THE CHALLENGES OF BRINGING CELL & GENE THERAPIES TO EMERGING MARKETS

Rio de Janeiro,
2022

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DIRETORA PROSPECTIVA

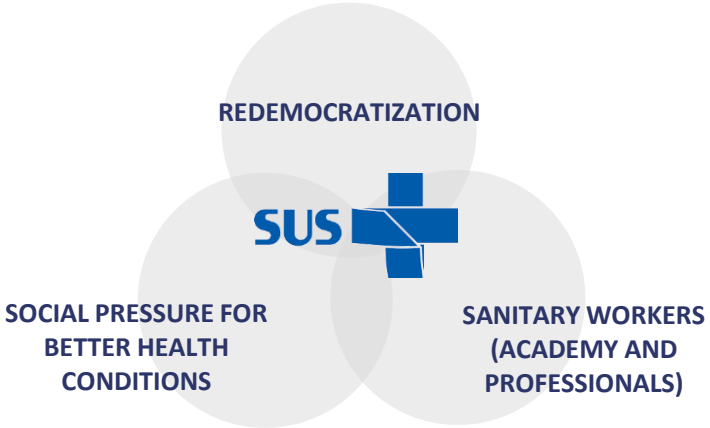
Lawyer, she has been working in the area of innovation, partnerships and access in health for over 15 years. She holds a PhD in public policy from UFRJ. She was responsible for the Partnership and Innovation area at Fiocruz's Center for Technological Development in Health. She structured and coordinated the legal sector of Farmanguinhos, the official public laboratory. Founder of the consultancy CURIe – studies and projects in health. She participates as an advisor in international health projects, such as the Global Virome Project. She has published several scientific articles in national and international journals. She is a professor, speaker, and reviewer for health journals.

ORGANIZATION OF THE HEALTH SYSTEM

PUBLIC HEALTHCARE (SUS)

SUS IS A SOCIAL PRODUCT WITH OVER THREE DECADES OF DEBATE

- Creation with the Constitution of 1988.Largest public health system in the world.
- Health is everyone's right and a duty of the State, through public policies (art. 196).
- The operationalization of the system was regulated two years later, with the publication of the Organic Law of the SUS (8080/1990).
- Constitution allows the participation of private health.



SYSTEM PRINCIPLES

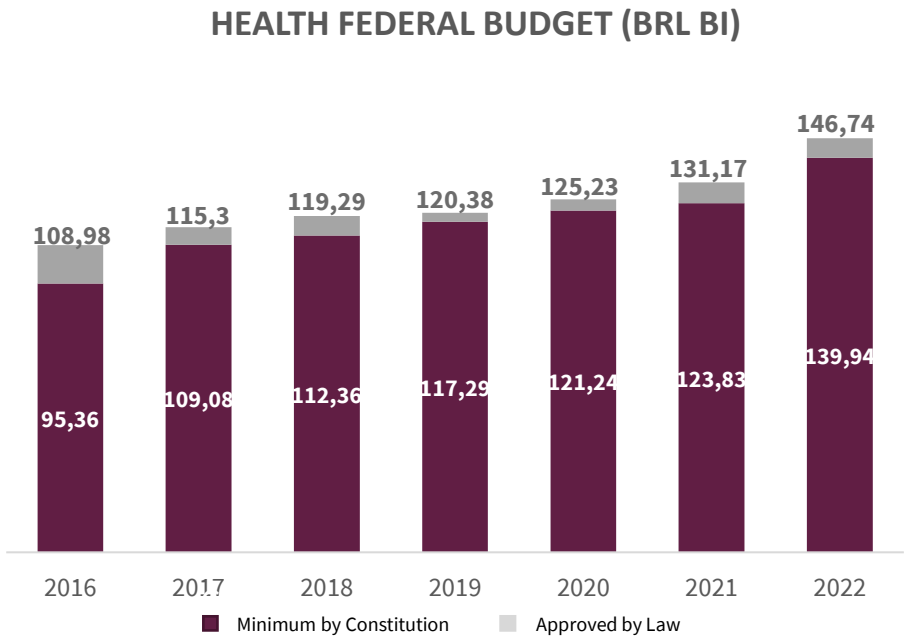
UNIVERSALITY

EQUITY

INTEGRALITY

INVESTMENTS IN HEALTH - FEDERAL

- No additional health investments (“Spending Cap”)
- Pressure from demographic and epidemiological transitions
- Cost reduction/rationalization logic
- Municipalities pressured to compensate investments due to restrictions imposed by limited federal budget and state debts
- Reviewing of public policies seeking to reduce public spending and increase efficiency
- Strengthening agendas of health promotion, prevention and basic healthcare
- Less flexibility in negotiations with the industry

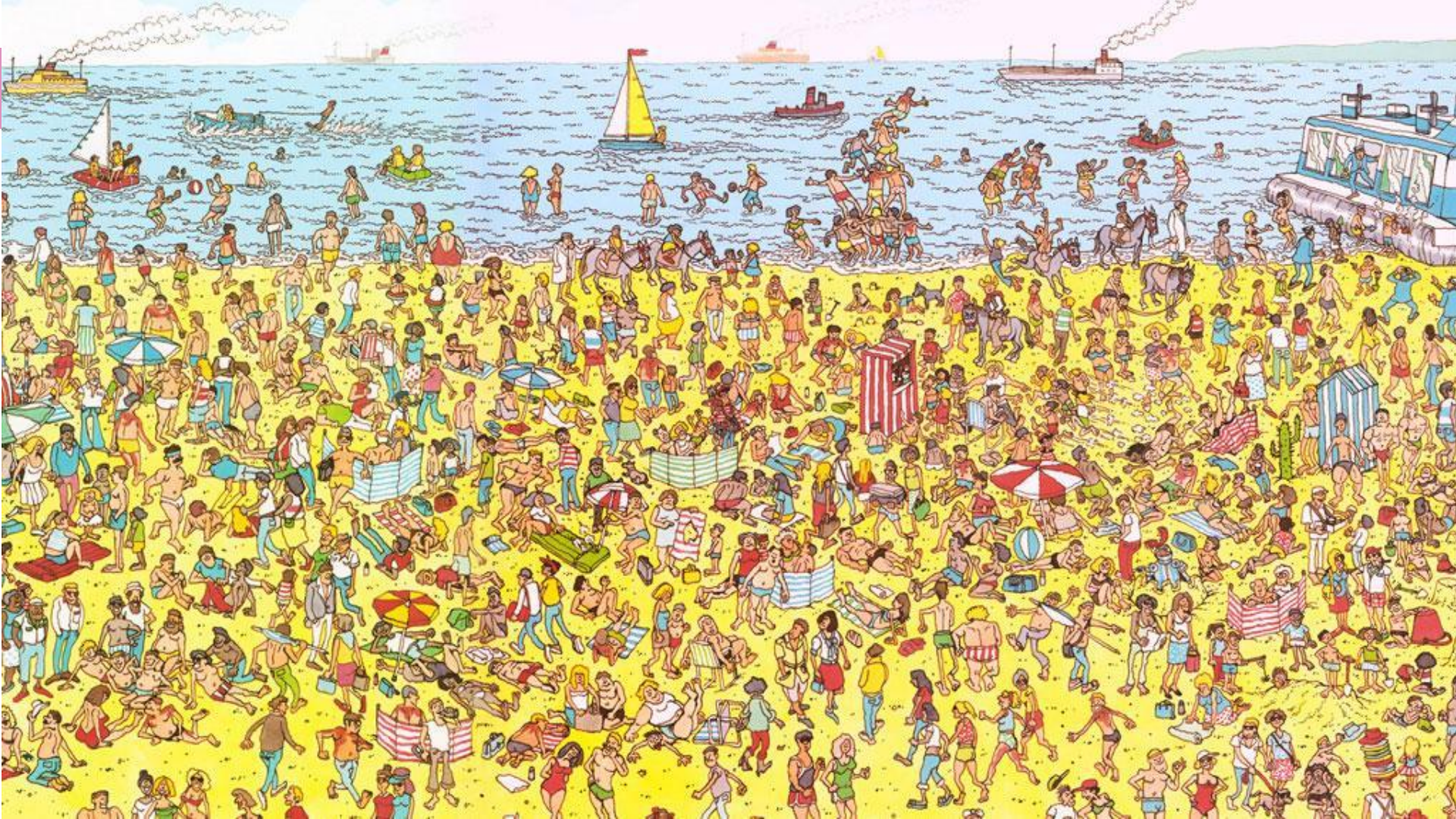


Source: Prospectiva, based on federal budget. Data from 2022 Budgetary Law.

COST VERSUS VALUE

- In Brazil, in a report published by Nurem/Anvisa, only 3% (three percent) of technologies approved in the country from 2004 to 2011 have shown some benefit to the patient health compared to existing therapies.
- Of the new drugs launched in this period, in Brazil, 97% (419 out of 433) did not have patent and/or did not prove any type of therapeutic gain in relation to the drugs that were already on sale in the Brazilian market

F: ANVISA, Efeitos da Resolução CMED n 02/04 no processo de análise de preços de novos medicamentos. Relatório Técnico, Brasília, DF



EVIDENCE-BASED DECISIONS

No. 277

RISK SHARING AGREEMENT - AN OPPORTUNITY TO THE BRAZILIAN PUBLIC HEALTH SYSTEM?

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Introduction

Risk sharing agreements (RSAs) are arrangements between payers and manufactures submitting the price of a new health technology to its performance in practice. Considered as a form of Managed Entry Schemes, RSAs are among other innovative and horizontal approaches used by Public Health systems in order to manage limited budgets and uncertainties on technology whist promoting access to new medicines. In 2010, Brazil has spent 12,5% of its health budget in medicines against 5,8% in 2003. Moreover, Anvisa reports that 3% of the medicines approved from 2004-2010 brought some benefit comparing to the existent technologies.

Objective

To analyze the feasibility of RSAs in the context of the Brazilian Health System, considering the advantages and challenges experienced by European Countries.

Methodology

A study is being carried out to verify the application of RSAs in Brazil in three different contexts:

i Trastuzumab, for partial indications

ii Ranibizumab, not listed on the ground of lack of evidence on effectiveness and cost-effectiveness

iii Cetuximab, currently under assessment.

Results

The above treatments have at least one RSA in place in more than one country:

i) In Italy, the MoH and Roche has an agreement in place to pay for Trastuzumab according to its performance in real conditions.
ii) For Ranibizumab, RSA assumes varies terms in UK, Italy, Netherlands and Portugal including payment for performance and monitoring registry.
iii) Cetuximab is object of agreement around pre-agreed clinical outcome in UK and payment by results in Italy.

Reimbursement of Ranibizumab in Brazil was denied on grounds on price- comparing to Bevacizumab. The RSA in place for Ranibizumab adopts the form of a cap dosing agreement, where the MoH pays an agreed limit of dosages while the company assumes the cost if patient needs to continue the treatment.

In Brazil, reimbursement of Cetuximab for head and neck cancer was denied on grounds of lack of cost-effectiveness. According to CONITEC, *The results suggest that cetuximab shows efficacy for a very specific subgroup of patient.* One of RSA roles is to reduce expenditure while also promoting rational use of medicines. In this case, the RSA could establish the reimbursement by the Brazilian MoH only in those groups where the medicine was proven effective. According to ordinances 18 and 19 2012 da CONITEC, Trastuzumab is reimbursed either to the initial as well to the advanced phase of breast cancer. According to Petramale, 52,680 patients are expected to benefit from Trastuzumab, but this number doesn't distinct from initial or advanced cancer. The use of a biomarker to elect the patients who would benefit from the treatment does not consist a RSA. To configure an RSA the price of reimbursement should be linked to performance of Trastuzumab in real world defined by positive biomarker test.

Conclusion

Despite the skepticism surrounding RSAs, especially concerning their financial and administrative burden, RSAs could be used to adjust prices of new technologies to their benefit in Brazil to promote access.

Trastuzumab was listed in Brazil for both initial and metastatic breast cancer, regardless of a lack of evidence of effectiveness, as an answer to the volume of lawsuits. RSAs may successfully address this.

The use of biomarkers to assess RWE in the Ranibizumab schemes could tackle the difficulties in choosing criteria and analyzing the outcomes.

For Cetuximab, the reimbursement process could impose an obligation for industry to rebate costs of any non-responders after 6 weeks, e.g. England.

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Evidence-Based Decisions

REGISTRATION

INCORPORATION

PRICING

AQUISITION

RISK SHARING AGREEMENT IN BRAZIL

Risk Sharing agreements

"Unlikely traditional agreements, the price of the technology is linked to future events that are not fully known and based in real world evidence"

F: HAUEGEN, RC. Tese de doutorado, 2015

Appl Health Econ Health Policy (2016) 14:1–8
DOI 10.1007/s40258-015-0182-5

CrossMark

CURRENT OPINION

The End of the International Reference Pricing System?

Ulf Persson[1,2] · Bengt Jönsson[3]

Campillo-Artero and Kovacs *BMC Health Services Research* 2013, **13**:181
http://www.biomedcentral.com/1472-6963/13/181

BMC Health Services Research

RESEARCH ARTICLE Open Access

The use of risk sharing tools for post adoption surveillance of a non pharmacological technology in routine practice: results after one year

Carlos Campillo-Artero[1*†] and Francisco M Kovacs[2,3†]

BRAZILIAN INIATIVES

Brazilian Initiatives – Hep C

'Brasil só vai pagar por terapia da hepatite C após cura do paciente', diz ministro da Saúde

Segundo Ricardo Barros, acordo foi feito com fornecedores de medicamentos para a condição. País espera tratar e curar as 657 mil pessoas que vivem com hepatite C no Brasil e eliminar a doença até 2030.

Por Monique Oliveira, 61

"A estratégia é o pagamento pela cura, e não pelo medicamento", disse Barros. "Também vamos estimular a concorrência para baratear o tratamento", completou.

Laboratório negocia teto de gasto para que SUS adote remédio que trata doença rara

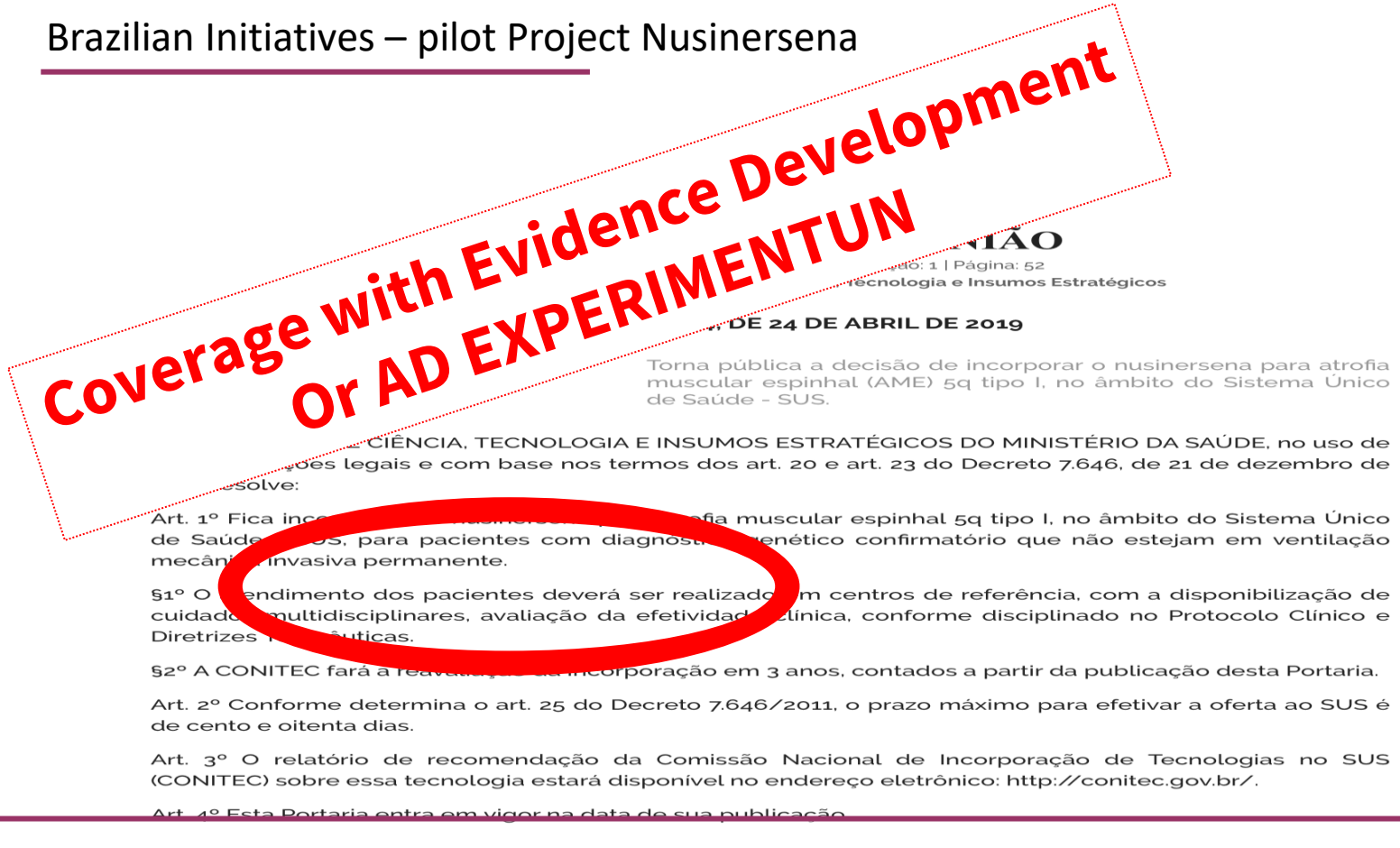
Se o total de pacientes for maior que a projeção da marca, excedente seria gratuito

Brazilian Initiatives – pilot Project Nusinersena

- Necessary six doses in the first year of treatment
- Judicialization: 106 patients were treated by order of Justice. In 2018, BRL 115.9 million was spent on the purchase of Spinraza. (Federal Senate website)
- After Reimbursment decision, the technology must be available in 180 days
- Criteria for monitoring the evolution of treatment included *increasing life expectancy, reducing the use of ventilation devices, and improving motor function and quality of life.*

Brazilian Initiatives – pilot Project Nusinersena

Coverage with Evidence Development Or AD EXPERIMENTUN



...NIÃO
...ção: 1 | Página: 52
...Tecnologia e Insumos Estratégicos

... DE 24 DE ABRIL DE 2019

Torna pública a decisão de incorporar o nusinersena para atrofia muscular espinhal (AME) 5q tipo I, no âmbito do Sistema Único de Saúde - SUS.

... CIÊNCIA, TECNOLOGIA E INSUMOS ESTRATÉGICOS DO MINISTÉRIO DA SAÚDE, no uso de ...ções legais e com base nos termos dos art. 20 e art. 23 do Decreto 7.646, de 21 de dezembro de ...esolve:

Art. 1º Fica inc... ...fia muscular espinhal 5q tipo I, no âmbito do Sistema Único de Saúde - SUS, para pacientes com diagnóst... ...enético confirmatório que não estejam em ventilação mecân... invasiva permanente.

§1º O ...endimento dos pacientes deverá ser realizado ...m centros de referência, com a disponibilização de cuidado... multidisciplinares, avaliação da efetividad... clínica, conforme disciplinado no Protocolo Clínico e Diretrizes T... ...uticas.

§2º A CONITEC fará a reavaliação da incorporação em 3 anos, contados a partir da publicação desta Portaria.

Art. 2º Conforme determina o art. 25 do Decreto 7.646/2011, o prazo máximo para efetivar a oferta ao SUS é de cento e oitenta dias.

Art. 3º O relatório de recomendação da Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC) sobre essa tecnologia estará disponível no endereço eletrônico: http://conitec.gov.br/.

Art. 4º Esta Portaria entra em vigor na data de sua publicação.

Ordinance 1279/2019 MoH and Bill 667/2021

Brazilian Experience

1. Risk-sharing agreement is the instrument for the reimbursement of health technologies entered into between the Ministry of Health and the pharmaceutical company that supplies the drug, due to uncertainties regarding:
I – the cost/effectiveness of the medication incorporated into the public system under real conditions; and
II – estimated consumption, considering the number of pills/doses and budgetary impact.

2. Objectives

3. Justification

4. Types

5. Criteria

Donation

Agreement 219/2020
Procedure

2. CLÁUSULA SEGUNDA – CRONOGRAMA DE ENTREGA

2.1 Cronograma de Entrega: [redacted] MG/ML, SOLUÇÃO INJETÁVEL .

Cronograma de entrega – [redacted] g/mL x 14mL			
PARCELA	**QUANTIDADE (Frasco-ampola)**		**Prazo máximo de entrega no almoxarifado das SES e/ou do Ministério da Saúde**
1ª	100%	**10.000**	Até 30 dias após a assinatura do contrato
	70%	7.000	
	30% (cessão não onerosa)	3.000	
2ª	100%	**10.000**	Até 30/09/2020
	70%	7.000	
	30% (cessão não onerosa)	3.000	
3ª	100%	**5.580**	Até 30/12/2020
	70%	3.906	
	30% (cessão não onerosa)	1.674	
TOTAL	100%	**25.580**	
	70%	17.906	
	30% (cessão não onerosa)	7.674	

2.3. O objeto da cessão não onerosa, a despeito da sua gratuidade, não exonerará a CONTRATADA de arcar com todas as obrigações previstas neste instrumento contratual, inclusive quanto a local, forma e prazos de entrega, e quanto às responsabilidades sanitárias no atinente ao conteúdo, ao transporte e atendimento das demais normas pertinentes, especialmente àquelas emanadas pela Agência Nacional de Vigilância Sanitária – ANVISA, as quais devem ser fielmente e estritamente cumpridas, estando a CONTRATADA, também, sujeita à aplicação de sanções pela inobservância de quaisquer das obrigações contratuais pactuadas.

GENE THERAPIES

OVERVIEW

The agenda has been developing rapidly, but the high cost of the procedures represents a barrier to access.

Gene Therapy

Anvisa

The Agency was a pioneer in creating a regulatory framework aimed at advanced therapies and gene therapy in particular. There are rules for conducting clinical trials, registration, and best practices involving the procedure, but the agency still lacks practical experience.

CMED

CMED does not yet have specific rules for pricing gene therapies. The Chamber has been setting prices on an ad hoc basis, including through clinical comparison with technologies not classified as advanced therapy. There is an effort to update Res. 2/2004, but still no clear outcome for gene therapies.

Conitec

A Conitec decided not to reimburse the gene therapy Luxturna, the only one assessed so far. The main barrier is the high cost and the lack of evidence

Risk sharing agreement are being considered.

Public Policies

MoH offers genetic tests to support the diagnosis of mutations involving a few gene diseases but is restricted to services and centers specializing in rare diseases. For these diseases, the discussions still do not mention gene therapies

RDC 505/2021 - REGISTER

This measure is considered a step forward in regulating the registration of advanced therapies by Anvisa.

Product Classes Definitions

- **Advanced Therapy class I:** advanced cell therapy product subjected to **minimal manipulation** and that performs a different function in the recipient from that performed in the donor.
- **Advanced Therapy class II:** advanced cell therapy product subjected to **extensive manipulation**, tissue engineered product, and **gene therapy** product.

General Guidelines

(I) Clinical trials of gene therapies conducted in Brazil need prior authorization from Anvisa.

(II) The agency may require post-registration data on additional evidence (about quality, safety and efficacy) of products.

(III) Advanced therapies involving Genetically Modified Organisms (GMO) necessarily need to be approved by the National Technical Biosafety Commission (CTNBio).

(IV) It is not possible to register a product for a specific patient, in an imminent state of life.

Registration Prioritization

At least one of the criteria :

- Used for rare, neglected, emerging disease, for public health emergencies or in serious debilitating conditions and in situations where there is no therapeutic alternative available;
- Have a new therapeutic recommendation or expansion of use for the pediatric population;
- Have had the conduction of clinical trials phase I or II in national territory.

EVOLUTION OF DISCUSSIONS - INCORPORATION OF TECHNOLOGIES AND ADVANCED THERAPY

Topic points under discussion in the new regulation of CMED directly impact the pricing of gene therapies. Despite the uncertain outcome, entities' positions are repeated and suggest some possibilities that can be adopted in the new resolution.

Pricing Criteria for Advanced Therapy

1. points out the problem, but do not point out a concrete way to solve it.
2. Creates of a new product category, but with **the same pricing rule as for Category I.**

Category I: New product with patent and that brings therapeutic gain in relation to drugs for the same indication.
Criteria: Price cannot be higher than: Australia, Canada, Spain, USA, France, Greece, Italy, New Zealand, Portugal.

Countries pool

The Resolution provides that prices cannot be higher than the lowest price within the countries pool, but the industry has suggested new formats :

1. **Exclusion of the manufacturer price** in the country of origin of the pool.
2. **Average of prices** charged in the pool of countries instead of the lowest price.
3. **Exclusion of countries in economic crisis** or that have government subsidies for drugs from consideration.

Analysis Deadlines

1. Faster analysis deadlines for technologies aimed at **rare diseases**, in line with Anvisa's fast-track resolutions that facilitate the process (RDC 204/2017 and RDC 205/2017).
2. Clearer criteria for delaying deadlines, in cases where the CMED finds great **complexity** in the technology analysis.
3. Sui generis changes in deadlines for each pricing category**.**

Legal Grounds

- Ordinance 1279/2019 Ministério da Saúde
- Law nº 8666/1993 Public Purchasing
- Law nº 14.133/2021 Public Purchasing
- Ordinance of CED
- Science, Technology and Innovation Law

Act 141333/2021

Legal Grounds

- Cooperation - Narrative change;
- Different competition models
- Extended term – 1, 5, 10 years (especially if strategic for the MoH
- the market can “propose and carry out studies, investigations, surveys and projects of innovative solutions that contribute to issues of public relevance”
- Contracting Efficiency;
- Prior negotiations
- Confidentiality in certain phases

Considerations

- Stronger Health Technology Assesment prior to the agreement
- MoH Guideline : Governance and procedure
- Capacity building : dedicatedy and interdisciplinary team
- Data Collection
- Compliance
- Economic Balace
- Transparence
- Flexibilities : Different Models and flexilble terms for each of them
- Industry Support in structuring the program
- Industry finantial support besides the Risk also in the execution
- Program assessment and review

QUESTIONS AND DISCUSSIONS

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