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New challenges in health technology assessment (HTA): the case of Zolgensma

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Abstract *Rare or orphan diseases have played an important role in the pharmaceutical industry. On the other hand, the impact of new technologies derived from genomic research has been growing in this industry, with new drugs being launched on the market at unsustainable prices for health systems and patients. This double tendency poses important and growing challenges to public policies on Health Technology Assessment, whose hegemonic rationale is based on cost-benefit analysis between therapies. The very high prices of these drugs require revisiting this rationale and the recent negotiations between the Brazilian Ministry of Health and Novartis regarding a possible risk-sharing agreement for the incorporation of the drug Zolgensma is an opportunity for this revisitation.*

Key words *Technological assessment, Technologies incorporation, Health policy*

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The incorporation of medicines poses new challenges for National Health Systems

Health systems, in particular the public and universal ones, but not only these, are being increasingly pressured with regard to the incorporation of new drugs in the list of products that they must offer to the populations under their responsibility. The pressure derives essentially from the increasing prices imposed by the big pharmaceutical companies (or even not so big ones, but in the process of becoming or disappearing), and at the same time owners of the technologies protected by patents and holders of great political power through lobbies on parliaments, governments, judiciaries and the press.

This price escalation stems from the complexity of processes arising from the shift, still in progress, from a technological and productive route based mainly on chemical synthesis to a biological route in which the relative lack of knowledge leads to a higher rate of failures and, as a result, a higher level of cross-subsidies[1]. On the other hand, the escalation also stems from investments by large pharmaceutical companies in the acquisition of assets that are, essentially, promising "prototypes" of new drugs, often biological. To exemplify, in the case of the medication discussed in this text – Zolgensma – 8.7 billion dollars were paid by Novartis to the company that developed it (AveXis) and which was absorbed by this big pharma company[2].

There is also a characteristic of industry, not only pharmaceuticals, in this stage of financialization of capitalism, which contributes to the explosion in drug prices. In a recent article, L.G. Belluzzo recalls that "*alterou-se a relação entre os recursos destinados ao investimento e aqueles utilizados para propiciar a elevação 'solidária' dos ganhos dos acionistas e da remuneração dos administradores...*"[3]. In other words, if senior executives do not deliver the expected dividends expected by shareholders, they are out of the game.

One of the consequences of this relatively new situation is its impact on the understanding and mechanisms of technology assessment (HTA) in order to be incorporated by health systems. The current intellectual and technical heritage of HTA is based on the rationale born in the United Kingdom (NHS) since the 1960s and whose main transformation milestone in public policy was the creation of the National Institute for Health and Care Excellence (NICE) in 1999. In the following 20 years, the model spread to many countries and was institutionalized in Brazil in 2011 with the National Commission for Technological Incorporation (CONITEC). This rationale can be synthetically and roughly defined as a cross between 'evidence-based medicine' and epidemiology and established a gold standard based on cost-benefit analyzes between therapies. With greater or lesser sophistication, this is the prevalent HTA model in the world and it is the one that has been experiencing increasing difficulties due to the reasons mentioned above.

In 2017, M. Mazzucato and V. Roy published a conceptual article where the logic of what they call 'value-based pricing' is discussed (and criticized)[4]. In proposing a new conceptual model of pricing, they start from three assertions, namely: (1) there is not a single direction in the choices regarding the innovations to be pursued, everything depending on the orientation of public policy; (2) the creation of value results from several stages and actors and not only from the final holder of the patents; (3) the risks and rewards of innovations must be shared and distributed to all actors involved in their creation.

The first assertion touches on the mission of an innovation policy, which should not be left exclusively to market reasons, but should contemplate the strategic objectives of each country or system. The second speaks of the growing complexity of scientific, technological and productive activities involved in industrial products aimed at health, which always involve the action of several public and private actors, from the research bench (here, predominantly with public financial support) up to the finished products, not all of which are duly considered when establishing the final price of the product. And the third assertion, which is of greatest interest in this text, concerns the division of risks and rewards – both financial and health-linked – involved in the incorporation of products, which are increasingly complex and whose mechanisms of action and precision in achieving the desired therapeutic targets are quite uncertain.

Among these drugs whose technological/productive complexity competes in importance with the uncertainty of their effectiveness, there are those intended for rare or orphan diseases[5]. The complexity stems from the fact that, in a growing number (but still not the majority), are drugs developed in a biotechnological route. Uncertainty is often a consequence of the lack of precise knowledge of the natural history of these diseases, their pathophysiology and the uncertainties surrounding the technologies used to face them. Complexity and uncertainty add up

when these rare diseases have a genetic etiology and this causes the investment risks to develop these drugs to increase a lot.

On the other hand, rare diseases are, as a rule, lethal or very disabling diseases and this gravity, added to their low prevalence, make the patients' families, with the objective of socializing their anguish and increasing their power of pressure, organize themselves into associations to claim the incorporation of medications and other patient support procedures. Some have links with pharmaceutical industries that produce drugs for the pathology that their associates have. When the anguish of families comes up against the budgetary and financial limitations of health systems, a crisis sets in.

The Orphan Drug Act and regulations for registering rare diseases with the FDA

An Orphan Drug Act was passed in 1983 in the United States to encourage the development of treatments for rare/orphan diseases. This law provides financial and regulatory incentives for pharmaceutical companies that develop drugs to treat diseases that affect a limited number of people – fewer than 200,000 people in the United States. In Brazil, a disease is considered orphan/rare when it affects up to 65 people in every 100,000 individuals (~150,000 patients). This definition is based on the criteria of the World Health Organization (WHO), which considers a rare disease when it affects less than 1 in every 2,000 individuals. The European Union established its rules for orphan drugs in 1999.

The Orphan Drug Act gave the FDA rules to approve this type of drug, in addition to protecting its market after registration. The law grants them seven years of market exclusivity after approval, against five years for other drugs. Other later rules are accelerated approval based on preliminary clinical results, allowing manufacturers to carry out more flexible clinical studies, with fewer participants and shorter duration. In addition, the use of surrogate endpoints in clinical trials is permitted[6]. In the face of limited evidence of efficacy and safety, labeling and package inserts with incomplete information when compared to other drugs are also acceptable. Finally, the FDA can act as a funding agency, supporting orphan product development projects that require approval.

There is a lot of variation in estimates of the current market value of drugs for rare diseases. One of the most conservative estimates the world market in 2021 at 119 billion dollars (about 8% of the value of the world drug market), with a projected annual growth rate of 12.8% between 2022 and 2030[7]. As of 2017, the FDA has approved more than 600 rare disease therapies since the enactment of the Orphan Drug Act. Since 1983, the growth in the number of registrations has been steadily increasing, with greater acceleration from 2014 onwards[8].

Rare diseases and gene therapies

Most rare diseases cannot be labeled as a genetic disease. These refer to diseases in which the lack or malfunction of one or more genes is the main cause of the disease. Despite more than 600 products approved, as of December 2022 the FDA has only approved three pharmaceutical products that utilize therapies for genetic diseases. Are they:

- Hemgenix (etranacogene dezaparvovec) – for the treatment of Hemophilia B. Produced by CSL Behring and offered for a single dose of $3.5 million.
- Luxturna (voretigene neparvovec) – for the treatment of Hereditary Retinal Dystrophy associated with mutation of the RPE65 gene. Produced by Spark Therapeutics and licensed to Novartis. Offered at a price of $850,000.
- Zolgensma (onasemnogene abeparvovec-xioi) – produced by AveXis, absorbed by Novartis, was offered in the United States in 2019 for the treatment of Spinal Muscular Atrophy for the price of 2.5 million dollars in a single dose.

Gene therapy is a promising approach for treating many genetic diseases, as well as some other diseases, such as some types of cancer. However, in its development, important challenges remain, among which the following stand out:

- Improving gene editing techniques: gene editing technologies such as CRISPR/Cas9 have evolved rapidly in recent years, allowing scientists to more accurately and efficiently modify the genome[(9)]. This opens up new possibilities for the development of gene therapies. However, uncertainties remain regarding the accuracy of the genetic editing carried out with this technology.
- The increased availability of delivery vectors: delivery vectors are needed to transport therapeutic genetic material into the patient's cells. Producing high-quality, safe vectors has been a challenge, but the availability of improved vectors such as lentiviruses, adenoviruses, and adeno-associated viruses (AAVs) is increasing.

• Improved regulation: regulation of gene therapies is complex and varies from country to country. As more gene therapies are approved, regulation should become clearer and more consistent, which can increase public, physician, and health authority confidence in these treatments.

• Scale-up of large-scale production: large-scale production of gene therapies is challenging, but advances in bioprocessing technology and vector fabrication are helping to make scale-up more feasible. And they should help reduce costs and make gene therapies more accessible to more patients.

• The long-term safety of gene therapies: as most genetic diseases are pathologies of low incidence and prevalence, the analysis of the long-term effects on patients who use these therapies makes the evaluation of these effects more complex regarding statistical significance for decision-making for registration and incorporation into health systems.

• The high cost of therapies for patients from different countries and social classes: in addition to the scale of production, the privileged regulatory status conferred on these products, associated with the global patent regime in force at the WTO (TRIPS agreements), tend to reduce the reach of these therapies in terms of the number of patients served. It is also worth remembering the Trips-plus devices included in patent laws in many countries, including Brazil.

• Challenges in the bioethical field: the development of molecular genetics and genomics is advancing much faster than the bioethical standardization related to its potential effects. In the field of medicines, so far it has been a matter of correcting genetic defects that cause diseases, but scientific and technological *húbris* can shift to "improving" human genomes, as, by the way, has already happened with the Chinese scientist He Jiankui, who claimed in 2018 to have created genetically modified humans to make them resistant to HIV using CRISP-cas9 technology.

Risk sharing related to high-cost drugs for rare diseases, in particular gene therapies

Risk sharing for high-cost drugs (Risk Sharing Agreements – RSAs) is a strategy resulting from agreements between governments, pharmaceutical companies and private funders to make drugs for rare diseases more accessible and sustainable. This strategy involves sharing costs among different stakeholders, including patients, public and private healthcare systems, and drug manufacturers.

In the context of drugs for rare diseases, in addition to the high cost, RSA is often used to deal with uncertainty regarding its efficacy and long-term safety. This can be done in several ways, as will be explained later.

The RSA strategy has been used in several countries, including the United States, United Kingdom, France, Germany, Italy, Spain, Portugal, Canada, Australia and Japan. The model agreements listed below show some drugs that have been the subject of RSA in different countries, such as Nusinersen (Spinraza) for the treatment of Spinal Muscular Atrophy. Kymriah (tisagenlecleucel) for treatment of Acute Lymphoblastic Leukemia. Orkambi (lumacaftor/ivacaftor) for the treatment of Cystic Fibrosis. Soliris (eculizumab) for the treatment of Atypical Hemolytic Uremic Syndrome.

Among the mechanisms involved in sharing agreements in different countries and for different drugs, the following stand out:

• Payment for results: in this type of RSA, the drug price is based on the performance of the treatment, measured through specific criteria, such as improvement in the patient's survival or quality of life. If the medicine does not meet the agreed criteria, the price is reduced or the payment refunded.

• Cost sharing: in this type of RSA, drug costs are shared between the manufacturer and the healthcare system. The manufacturer agrees to lower the drug price if the healthcare system agrees to share the cost of treatment, such as hospitalization or supportive care.

• Conditional access: in this type of RSA, the drug is approved for use in specific conditions, such as patients with severe symptoms or who have not responded to other therapies. The results are monitored and, if the medicine does not show the expected results, the use can be discontinued. An example is the agreement between the NHS and the company Gilead for the treatment of Fabry disease with the drug Galafold.

• Tiered pricing: in this type of RSA, drug pricing is based on the outcome of treatment for each patient. For example, the drug price can be higher if the patient shows significant improvement, but it can be reduced if the patient does not show improvement.

• Performance contract: In this type of RSA, the manufacturer and the healthcare system agree on specific performance goals for the drug, such as reducing hospitalizations or decreasing the

need for other treatments. If the targets are met, the drug price is maintained, but if the targets are not met, the price can be reduced. An example is the agreement between the NHS and the company Vertex for the treatment of cystic fibrosis with the drugs Orkambi and Symkevi.

The agreement to be signed between the Ministry of Health and Novartis regarding the drug Zolgensma, for patients with spinal muscular atrophy type 1 (AME in the Brazilian acronym)

Spinal muscular atrophy (AME) is a rare genetic disease that affects the nervous and muscular systems and is caused by a mutation in the SMN1 gene, responsible for the expression of the SMN protein (survival motor neuron), necessary for the survival of the motor neurons that control the muscle movement.

The lack or reduction of this protein leads to the progressive degeneration of motor neurons, resulting in their atrophy with consequent weakness. Symptoms of AME vary according to the severity of the disease and age at onset, but can include difficulty breathing, swallowing, moving arms and legs, as well as problems with posture and balance.

There are several types of AME, which are classified according to the age of onset and the severity of the disease. The most serious type is AME type 1, which usually manifests itself in the first months of life and can lead to early death. Types 2 and 3 are less severe but still cause significant physical impairment and can have a significant impact on quality of life. There is also type 4, which allows the patient to lead a more active life.

Most available treatments are not curative. They help manage symptoms and slow the progression of the disease. These drugs have different mechanisms of action that do not include genetic alterations and require continued administration. In addition, physical therapy and occupational therapy can help maintain muscle strength and improve patients' quality of life.

Currently, there are some drugs approved for the treatment of SMA. They were developed to treat different types of SMA, based on the specific mutations that cause the condition. Below are some of the drugs available and the companies that produce them:

Spinraza (nusinersen) – is an injectable drug approved for the treatment of all forms of SMA. It is produced by the company Biogen.

Evrysdi (risdiplam) – is an oral medication approved for the treatment of all forms of SMA in patients aged 2 months and older. It is produced by the company Roche.

Zolgensma (onasemnogene abeparvovec) - is an approved gene treatment for SMA type 1. It was developed and produced by the company AveXis, absorbed by Novartis. If the effectiveness of this drug is confirmed for all eligible patients, including the permanent and functional expression of the missing protein, with a significant improvement in quality of life and in the absence of important side effects, it could be considered a curative product.

In 2021, following advice from NICE, the NHS signed a Zolgensma risk-sharing agreement with Novartis. Its main terms involve:

• Payment for the drug will only be made if the therapy produces significant clinical improvements (not surrogate outcomes) in patients with SMA type 1, the most severe type of the disease.

• Payment for the drug will be spread over five years, with a percentage of the initial payment (20% of the total price) being refunded if the therapy fails to deliver the expected clinical results.

• The agreement provides free access to the therapy for patients who received it as part of the original Novartis clinical trial. This item is likely to be lapsed unless Novartis continues to recruit patients by expanding the Phase III clinical trial. Finally, the agreement also provides for access to clinical and outcome data to assess the therapy's long-term effectiveness.

• Eligible patients must have less than six months of life with SMA type I and spend more than 16 hours a day without the need to use invasive ventilation methods.

• With more than six months and up to two years to live, eligibility must be assessed by an independent panel of experts.

The full agreement between the NHS and Novartis, subject to commercial confidential information, is published and can be viewed at: https://www.nice.org.uk/guidance/hst15

On December 30, 2022, the Brazilian Ministry of Health and Novartis signed a commitment term for risk sharing with a view to incorporating Zolgensma into the public health system (SUS). The drug had its incorporation suggested by CONITEC and after the signature of the possible sharing contract, a Clinical Protocol and Therapeutic Guidelines necessary for the agreement to enter into operation and the drug to start being used should be constructed.

From what can be extracted from the press reports, given that so far there is still no contracted agreement, it is a sharing project in the form

of payment for results, similar to the one signed between the NHS and Novartis.

The details of the understanding between Novartis and SUS have not yet been released and what follows was taken from news in press organizations and from a CONITEC note published on the internet (https://www.gov.br/conitec/pt-br/assuntos/noticias/2022/dezembro/ms-e-novartis-firmam-compromisso-para-elaboracao-do-acordo-de-compartilhamento-de-risco-para-ame).

Originally, the company requested a price of BRL 12 million/treatment in the country, and the Chamber of Regulation of the Medicine Market (CMED) set a maximum sale price in Brazil of BRL 6.5 million. The medicine was initially offered to the SUS for BRL 6.4 million/treatment and, in an understanding with the Ministry of Health, the price of BRL 5.7 million was reached. Novartis also offered a 3% discount on the value of each dose, around R$ 170,000, to be used for screening children with AME. The payment will be in five years, with installments of 20% of the total per year. The company will only receive all installments if the child reaches certain developmental milestones - such as holding his head up and sitting up - and if they are maintained until the fifth year. The agreement provides for the purchase of a maximum of 250 doses in the first two years, and the provision of an additional 40 treatments by the company at no cost, if necessary. It is not clear whether the financial resource will be returned to the ministry if there is no adequate evolution attested by a committee of experts.

The final proposal recommended by CONITEC was payment in five years, with 20% of the drug price divided annually. According to available information, the manufacturer will only receive the installments after the first year of the infusion if the child reaches motor milestones and maintains them at the end of the fourth and fifth year. That is, the company receives the first installment at the time of infusion and the payment of the remaining installments will be linked to the result - no death, no evolution to mechanical ventilation and good motor progress according to the Chop-intend[10] scale. The patient will undergo an evaluation by a specialized medical team, indicated by the Ministry of Health, and if they reach the motor milestones, the company will receive the second installment. Otherwise, it no longer receives the values. According to former minister Queiroga, "In practice, we are going to detail together with the company some terms of this contract on the acquisition, the specialized places that will be able to infuse this therapy, and especially a team that has the capacity to monitor these outcomes so that we can have the attestation of these results and, later, the payment to the company" (free translation).

Dispensing of the drug must serve all patients registered in the Specialized Component of Pharmaceutical Assistance Policy who meet the inclusion criteria for using the drug as recommended in the Clinical Protocol and Therapeutic Guidelines for Spinal Muscular Atrophy.

The legal forecast for offering the new technology in the SUS is up to 180 days from the date of publication of the incorporation ordinance.

The agreement also includes the training of professionals to handle the product, which is administered through a venous infusion.

Some uncertainties and concerns

The first thing to do is to demand that it be widely disseminated in its entirety, with due regard for commercial restrictions that include confidentiality clauses. In addition, there remain some doubts that are worth enunciating.

• The first is to estimate, with as much precision as possible, the prevalence of AME in Brazil. The information available on the Internet is widely divergent depending on the source used. According to the National Institute of AME, there are 1,509 patients, of which 511 are type 1, 508 are type 2 and 367 are type 3. The Brazilian Association of AME estimates a prevalence of between 5,000 and 10,000 patients for the four types. And the portal for rare diseases and orphan drugs (ORPHANET) estimates a prevalence of 1 case for every 30,000 people, which provides an approximate number of 7,000 patients in the country. It is essential to clarify which estimate MS works with. The already mentioned National Institute of Spinal Muscular Atrophy estimates that more than 900 patients are currently being treated with Nusinersena, 108 with Risciplam and 119 received Zolgensma, with 84 of them receiving the medication by the Public Power, through the judicial process.

• Another important aspect is to know clearly how the specialists who will evaluate the clinical evolution of the patients will be chosen, as well as the criteria used in this choice. The agreement between Novartis and the NHS provides for a multidisciplinary group. It is important to ensure that there is no conflict of interest in the constitution of this committee.

• According to current regulations, products and processes incorporated by SUS must necessarily be incorporated into the list of procedures of the National Supplementary Health Agency (ANS, the Brazilian private health system). Therefore, during the term of the agreement between SUS and Novartis, health plans must, obligatorily, provide the medication, probably according to the same model established in the agreement with SUS. It will therefore be necessary to establish strict criteria for inclusion of patients in the SUS program to establish the rules for dividing them (and expenses) between the ANS and the SUS. If all patients eligible under the terms of the agreement, with or without health plans, are registered in the Specialized Component of Pharmaceutical Assistance of the Health Ministry, how will the distribution of drug expenses be established between the SUS and the private plans? Expenses reimbursement experience carried out by the SUS with patients who have private health plans has been unsuccessful and may not be a good solution. An alternative would be to define an *ex-ante* rule for the allocation of patients that would be included in the agreement with the pharmaceutical company. The agreement would therefore be a tripartite agreement – SUS, ANS and Novartis. Or, at least, between MS and Novartis with the consent of the ANS.

Research on AME in Brazil

There are ongoing studies on AME country. Among them stand out:

• The Sobres project (Brazilian Observational Study of the Reality and Epidemiology of Spinal Muscular Atrophy) is a multicenter observational study conducted by the Center for Regional Development and Planning (CEDEPLAR) of the Federal University of Minas Gerais (UFMG) in partnership with the Brazilian Association of Muscular Dystrophy (ABDIM) and the Brazilian Society of Pediatrics (SBP). The study began in 2017 and plans to include around 1,000 participants, including children and adults, with all types of AME. So far, more than 500 participants have been recruited in 20 research centers spread across all regions of Brazil. Its objective is to estimate the prevalence, survival and quality of life of people with Spinal Muscular Atrophy (SMA) in Brazil, in addition to assessing the quality of care and the availability of treatments for the disease in the country. Among the main results obtained so far, the identification of a higher prevalence of the disease than previously estimated stands out, with an average of 1 case per 10,000 live births, which represents a potentially affected population of around 2,000 people. in Brazil, which is close to the estimate of the National Institute of AME.

• The AME Unidos Project is a multicenter study coordinated by the Federal University of São Paulo (UNIFESP). Its objective is to evaluate the impact of Spinal Muscular Atrophy (SMA) on the quality of life of patients and their families. The project also seeks to identify factors that may influence the evolution of the disease. The project started in 2015 and currently has the participation of 19 research centers distributed in 11 Brazilian states. AME patients and their families are invited to participate in the project and are submitted to clinical, genetic and neurological evaluations. The project also evaluates the effectiveness of different treatments for SMA, such as gene therapy, disease-modifying drugs and physiotherapy. Finally, the project intends to create a national registry of patients with AME.

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Coda

Based on the analysis of a concrete case, this text intended to provoke a debate on a general topic of great importance for public health policy. The current process of research, development and production of drugs governed by medical chemistry (random screening and rational design screening) is slowly giving way to items produced by a biological Route[11,12]. This process, which is far from being concluded, poses challenges in several fields, one of which is the evaluation and incorporation of technologies, which is seen dealing with new drugs at prices that are inaccessible to health systems and, even more so, to consumers. patients and their families. Perhaps the rare diseases subject to gene therapies are the tip of this iceberg which, if not properly debated, could lead public health systems to major crises in the definition of what is fair, ethical and sustainable.

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