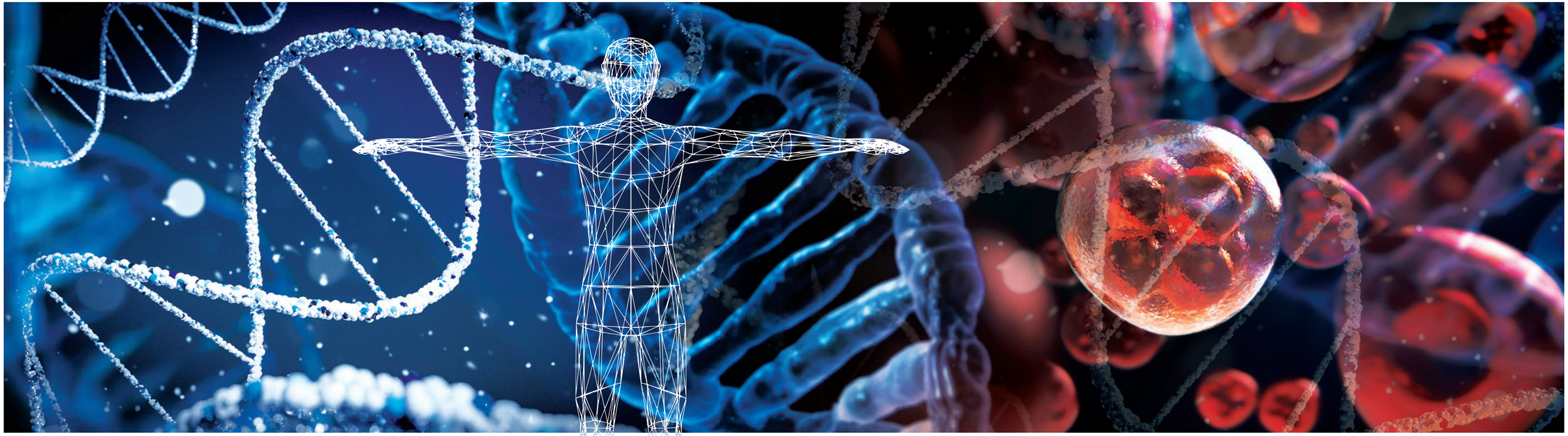

The **future** has already begun

The accelerated advance of new technologies overcomes most optimistic worldwide predictions

Most optimistic forecasts pointed to 2030, but the future arrived much earlier. We are in 2021, and according to data from the Brazilian National Agency for Sanitary Vigilance (Anvisa), there are already 47 Advanced Therapy Medicinal Products (ATMPs) registered worldwide, two of which in Brazil. Other 15 had clinical trials approved in this country. Gene therapy, advanced cell therapy and tissue engineering constitute the forefront of innovation in health treatments. To measure the impact of these technologies on patients' lives it suffices to think on their efficacy against cancer, for example. "Today we are able to produce an exponential attack on tumors that is much more potent than chemotherapy and achieves remission even in patients with one relapse or multiple relapses", states Professor Marco Aurélio Salvino, from the Federal University of Bahia (UFBA).

Professor Salvino's specialty – CAR-T Cell therapy, earned its first win in Latin America in 2019, and today – only two years later – its progress is a surprise even to the medical community. This does not imply that this innovation is already exempt of adverse effects. What is impressive on it is the speed with which these effects are being solved. "Today, we know already how to manage many events generated by the CAR-T Cell treatment, regardless of the extreme care required", cautions Prof. Salvino.

HIGH PRECISION

CAR-T Cell therapy uses a cell extracted from the patient's tumor as a weapon of destruction, modifying it so as to turbo-charge it with a protein that enables it to bind to the tumor and immediately trigger a mechanism that will destroy it from the inside. This "fitting" is exactly where the treatment sophistication resides. It all starts with the definition of the perfect target and the ability to hit it. Differently from chemotherapy, that works as an incendiary bomb launched at the patient's body, the CAR-T Cell method is a high-precision bombing.

"Diseases are the perfect target, for which we created a specific construct, a vector able to precisely find what needs to be fought, and reduces collateral effects, explains Salvino. "When the modified cell is returned to the patient body, it identifies the tumoral antigen and uses its set of receptors to penetrate it, proliferate in it, expand and destroy the neoplastic cell", he explains. "Each modified lymphocyte is unique, designed to find and fight a specific tumor", adds Prof. Salvino with great enthusiasm for the progressive quality control of the overall process and result.

PATIENTS JOURNEY

Besides chemotherapy, also bone marrow transplants could eventually be retired for good. “Years ago, when we thought on bone marrow transplants, our dream was to find a therapy without the uncontrollable side effects that we had to deal with”, says the professor who coordinates the Center for Bone Marrow Transplants of the Hospital das Clínicas of the UFBA and the Cell Therapies Units of Hospital São Rafael, in Salvador. This is exactly what CAR-T Cell brought about.

Cancer is just one of the various diseases in the crosshairs of advanced therapies. Technologies potentialities are mobilizing scientists all over. In 2019, 315 clinical trials aimed at assessing the effectiveness of CAR-T Cells against different infirmities. In two years, this number almost doubled to 615, 23 of which are currently in phase III, i.e., very close to becoming regular treatments.

RARE DISEASES

These totally customized therapies are the major hope of researchers to face rare diseases. The Medical Genetic Service of Hospital das Clínicas in Porto Alegre (HCPA) – an international reference center for the diagnosis and treatment of these diseases – has already submitted to Anvisa, from 2018 on, 10 clinical trials, 9 of which involve rate pathologies. It is estimated that 13 million Brazilians are affected by this type of illness. These diseases are generally chronic, degenerative, and incapacitating, most of them genetic, mainly affecting children. They demand several hospital interventions and 30% of patients die before they are 5. Advanced therapy can solve many of these problems with just one intervention.

It is a real revolution, but there are still many questions on how to make access available since each patient requires individualized treatment. “These are not off-the-shelf products. They require specialized centers that can be adapted to offer the specific treatments”, states Salvino. Professor Guilherme Baldo, who lectures at the Physiology Department of the Federal University of Rio Grande do Sul (UFRGS) and develops research work at the Center for Gene Therapy of HCPA, stresses this alert of the researcher from Bahia: “New therapies require highly trained professionals and complex protocols, besides a physical structure that is compatible with all the requirements to ensure the best results”.

Both specialists mention that the country urgently needs to face this challenge. “Brazil, the country that organized the National Transplant System and created an exemplary treatment model, accumulates knowledge to be able to deal with these complexities. We have not started this journey from zero”, states Salvino.

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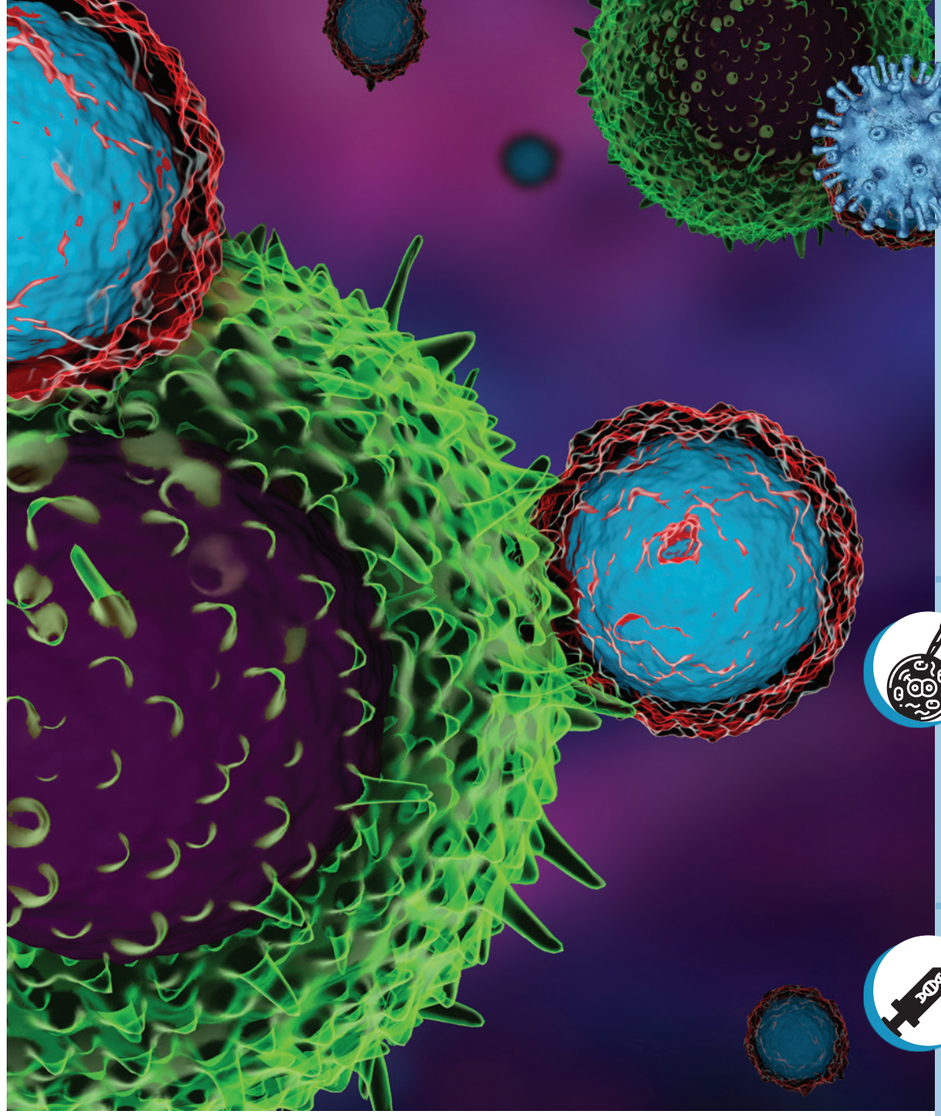

T-Cells attack cancer cells

> *“Cell therapies are a clinical revolution and are changing the perspective of patients who up to now had no hope for cure.”*

Marco Aurélio Salvino
Coordinator of the Bone Marrow Transplants at the Hospital das Clínicas da Universidade Federal da Bahia

ADVANCED THERAPIES

Gene therapy, cell therapy and tissue engineering are the three different fronts in which advanced therapies are divided. Despite being able to walk together, it is important to understand the differences among them.

CELL THERAPY involves the administration of whole cells, typically stem cells, for the treatment or cure of a disease. For example, the culture of cells in the patient cartilage tissue to repair problems caused by traumas.

Whereas GENE THERAPY provides for the injection of gene material (DNA or RNA) to induce, block, or replace a gene of interest. In other words, the deficiency of a lipoprotein called lipase causes pancreatitis attacks on the patient but can be cured with a drug that contains a modified virus that is able to carry the gene in charge of the lipase production.

TISSUE ENGINEERING is the development of artificial tissues used in humans, as an alternative for obtaining organs for transplants, similar to the cultivation of the patient’s epithelial cells of the cornea to repair damages.

PATIENTS JOURNEY

Neonatal **Screening** is the key to the success of **treatments**

Early diagnosis changes the course of rare diseases

"We have access to innovative resources, but public policies do not keep up with the speed of Science", as stated by Brazilian Senator Mara Gabrilli. This statement objectively exposes the country's reality. While Medicine speedily evolves, offering state-of-the-art treatments for diseases that were fatal until recently, Brazil is not able to ensure even the first step towards cure – early diagnosis.

This is a fundamental issue since, despite bringing about great progress in the attention to rare diseases, advanced therapies very often do not revert previously acquired sequelae. Time has a direct impact on outcomes, and late diagnoses sweep away the ambition of cure of new methods, since most of these diseases evolve very rapidly – 30% of patients die before the age of 5. "Neonatal screening is the key to success", stresses Roberto Giugliani, coordinator of the National Institute of Science and Technology for Medical and Population Genetics.

Without being checked at birth, genetic illnesses are investigated when the first symptoms appear. That is when the family's ordeal starts. The lack of specialized centers and trained professional teams, besides the access to sophisticated tests turn the patients' life into a real battle. Most of them face comings-and-goings to doctors' offices until they receive the correct assessment of the type of disease they have. Once identified the

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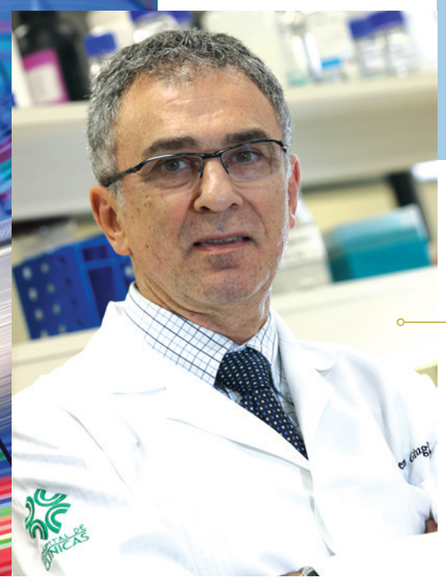
anomaly, the patient is submitted to a fragmented assistance. Very rarely the public health system will provide a global evaluation of his condition.

"We need multidisciplinary teams to adequately assist patients with rare diseases. The high cost of advanced therapies is frequently discussed, but to innovate we must have trained professionals to make the right diagnosis in the child right after birth and follow him or her up. If we do so, all this investment will be worth spending", emphasizes Antoine Daher, president of the Brazilian Federation of Rare Diseases Associations.

Photo: Erasmo Salomão/MS . Flickr: Ministério da Saúde

Antoine Daher
President of the Brazilian Federation of Rare Diseases Associations



Roberto Giugliani
Coordinator of the National Institute of Sciences and Technology for Medical and Population Genetics

PATIENTS JOURNEY

Hematologist Edvan Crusoé, from Hospital Universitário Professor Edgard Santos, in Salvador, argues that if we face the disease early enough, therapeutics will be much cheaper. The Executive Director of the Brazilian Association of Lymphoma and Leukemia (Abrale), Catherine Moura da Fonseca Pinto, goes beyond, pointing out that late diagnosis puts another burden on the health system due to the costs with assisting patients who were not previously treated.

Another difficulty to overcome in the health public system is the lack of permanent follow-up of patients. According to Roberto Giugliani, to use new therapies it is paramount to carry out periodic tests and provide regular assistance. "Data collection during visits is insufficient. And doctors cannot systematically follow their patients due to the system's setbacks. Patients find it very difficult to make an appointment and when they finally do it, they have problems getting to the hospital or the appointment is transferred".

Dr. Têmis Maria Félix, president of the Brazilian Society of Medical and Genome Genetics, considers this fragmented support to be the system's main bottleneck. "We must understand who the patients are, where are they, what type of therapy they are receiving, because only having this at hand it is possible to make a global assessment and define the adequate treatment", states the geneticist.

Têmis Maria Félix
President of the Brazilian Society of Medical and Genome Genetics

"We have a critical point – access, but an early and correct diagnosis makes therapy cheaper."

Edvan Crusoé
Hematologist of the Hospital Universitário Professor Edgard Santos, in Salvador

In the **USA**, 60% of children with SMA are already undergoing treatment

FIVE YEARS AGO, SPINAL MUSCULAR ATROPHY (SMA) REPRESENTED A DEATH SENTENCE. TODAY, CURE IS A REALITY

In the United States, 60 out of every 100 children with Spinal Muscular Atrophy (SMA) are already undergoing treatment. The bleak context of 5 years ago, when this disease was still considered untreatable, gave room to a new life prospect to thousands of people. "Today we are already speaking of curing patients with SMA", states Kenneth Hobby, president of CureSMA, an organization that investigates and promotes new discoveries and methods to treat this condition. "From 2017 on, with the use of new advanced therapies, we were able to change the natural history of the disease. We have children who are walking, whereas years ago they wouldn't even survive", he rejoices.

Being the main worldwide cause of the death of babies due to genetic anomalies, SMA is a rare condition that affects 1 in every 11,000 live births. It interferes with the motor ability to produce the SMN protein, which is essential for the survival of motor neurons that otherwise will die due the lack of this substance. Infants affected with the disease progressively lose muscular control and strength and have difficulty to walk and move; and as the condition evolves, they cannot swallow, hold their head and, finally, breathe. The most serious stage of the illness, Type 1, called Early Onset SMA, affects neonates and babies.

Late Onset SMA is more common in older children, teenagers, and adults, who slowly lose their ability to stand or walk on their own. independently.

In 2016, the FDA, US regulatory agency, approved the first therapy to treat SMA and already in the first quarter of the following year, patients with the disease started to benefit from it. Other therapies followed. Most of them help increase the quantity of the SMN protein in the patients. "Along this journey we witnessed fast and dramatic changes both for patients and the community. We expanded the number of beneficiaries. Until year end, we hope to include 70% of the patients with the disease in the treatment programs", states Hobby.

This success is directly linked to the testing process of neonates. "We are covering almost all births with the SMA neonatal screening. Today, we test 85% of babies and by year end we hope to attain 95%. This gives us the possibility of reaching the correct diagnosis and treating them before neural damage occurs, he explains.

Fast diagnosis and an early therapeutic support are paramount for the therapy's success, since the earlier it is applied, the more impacting it will be.

"We are covering almost all births with the SMA neonatal screening. Today, we test 85% of infants and by yearend we hope to attain 95%."

Kenneth Hobby
President, CureSMA

PATIENTS JOURNEY

The HCPA reference center is a **model for Brazil**

In four Years, the Rio Grande do Sul hospital multiplies by 10 its clinical trials number

Hospital de Clínicas de Porto Alegre (HCPA)'s first clinical trial on advanced therapies was submitted for approval in May 2018. Only four years after that experience, which was rejected by Anvisa (the Brazilian National Agency for Sanitary Vigilance), the hospital set the record straight, and proudly shows today a list with nine other trials on gene therapies, three of which are already I use and seven are awaiting the support from the regulators.

"Every institution must overcome the hindrances of their own lack of experience to be able to start a clinical trial. But when we started it not even Anvisa's full regulations had been published", recalls professor Guilherme Baldo, of the Physiology Department of the Federal University of Rio Grande do Sul (UFRGS), that is part of the Center for Gene Therapy of HCPA. Back in 2018, Brazil hadn't met all the requirements to deal with matters related to advanced therapies nor had an exact idea of what would be necessary to carry out a safe clinical trial.

Nevertheless, those difficulties contributed to finetune the hospital's procedures, mobilizing strengths to create the conditions of excellence in this area. And it didn't take long. Out of the seven trials that are awaiting approval, one of them was fully developed by the institution's own researchers – a proof of the standard of excellence attained by the scientific work carried out by local specialists.

PROTOCOLS FOR VARIOUS DISEASES

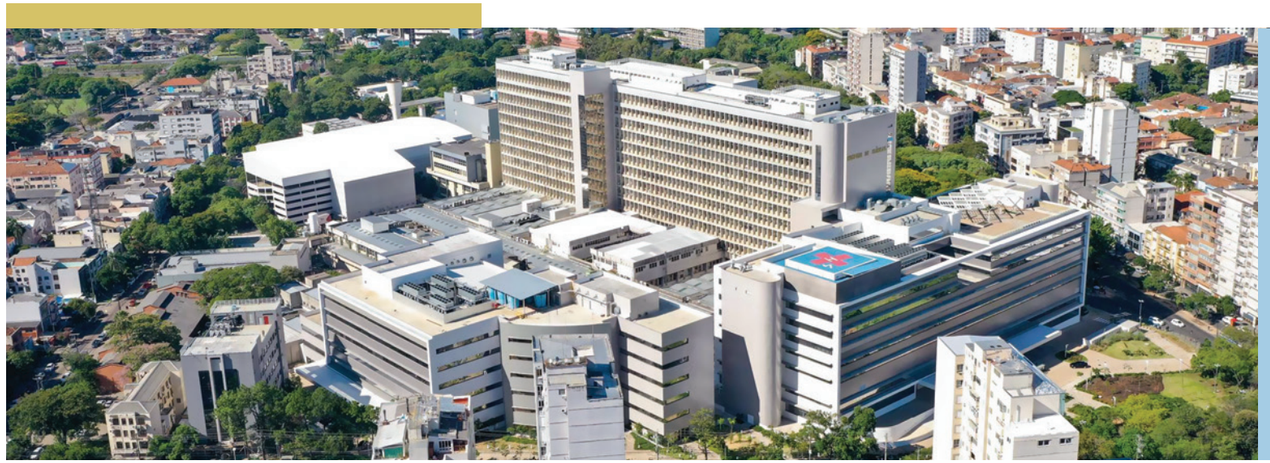
HCPA's international recognition as a reference center for advanced therapies and clinical trials is a story that began 20 years ago, when the institution made room for research. In the huge hospital complex of the state capital city, a small building named Center for Experimental Research was launching its pioneer work. That is where the three units responsible for the overall success were located.

The Center for Gene Therapy is one of them. It was the first "child" born, and throughout the years it formed a group of high-level professors and staff, who oversee the development of protocols for various gene therapies. Another unit is the Technology Center for Cell Therapy, an area where HCPA researchers started to work with the products in clinical trials. And finally, the third one is the Medical Genetic Service, an institution that bears the seal of the World Health Organization (WHO) as a reference center for the diagnosis and treatment of rare illnesses.

CASA DOS RAROS (HOUSE OF THE RARE CASES)

Another HCPA initiative is the "Casa dos Raros", Center for Comprehensive Care and Training of Ilnesses, a pilot project for a bigger plan that intends to create various similar center throughout Brazil, ensuring treatment and fostering new research work in the country.

Construction works of the "Casa dos Raros" is planned to be over by year end. Besides offering specialized opinions and treatments with the most advanced modern therapies, highly trained multidisciplinary teams will connect with professionals and patients from distant places throughout Brazil via telemedicine, thus amplifying access to a fast and accurate diagnosis.



Jefferson Bernardes/PMPA

"The demand for clinical trials has increased much, but health institutions must get ready for it, with proper structuring, personnel training and adequation to regulatory issue."

Guilherme Baldo

Professor at the Physiology Department of the Federal University of Rio Grande do Sul (UFRGS)

Gene Therapies **Timeline**

Throughout almost one century, researchers from various countries worked on different areas of knowledge to develop those treatments that are today the hope for patients, all over the world

1928

Observing that bacteria capable of causing a disease were able to "transfer" this characteristic to live bacteria that had lost it – even after they were dead, British MD **Frederick Griffith** described the transformation principle, but did not discover its cause.

1944

Three physicians — **Oswald T. Avery**, **Colin M. MacLeod** e **Maclyn McCarty** — discovered that DNA is the molecule of heredity.

1952

American physician **Joshua Lederberg** describes the process through which bacterial DNA is transferred from one bacterium to another by a virus; he gives it the name of transduction.

1953

British physician **Francis Harry Compton Crick** and North American physician **James Dewey Watson** develop the double helix model for the DNA molecule.

1961

American geneticist and virologist **Howard Martin Temin** describes how tumoral viruses act on the cell's genetic material through reverse transcription, concluding that genetic mutations can be inherited through viral infection.

1962

Polish oncologist **Waclaw Szybalski** performs the first documented transfer of an inheritable gene into mammals' cells.

1968

Researchers **Stanfield Rogers** and **Peter Pfuderer**, both American, demonstrated the concept of proof for genes transference mediated by viruses.

1989

American researcher **Steven A. Rosenberg** performs the first officially approved gene transfer to humans.

1990

Researchers from the **National Institutes of Health**, in the United States, apply gene therapy in humans, for the first time, to treat the necessary gene alteration (mutation) to form the adenosine-deaminase enzyme (ADA).

1999

Jesse Gelsinger, 19, dies with multiple organ failure after being submitted, at the University of Pennsylvania (USA), to gene therapy to correct OTC deficiency (Ornithine transcarbamylase enzyme). This paralyzed clinical trials for a long time.

2003

China is the first country to approve a gene therapy product, to be used to treat head and neck cancer.

2009

The **USA** registers the first successful gene therapy phase III clinical trial.

2012

For the first time, the European Regulatory Agency (**EMA**) recommends the approval of a gene therapy product in the **European Union**.

2020

Brazil approves first gene therapy product to be used in this country.

BIOSAFETY

Risk assessment, one of the hindrances to **regulation**

The safety uncertainty expands the long avenue towards registration

The emergence of Technologies that are revolutionizing the way we treat diseases imposes, among other demands, a fresh look at the risk analysis of medications, currently regulated by Law 11.105, of 2005. "We are undergoing a revision process since these treatments demand a special rule-setting and bring about several issues that raise other questions", explains Rubens José do Nascimento, Executive-Secretary of the National Biosafety Technical Commission (CTNBio).

Among these difficulties, he points out the fact that very often the patient becomes the end-product of the technique. "Legally, the patient is considered a genetically modified organism (GMO), and we are not sure how this should be regulated", says Mr. Nascimento. Today, assessment is made on a case by case basis, and it tries to mitigate individual and collective risks with an analysis based on scientific data, but challenges only increase as and when the registration process advances.

The road to prove product efficacy, safety and quality is long. In Brazil, new medications must go through the stages of development, non-clinical trials, and clinical trials to finally get to registration. Then, it goes on to the monitoring cycle, with a series of demands, among which quality assurance, specific efficacy trials, adverse events follow-up, post-use continuous oversight, for at least 5 years. In the case of advanced therapies, this term is extended to 15 years.

> ***"Rare illnesses require special rule-setting. Treatment complexity is ever increasing and it must be analyzed with great care and scientific accuracy."***
>
> **Rubens José do Nascimento**
> *Executive Secretary of the National Biosafety Technical Commission(CTNBio)*

BIOSAFETY

> *"Regulating advanced products is a difficult and complex process. We must exhaustively check all the safety and efficacy lines."*

João Batista Silva Junior
Head of the Blood, Tissue, Cells and Organs Management at Anvisa

Registration requires a documental dossier, with a series of specific matters on the risk predictability. However, in the case of innovative products, it is more difficult to previously size the threats. "This obliges us to invert the focus towards post-use monitoring", states João Batista Silva Junior, who is in charge of the Blood, Tissue, Cells and Organs Management at the Brazilian National Agency for Sanitary Vigilance (Anvisa).

In this stage of the process, another complicating factor comes up: the lack of clinical protocols that enable pointing specifically at shortcomings and making a sound reassessment of the incorporation. And yet, there is the issue of logistics, that also calls for a specialized approach. For advanced treatments, time is fundamental. Since very often there are no intermediaries in the distribution chain, the products leave the place where they we made and go straight to the hospital or reference center treating the sick patient.

"This is a major concern. For instance, recently we had to test a model of import and export of cells; cells left Brazil; they were intended to produce a specific therapy; and only then they came back to the patient genetically modified.

HISTORY OF BIOSAFETY IN BRAZIL

The first standardization of biosafety in **Brazil** *was enacted in* **1995**, *when genetically modified organisms were still seen by the general population with distrust. In this environment the legal discussion on biotechnology in Brazil started and, among the main conflicts, the norm created didn't have a clear definition of competences and responsibilities, and resulted in unlawful actions. In* **2004**, *a major debate on human cloning resulted in a bill of law that encompassed research of stem cells and biosafety for* **GMOs** *(Genetically Modified Organisms). This bill Number* **11.105**, *enacted in* **2005**, *is in force until today.*

It all went well, but we still have to polish this format, since we cannot let problems of incoming and outgoing from the country harm the outcome", states Anvisa's manager.

Despite all the obstacles, significant strides have been made. Two gene therapy products had their registration approved here in Brazil. Although challenging, the requirements of the regulation process cannot block access to the new world order in health. In the case of rare illnesses, priority target of the innovation, the approval of new products means hope for a cure or improving quality of life for millions of people, most of them children, condemned to a kind of life marked by limitations and early death.

BIOSAFETY

Intelligent use of data sheds light on clinical trials

Real life studies help map the efficacy of treatments

Otávio Berwange
Academic Research Organization (ARO) Director Hospital Albert Einstein

One of the biggest challenges to the incorporation of advanced therapies in health systems lies on measurement on the effectiveness of treatments. To implement the use of new products and procedures, regulators all over the world want to be sure that the results of clinical trials – conducted in controlled environments and with a restricted population – are being reproduced in the real world and will pay back the investments.

But, in the case of rare illnesses, this assessment is more complex. Innovative therapies have personalization as one of its characteristics, and the effectiveness measurement is a complicated work, very distant from the traditional randomized models. One of the fronts that have advanced on this topic is the team in charge of the Academic Research Organization (ARO) of the Hospital Israelita Albert Einstein, in São Paulo, under the leadership of physician Otávio Berwange.

This department, run by Dr. Berwange, is the one in charge of the coordination of clinical trials run by HIAE in various medical centers of Brazil, and its looks for parameters that enable the assessment of the results obtained and clarify issues not solved during the trials. “Under these conditions, real life trials have an important role also in the investigation of clinical findings”, explains the physician.

With the help of new technologies, new data are collected from different sources, such as the movement in pharmacies, death certificates, lab tests and even social media posts and complaints from consumers in those channels, so as to build a mosaic of information that complements the observational data collected in controlled trials (RCTs).

Berwange states that these real-life studies are an efficient mechanism to improve the allocation of funds available for health, enabling the access to advanced therapies. However, this requires rigor. “It is necessary to previously define a clear question aiming at the answer we want to obtain, and have a statistic analysis protocol, previously established, to generate real-world evidence. Therefore, it is not a matter of data availability, but rather of intelligence applied to data”, explains the expert.

According to him, despite the limitations and divergences among decision-makers on the origin and degree of reliability of the evidence at hand, prospects are positive. “In the United States, the FDA (Food and Drug Administration) has been using this type of study not only to monitor post-marketing safety and the adverse events, by also to make decisions on the liberation of new therapies”, he recalls.

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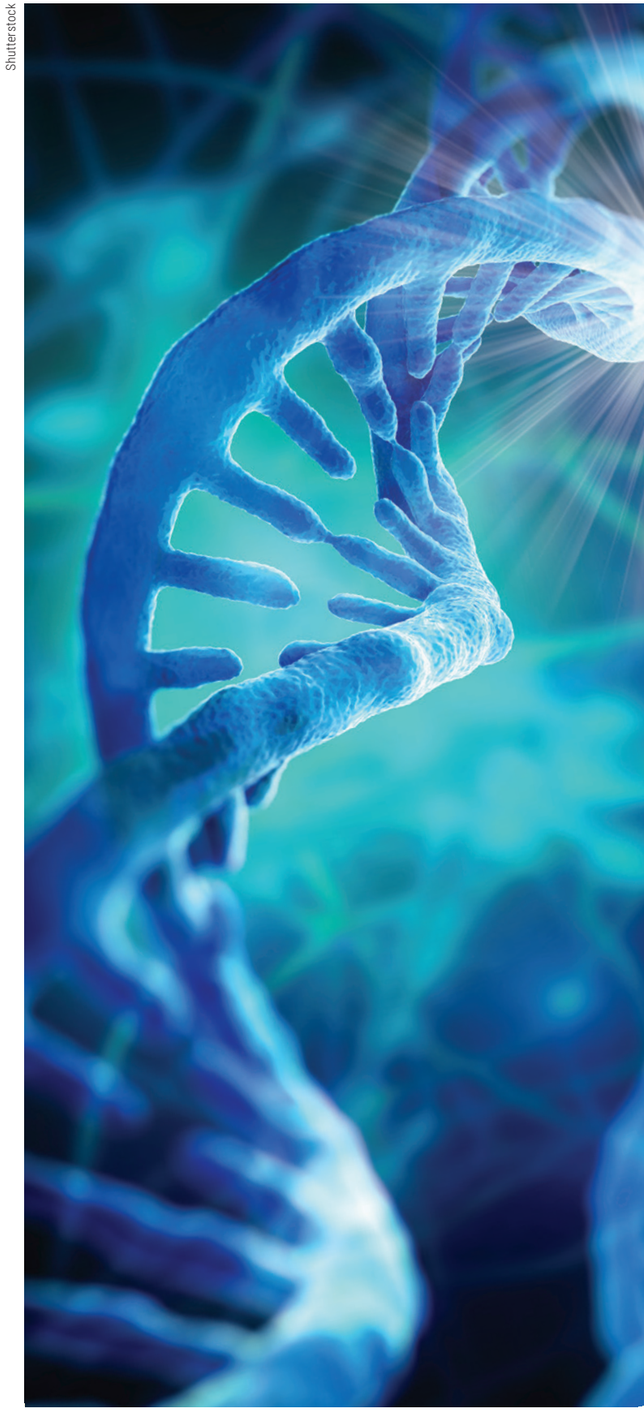

MARKET

Cutting-edge technologies call for new pricing rules

Created for continuous use treatments, the legislation does not meet the transformation of Medicine

Throughout the world, advanced therapies are a synonym of high cost, and one of the current major debates is how to create a pricing mechanism that can offer system sustainability to ensure more predictability and judicial security to all those involved.

In Brazil, drugs and therapy pricing is still ruled by Resolution No. 2 of 2004, of Anvisa's CMED (the Medicines Market Chamber of Regulation). Since that distant month of March 2004, 17 years went by and were characterized by innovations that transformed Medicine. Throughout that period, we witnessed new gene therapies and advances that have changed all the treatment logic.

Drafted at a time when the norm was continuous use treatment throughout the life of the patient, the current legislation lost its purpose. In this new reality, innovative modalities allow for one only application, and this changes it all. "Resolution no. 2 does not answer the pricing needs of a vibrating market, with all this new therapeutic generation that, in 2004 probably sounded like science fiction", explains Bruno Abreu, Sindusfarma´s director of Market and Legal Affairs.

Romilson Volotão, executive secretary at CMED, depicts the difficulties in this field using the only two Advanced Therapy Medicinal Products (ATMPs) registered in Brazil – Luxturma (indicated for the treatment of retina hereditary dystrophy), and Zolgensma (the hope for patients with spine muscular atrophy), both from Novartis Pharmaceuticals. The first problem was the absence of an international price to be compared among the nine countries that form the basket called for in the 2004

> *"Our regulatory structure needs an advance; it was not drafted for innovative therapies. It was created to price traditional drugs."*
>
> **Romilson Volotão**
> *CMED Executive Secretary*

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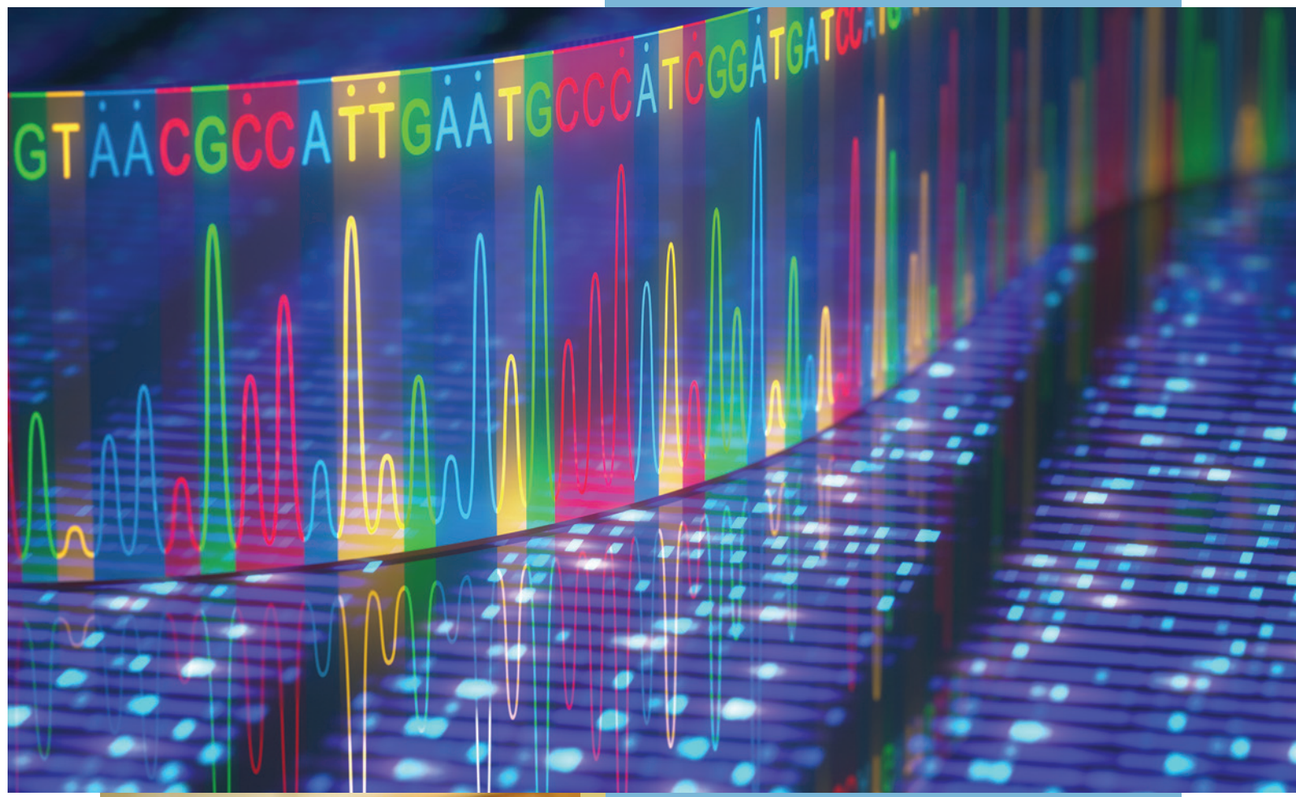


> *"The pharmaceutical industry has greatly invested in research and development, and I would like to have more legal security to bring the innovation down to Brazil, never forgetting patients, at the other end."*
>
> **Bruno Abreu**
> *Sindusfarma´s director of Market and Legal Affairs*

MARKET

resolution: Australia, Canada, Spain, United States, France, Greece, Italy, and New Zealand. "Of these nine countries, we only had the amount charged in the United States, where the pricing system is different from ours", he concluded.

In the case of the two treatments, the solution found was to appeal to Article No. 20 of Resolution No. 2, that provides for "omissions"; i.e., cases that do not fit any of the foreseen categories. "Those cases were sent to the Technical-Executive Committee of CMED. The latter assessed and approved the proposal for a rational price established by the Executive Secretariat. The solution for both treatments was similar, with the establishment of a temporary ceiling that was suitable to the pledge signed between the manufacturer and Anvisa's registration department, calling for a 15-year period with a special follow-up", adds Volotão. The follow-up includes the requirement of annual reports on the eventual existence of international prices and additional clinical trials. Based upon this data, prices could be revised.

The problem with this exception is that it rules out the necessary predictability that enables the full chain to act in a balanced form. "It is a safety valve that was created to expedite the process, but it must be used as little as possible; it should be used only when there is no other way to accommodate the current standardization", states Volotão. In his view, new technologies call for equal innovation in pricing. "One of the possibilities would be working within some kind of regulation sandbox, an environment that foresees the flexibility of norms on specific products – products that are analyzed to be on a test mode for a trial period, with softened rules", he concludes.

There is another complex aspect in Resolution No. 2: the requirement of "robust" evidence of therapeutic gains in comparison with existing treatments. This assumption corroborates the argument that the current norm imposes rules that cannot be met in an innovative drug, mainly if we consider the products intended for rare illnesses – until that moment, these products did not have alternatives in Brazil nor abroad to enable comparison.

> *"Gene therapies are increasingly more frequent; we shall face more judicialization, with much higher value than the incorporation."*
>
> **Lucas Redecker**
> *Member of the Brazilian Chamber of Deputies*

MEASURING VALUE

"We must follow the logic of agreements based on value, not on price", states César Abicalaffe, president of the Brazilian Institute of Value in Health (IBRAVS). Adding that the most important point is to have a health system that delivers patients results, clinical outcomes. Adalton Ribeiro, Specialized Consultant on Assessment of Technology in Health (ATS) insists on the legislation, aiming at going further down on the issue of value. "When we consider the relation between CMED and the incorporation of new drugs, the question is: will this price, which is fair in terms of its efficacy, make technology financially accessible?", he questions.

Vanessa Teich, Economy of Health superintendent at the Hospital Israelita Albert Einstein, says that today there is a major difficulty in properly measuring the cost-effectiveness relation.

It is therefore necessary to have a higher automation of processes in obtaining real life data. The necessary infrastructure and development, which are upfront expensive, could be subsequently replicated, at scale. "I understand it is also of the interest of the Ministry of Health that we might follow up the use of therapies to measure the value we deliver to patients", she adds.

Adalton Ribeiro
Specialized Consultant on Assessment of Technology in Health (ATS)

César Abicalaffe
President of the Brazilian Institute of Value in Health (IBRAVS)

Gabriela Tannus
Senior Partner of AXIA.BIO Life Sciences International

Pexels

Until we have the scaled costs, automation investments remain a problem. One more, in fact. "We must think on how to use the data at hand, in this complex funding environment", states Guilherme Julian, director of Real-World Insights at IQVIA, a leader in Science Technology and Human Data. "Obviously, we need electronic medical records, and systems interaction, but these are tools that take time to be implemented", he adds. As an example, he mentions the study (still in press phase, under revision) on the efficacy of two vaccines against Covid-19 in Brazil, made in partnership between the London School of Hygiene and Brazilian universities, with Datasus data. "The joint effort of various players enabled us to have longitudinal information on 75 million people".

In the meantime, movements in quest of a consensus to place Brazil in the map of advanced therapies are taking place, notwithstanding in an incompatible speed, in terms of new technologies – and of saving lives. On July 27, 2021, The Secretariat for the Competition and Competitiveness (Seae) of the Ministry of the Economy of Brazil opened a public comment (No. 02/2001) under the declared intention of enhancing the existing models to incentivize – and not to hinder – innovation. "Can't we make some adjustments to the existing models?", questions lawyer Tiago Farina. "For example, we could change Decree No. 7646, that regulates Conitec, to create a joint incorporation ordinance together with the Ministry of Science and Technology and the Secretariat of Specialized Health Assistance, so that after 180 days it already informs the price", he adds.

Between adjustments to the current legislation and more in-depth proposals for change, all those involved agree in terms of its urgency. "The pharmaceutical industry has invested much in research and development, and it needs more legal security in order to bring innovation into Brazil", states Bruno Abreu. "ATMP (Advanced Therapy Medicinal Product) frontiers have offered renewed hope that change the course of the people life history. We must discuss pricing in a sound way, one that brings security and predictability", he concludes.

Guilherme Julian
Director for Real-World Insights at IQVIA

"*In fact, we face a series of limitations in the implementation of innovative models, but the Ministry of Health cannot the pessimistic one.*"

Tiago Farina
Public Health Lawyer

MARKET

USA test new parameters to cope with costs

High innovation reward turns the QALY gain much higher

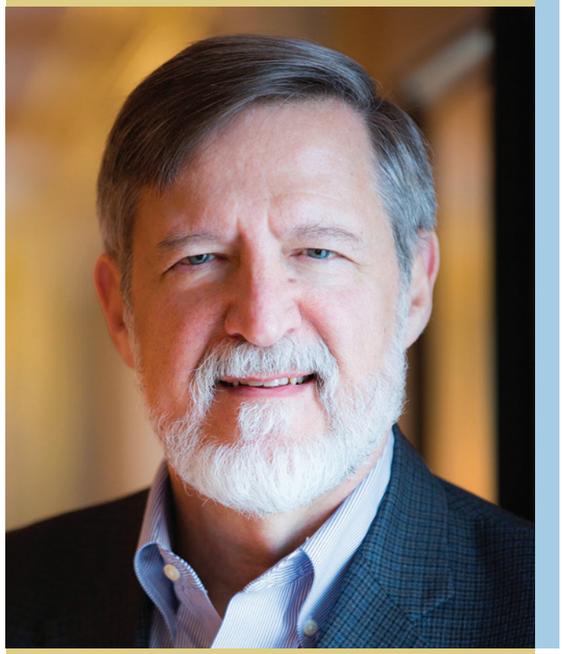
Not even the richest country in the world escapes from having to face the dilemma of advance therapies cost-effectiveness, especially when it refers to providing treatment for rare illnesses patients. In the US, it is estimated that those diseases affect around 30 million people, forcing system's managers to find new parameter to allocate funds for health. How can we assess whether costs meet needs and perspectives?

The use of the QALY measure — quality-adjusted life-years — to guide these decisions becomes more complex when we analyze the result of innovative therapies. The person indicating it bases himself on the assumption that health, or the improvement in health, can be measured based on the amount of time gained in terms of quality of life. Therefore, QALY is an assessment of the benefit arising from a given treatment. However, advanced therapies differ from traditional ones because they bring about the so-called health benefit for a long life, often after the administration of a single dose.

"The QALY gain with some advanced therapy medicines is much higher", states Professor Louis Garrison, co-director of the Global Medication Program of the School of Pharmacy of the University of Washington, "but this gain, despite being high, its cost is also high, and creates problems for health systems that were not designed to deal with a model of one-time large investments", he explains.

In this type of treatment, the challenge therefore is reconciling QALY gains with the value a given intervention can bring about in terms of safety and hope. "When we compare the life gain of using different solutions with the cost of these innovations, one of the important points to take into account is knowing that there is an available and accessible technology to treat problems", says Professor Garrison. However, he also recognizes that the sustainability of the entire system is put to the test. It is a high risk versus high reward situation.

He goes on, saying that another crux in this debate lies on the fact that treatments could have a distortion in their price. When comparing the price of an advanced therapy product with a traditional one, we conclude that the difference is huge. Nevertheless, when considering the cost of the disease throughout the course of the patient's life, there are several traditional treatments that are regularly used that will eventually be more expensive.



> *"Yes, the cost of drugs is high, but there are many other therapies that eventually are much more expensive when we calculate their cost throughout the life of the patient. This should be our perspective, not just the cost of a one-time medication."*

Louis Garrison
Co-director of the Global Medication Program of the School of Pharmacy of the University of Washington

The calculation is not accurate, but one estimate made in the United States got to the amount of US$ 1 trillion. Of this total, indirect costs – such as the ones arising from work absenteeism – weigh more than medical expenses – prescription drugs, for example, wouldn't exceed US$ 48 billion. "This should be our assessment perspective, not just the cost of a one-time intake of a new treatment", supports Garrison, pointing out that the goal of new therapies is to reduce this economic burden and compensate innovators for eliminating part of this amount.

Today, the threshold of the cost-effectiveness adopted in the United States is less than US$ 150 thousand per QALY. In the case of rare illnesses, the threshold is much higher. "This is already being adopted in several health services that are willing to pay more per QALY in rare illnesses. It is an economic reasoning that is related to uncertainty", he says.

But how do health systems deal with this? For the time being the solution has been to test new approaches. "There are cases in which the manufacturer makes a discount if the patient does not respond to treatment. We have also made an agreement to pay an annuity distributing costs throughout time. We still have the example of a private health plan that cut a deal with the manufacturer to condition payment to outcome, paying in 30 days, 90 days and 30 months", Prof. Garrison exemplifies, reminding us that there several ongoing clinical trials to be effective in the next decade. In the future, we could have a situation in which costs are much smaller.

MARKET

The **success** in fighting **Aids could** be replicated

General coordination is key to leverage the quest for solutions

A decision made by the Ministry of Health some years ago changed the course of the Aids epidemics in Brazil, transforming the country in international reference in the disease control and prevention. A similar mobilization – this time focusing rare illnesses – could accelerate the course of history and expand the care to patients with this type of disease.

Elizabeth de Carvalhaes
Executive president of Interfarma

"When the Ministry of Health takes upon itself the responsibility and starts leading the action, it encourages society to act jointly", states Elizabeth de Carvalhaes, executive president of the Research-based Pharmaceutical Manufacturers Association (Interfarma). "This serves to better guide Congress, Anvisa, the pharmaceutical industry and all those who work in this area", she concludes.

When creating the Fight Aids Policy, known as "Treatment for All", in 2014, the government started to expand fast testing, offering universal access to treatment, and distributed free condoms, besides information campaigns on the media at regular intervals. "Few countries were able to coordinate such a system to fight this serious illness that at the time was fatal, like Brazil. We enhanced the pharmacological attention, improving the scientific quest for solutions, and attended and aggregated patients", states Carvalhaes. Today, we have one of the best HIV/Aids programs in the world – a model that revolutionized treatment and the disease history.

The time has come to replicate this formula in the field of rare illnesses. The establishment of a general coordination body within the structure of the Ministry of Health, foreseen by Ordinance 199, would make the difference in fostering the system to look for solutions – legislation, technology, the academia – similarly to what happened in other moments of our history. Due to its specificities, the complexity in facing rare diseases remains larger than an epidemic such as the one we faced with Aids. That is why specialists are emphatic in stating that it will only be possible to transform in cure the promise of innovative therapies for this type of disease if we work together.

FUNDING

The adoption of new **therapies** calls for the **modernization** of agreements

To attain economic viability, it will be necessary to reinvent the health system

If shortly ago advanced therapies were a product of imagination, their becoming a reality came along with the impositions of real world. The challenge of incorporating these brand-new technologies to the health system is as big as the scientific challenges involved in the development of new medications and treatments. In other words, it's about making them economically viable. For the specialists, this mission goes through changing the outdated legislation, and a sound discussion on our own health system.

Obviously, the problem No. 1 is budget. "There is financial limitation, and from what I see the discussion on incorporation is being dealt through the optics of paying for treatments rather than from the ability to do it", states Nelson Teich, former Minister of Health. "The way we are evolving, we will have more and more innovation. And this implies in more and more resources for an incredibly smaller number of people – and our country will be more and more unequal". Teich goes on stating that the current budget is finite; therefore, adopting new therapies means reallocating resources earmarked for other diseases.

Nelson Teich
Former Minister of Health

Photo: Anderson Riedel/PR. Flickr: Palácio do Planalto

Eduardo Calderari
Executive Vice President of Interfarma

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The problem is that proportionally the amount the country earmarks for Health is small – a reality even more real when we consider the disinvestment in the system greatly arising from the spending ceiling foreseen on the Constitutional Amendment 95, of 2016. “Brazil spends 3.8% of its Gross Domestic Product, which is much less than several Latin American countries such as Uruguay, Chile, Argentina, Colombia and even Nicaragua, El Salvador and Panama”, says André Medici, Senior Economist at the World Bank. “In Europe, public spending in Health is 70%; in Brazil it is 43.93%, and the largest share remains with private expenditure, 56,07%, that are personal, and with health operators”.

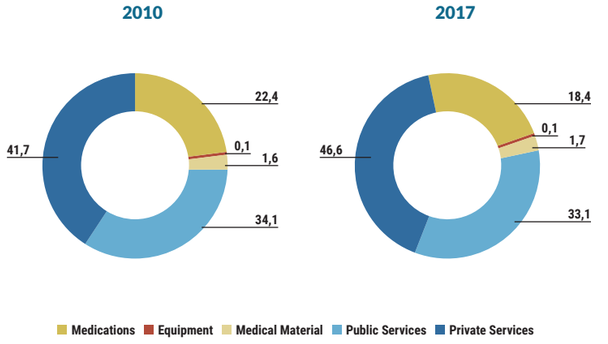
There are additional problems, too. Deficiency in systems’ data collection, pricing and especially judicialization, which drains billions from the system, year after year. According to data from the Ministry of Health, in 2019 alone R$ 1.37 billion were spent with the purchase of high-cost medications and the judicial deposits to pay patients back. In 10 years, from 2010 to 2019, the impact on the budget added up to R$ 8.16 billion. And the planning is also jeopardized because these were unforeseen expenditures.

André Medici
Senior Economist at the World Bank

Angelo Maiolino
Medical Coordinator at the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH)

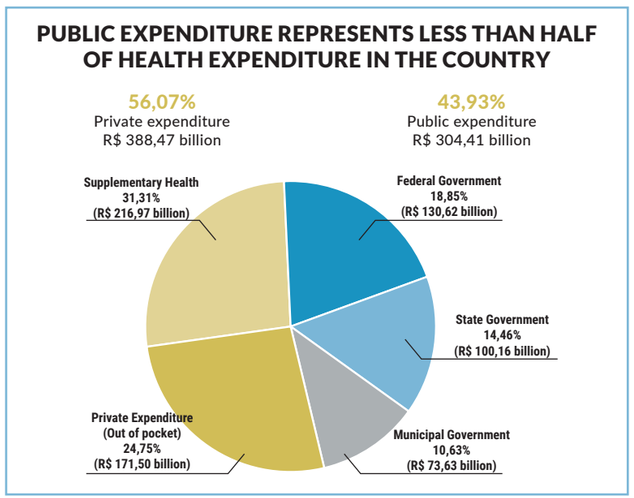
Lindemberg Assunção Costa
President of the National Institute for Pharmaceutical Assistance and Pharmacoeconomics

DISTRIBUTION OF TOTAL EXPENSES OF HEALTH IN BRASIL DIVIDED BY EXPENDITURE CATEGORIES: 2010-2017



Source: Health Satellite-account: Brazil 2010-2017

PUBLIC EXPENDITURE REPRESENTS LESS THAN HALF OF HEALTH EXPENDITURE IN THE COUNTRY



Source: National Association of Private Hospitals (Anahp)

> *“Brazil spends R$ 3,60 on Health per person per day. We face a triple crisis: economic, sanitary, and ecologic. This generates a complicated budget possibility.”*

Áquilas Mendes
Full Professor of Political Economics at the School of Public Health of the University of São Paulo

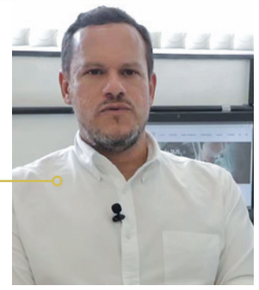
All that must be dealt with the necessary transparency when dealing with public money. The same transparency and clarity that are also necessary when defining the criteria that will guide managers to choose those medications and treatments to be prioritized at the time of resources allocation. “Obviously, the incorporation of new technologies calls for criteria, and so does disincorporation, which is extremely relevant and rarely discussed. We have to bring medical societies into this debate”, says Angelo Maiolino, Medical Coordinator of the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH).

“There is no doubt that the severity of the disease must be considered a strong criterion for the adoption of an advanced therapy”, states Lindemberg Assunção Costa, President of the National Institute for Pharmaceutical Assistance and Pharmacoeconomics. However, he points out that the most important principle is that of equity – that despite being very dear to SUS (the Brazilian Unified Healthcare System), it falls apart with the judicialization of Health, as an example.

This takes us to another important point on this discussion. “Brazil has a complex health system, with fragmented funding models.

FUNDING

Maicon Falavigna
Associate Professor at McMaster University, Canada



Augusto Guerra
Coordinator, Collaboration Center at the Brazilian Unified Healthcare System (SUS) for the Assessment of Technologies in Health, Federal University of Minas Gerais

> *"Dialogue is today one of the challenges for ANS: Bringing to the fore the issue of advanced therapies. Normative aspects must be discussed and enhanced in order to attain sustainability."*
>
> **Ana Cristina Martins**
> *Relations Specialist at the Brazilian Agency for Supplementary Health (ANS)*

And this situation is aggravated by the decentralization of management in three levels: federal, state and municipal, in addition to the division between the public and the private sectors", adds André Ballalai, Global Director at Pricing & Market Access of IQVIA, who considers the definition of some strategic points in the country as a possible way to start the incorporation.

Maicon Falavigna, Associate Professor at McMaster University, Canada, considers that this idea of a decentralized model is a threat to the system's equity. "The risk exists that these therapies are not adequately implemented in several places", he states, emphasizing that obviously there is no need for the implementation of specialized centers in all the states of the union; but a single referral is indispensable in order to be able to exchange patients from different regions and thus treat all Brazilians. Roberto Giugliani, Professor at the Genetics Department of the Federal University of Rio Grande do Sul, echoes this approach: "It is fundamental to work on a national scale".

The subject is controversial. "I have my doubts as to whether the Brazilian model is the most interesting one", states Lindemberg Assunção Costa, who gets back to the subject of judicialization as the biggest cause for the lack of equity. "In theory, the Brazilian model is good, but in practice what we see is the

> *"Regulation in the supplementary healthcare faces some situations in which it is possible to share managing risks among the healthcare operators. The market needs to get organized."*
>
> **Paulo Roberto Vanderlei Rebello Filho**
> *Director at the Brazilian Agency for Supplementary Health (ANS)*

Photo: Cris de Brito

Wilson Follador
Executive-Director at Sano-Efiko

Renata Curi
Health Law Specialist

expenditure of R$ 7 billion in judicial suits. How much of this sum would we spend if we ran a pilot plan in five different states?", he questions.

PRIVATE MARKET

To expedite incorporation, the dialogue among all the agents involved in this process becomes unavoidable, an attitude that is even more determining when supplementary health comes in. "Today, one of the challenges is to put these issues on the negotiation agenda, with patients and healthcare operators", says Ana Cristina Martins, a specialist on regulation at the Brazilian Agency for Supplementary Health (ANS), emphasizing the extreme diversity in this sector. "There are different sizes of operators, various managerial forms, and this enlarges the difficulty in using and monitoring these new technologies".

This is one more evidence of the mismatch between our legislation and innovation, which calls for a per-procedure remuneration, not per-clinical outcome. According to Paulo Roberto Vanderlei Rebello Filho, Director at ANS, the Agency has been encouraging healthcare companies to think over their business models to be able to make the transition between a

FUNDING

disease-based model to one based on value, i.e., clinical outcome and quality of life for the patient's life. "The market needs to reorganize, and find ways for viable funding, with costs that increase more and more", states Rebello Filho.

Today, supplementary health beneficiaries change their health plan when changing jobs; this discourages long-term investment. "This window generally covers three to four years, and private managers must pay health plans for 10 years in order to cover the treatment of a patient who will probably remain with them for a short time", notes Ballalai. "For the World Health Organization" health goes beyond disease; it is the most perfect physical, mental and social well-being state. Stated like that it is beautiful, but if we want all the health possible, we must be prepared to pay for it", stresses Wilson Follador, Executive Director of Sano-Efiko. Risk assessment is the harsh reality we face.

Jayr Schmidt Filho, Head of the Department of Hematology, Transfusion and Cell Therapy at the A.C. Camargo Cancer Center, explains that there are foreign models that are doing OK, but it is difficult to transplant them to the Brazilian reality. "When we discuss advanced therapies, we face a very innovative scenario – i.e., triangulation: the payer, the service provider (hospital) and the supplier (the industry)". Traditionally, models take into account the first two, without the therapy or drug supplier. "As and when we include the industry – a third entity has an increasingly greater cost –, the discussion of new possible models for Brazil is on the table", he concludes.

Despite the harshness of reality, the main convergence point in these discussions is that patients should be the focal point. Angelo Maiolino summarizes the task dimension: "We have been dealing and learning a lot trying to help this process of incorporation of medications not only in the private system, but also in the public. And we clearly realized that the already huge budgetary challenges, will increase. But access and success have represented a real revolution for patients". Reviewing the legislation and tailoring it to this new age is ensuring that advanced therapies do get to those who need them most.

> *"We have no doubts as to its efficacy. We have been following up the scenario in other countries since 2017, but we understand that the reality In Brazil is quite different from other markets."*

Jayr Schmidt Filho
Head of the Department of Hematology, Transfusion and Cell Therapy at A.C. Camargo Cancer Center

Vânia Canuto
Director of Health and Technology Management and Incorporation at the National Commission for the Incorporation of Technologies in the Brazilian Unified Healthcare System (SUS)

Conitec points out challenges in incorporation

There are several steps to be covered between scientific discovery and its translation into quality of life. Conitec – the Commission established 10 years ago to assist the Ministry of Health in incorporating new technologies – has been decisive throughout this avenue. To make decisions, the institution uses multiple criteria based on evidence, encompassing from clinical matters – such as safety and efficacy – to economic impacts and ethics. Vânia Canuto, Director of Health Technology Management and Incorporation and Innovations at Conitec, lists some of the multiple factors that still must be faced to have innovation become common practice.

- LEGAL ASPECTS IN FUNDING AGREEMENTS – PAYMENTS MADE TODAY WITH FUTURE BENEFITS.
- HIGH PRICES – RISK OF SYSTEM COLLAPSE.
- PRICE AND COSTS TRANSPARENCY.
- POTENTIAL REDUCTION IN HEALTH COSTS VERSUS INCREASE IN RELATED AND NON-REALTED COSTS.
- REALOCATION OF FINANCIAL RESOURCES FROM OTHER DISEASES.
- BUDGET FORECAST – WE CANNOT COMMIT FUTURE BUDGETS.

Despite all the difficulties, some actions on the post-incorporation monitoring start to appear. "We are creating a term of commitment between the Ministry of Health and the Industry to follow up these actions. We also have a pilot study under the industry's responsibility and funding; and we are considering a report model for future reevaluation of technologies", informs Canuto.

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Innovative models open the doors to sustainability

Options being examined go from extended payments to variable tranches, up to reinsurance

New payment and management terms in the health industry are being studied in Brazil and all over the world, with the purpose of finding balance between necessity and reality in terms of advanced therapies. Regardless of the type of agreement reached, the change in paradigm is inevitable. “Treatments are acutely expensive, but they will pay out with time. That is why they demand a different reasoning”, states Marco Salvino, Program Coordinator for Bone Marrow Transplantation at the Hospital das Clínicas da Bahia.

Among the formats most used in countries that use a unified healthcare system is the risk sharing agreement, in which payment is linked to the outcome of the innovation. Payer and the technology supplier take upon themselves the fact that there are uncertainties as to the benefits and share the responsibility.

Besides the United States, countries such as England, Italy, France, Spain, and Australia have already tested the model. Professor Juliana Álvares, researcher at the Collaboration Center of the Brazilian Unified Healthcare System (SUS), visited a few countries to observe the execution of this alternative. She points out the need to consider the various risk types, and not only those risks linked to the product benefits.

“In Spain, there are agreements in which the specialized hospital’s structure is a shared responsibility. Sharing risk is not only getting discounts on medications or returning them when the results are not met. It is everything the patient needs to go on”, states Álvares.

The difficulty in implementing the sharing model, even when limited to the technology offer, does not only reside in measuring treatment effectiveness, but also in establishing terms for the review of its validity conditions. For André Ballalai, Global Director for Pricing & Market Access at IQVIA, the answer is simple. "The risk sharing agreement has a date and time to end. The moment there is no more uncertainty, it stops existing”, he adds.

Ballalai also states that payment based on outcome can be made in installments with higher risks, in the short term. Since uncertainty generally takes place in the beginning of implementation, the amount of these installments could be adjusted as and when risks decrease. This proposal is seen with good eyes by Renata Curi, a specialist in Health Law. “Among the most innovative models, it seems reasonable to have an extended payment throughout time, accompanied by a variation in installments”, states Curi.

> *“Is Brazil ready to implement advanced therapies? Nobody is 100% ready! It is necessary to start and enhance the system.”*
>
> **André Ballalai**
> *Global Director for Pricing & Market Access at IQVIA*

Goldete Priszkulnik
Vice-President of the Brazilian Society for Audits in Medicine

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> *“Sharing risk is not only getting discounts or returns when results are not met. It is everything the patient needs to go on.”*
>
> **Juliana Álvares**
> *Researcher at the Collaboration Center of SUS (the Brazilian Unified Healthcare System)*

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According to Ballalai, to dodge the difficulty of commissioning that such an arrangement can bring about, the solution would be to implement an incentives program. "The USA adopts the logic of rewarding the one who delivers the best health service. When outcomes improve, remuneration also improves. Those that deliver less, have their payment also reduced", he explains.

Another format under discussion is the reserve fund, that foresees setting aside a lump sum to be earmarked for advanced therapies or an amount to be spent by patients. A similar approach – with private funding – would be the creation of individual fundraising accounts to finance a possible need for an advanced therapy, so that each person would earmark his premium as if it were an insurance to be used "if" and when the person really needed such a treatment.

Also in the health specialists' radar is the adhesion model, in which it is defined an amount to treat a given disease – regardless of its cost and duration – and the largest possible number of patients affected by the disease would be treated with this payment. This system is used in the United States for some diseases.

The quest for formats that can ensure the incorporation of advanced therapies products and procedures is also being discussed in Supplementary Medicine. Goldete Priszkulnik, Vice-President of the Brazilian Society of Medical Audit, stresses that the industry cannot use a single model. "Healthcare operators will have much more difficulty in doing it. The solution will be to study case by case and establish models that are adequate to the capacity of each segment". She explains.

One of the options facing this sector is reinsurance – when a company in a better economic status takes over part of the risks of another by means of some type of financial accommodation. In such a format, risks are pulverized. Austral Resseguradora's Arthur Mascarenhas explains that this practice is relatively new in Brazil. It was only last year that Brazilian Agency for Supplementary Health (ANS) allowed healthcare operators to sign agreements directly with reinsurance companies, usually foreign companies that work with annual contracts to protect them from price spikes, i.e., for example, helping to avoid the volatility caused by the high cost of advanced therapies. "Healthcare operators can reinsure just part of its portfolio or take into account products for specific diseases, but this market is still new and must be studied", adds Mascarenhas.

The sustainability of new treatments is a concern for all the health chain, including patients. Catherine Moura da Fonseca Pinto, executive director of the Brazilian Association for Lymphoma and Leukemia (Abrale), states that ensuring access is a must, however it is impossible to ignore financial risks. She upholds the adoption of an all-encompassing partnership among public power, pharmaceutical industry, health providers and insurance companies so that we can create an encompassing base that is able to house different models, at one time.

According to the specialist Renata Curi, the collaboration among the various agents in the health chain will be fundamental to place Brazil in the route of innovation. "Establishing public-private partnerships is a must of the State, is part of the Federal Constitution, and the pandemic made this quite clear and open", she states.

> ***"Healthcare operators can reinsure part of the portfolio, but the market is still very young and requires a sound study."***
>
> **Arthur Mascarenhas**
> *Austral Reinsurance Company*

Catherine Moura da Fonseca Pinto
Executive Director, Brazilian Association for Lymphoma and Leukemia (Abrale)

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