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Editorial – Volume 1 – nº 02- 2023

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Profa. Dra. Verônica Scriptore Freire e Almeida

Editor-in-Chief

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ANALYSIS OF THE IMPACT OF THE IMPLEMENTATION OF THE ACCELERATED HEALTH REGISTRY OF GENE THERAPIES IN COURT CASES IN BRAZIL [1]

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Abstract

This article will analyze the impact of the implementation of the accelerated registration mechanism, known as fast track, adopted by the Brazilian Health Regulatory Agency (ANVISA) in relation to gene therapies, in court cases in Brazil. Exploratory research was used, with a quantum-qualitative approach and embedded methodological design, analyzing the characteristics of the accelerated health registration regime and the current situation of the judicialization of health, through the collection of bibliographic research, documents and case study, including examination of data produced by the Ministry of Health and the Attorney General's Office (AGU). The research identified the misuse of the primary purpose of establishing fast track through the immediate litigation related to newly approved technologies and the increase of convictions in individual lawsuits to impose to the federal government the provision of such technologies in recent years. The evidence obtained points to the need for policy and regulatory adjustments to safeguard greater fairness of the public health system and that collective access to new technologies is ensured when they are safe, meaningful in outcomes and cost-effective.

Keywords: court cases, fast track, gene therapies, vulnerability of public health system.

Introduction

This article will analyze the impact that the introduction of the accelerated registration mechanism, known as Fast Track, adopted by the National Health Surveillance Agency (ANVISA) in relation to orphan drugs, causes in the judicialization of health related to the supply of new technologies for rare diseases.

Through exploratory research, with quantum-qualitative approach, the characteristics of the accelerated health registration regime and the current situation of health judicialization will be analyzed, by collecting bibliographic, documentary and case study data, including examination of data produced by the Ministry of Health and the Attorney General's Office for the year 2021. The research considers an embedded methodological design, in which, according to Creswell and Clark (2007, p 67), quantitative data are adopted to explain qualitative results.

The combination of two approaches, from the perspective of the convergence of classical methods in a social science-oriented typology, as explained by Souza and Kerbauy (2017, p. 38), will enable a broader visualization of the problem. Such combination contributes to enrich the findings related to the development of the social processes and dynamics that includes the judicialization of health to provide new technologies.

It was identified, from the collection of statistical data produced by the Ministry of Health, an exponential increase in the values spent by the federal government on court convictions for the provision of medicines for rare diseases. Considering that the ANVISA accelerated registration regime of medicinal

products for this group has been introduced in recent years, this study will examine the possible impacts that legislative modification may have promoted in such a scenario.

For a better understanding of the problem involving the new institute of health registration in the field of the judicialization of health, in the first part of the text it will be analyzed the scenario of application of the accelerated health registry in Brazil and its main characteristics.

In the following session, the differences between the Brazilian health system and the United States, as well as the nature of the evaluation bodies of new technologies in the Brazilian health system, which contains two bodies with different evaluation premises.

Finally, the impact of the new fast track rules on the judicialization of health will be analyzed, in particular with regard to the increase of the convictions of the federal government for the provision of new high-cost technologies through individual lawsuits.

The present study aims to promote reflection on the distortion of the primary purpose of establishing fast track and on the need for political and regulatory adjustments that aim to safeguard greater equity of the public health system and that

collective access to new technologies is ensured when they are safe, meaningful in outcomes and cost-effective.

1. History and reflections on the introduction of fast track in the Brazilian sanitary regime

The Resolution of the Collegiate Board (DRC) n. 205/2017 of ANVISA, introduced in the Brazilian system the mechanism of accelerated health registration for medicinal products for the treatment of rare diseases, through the reduction of deadlines of analysis of registration submission and flexibility of the clinical trial stages presented in the safety and efficacy reports.

Since 2007, ANVISA already adopted priority analysis regarding certain registration petitions in the area of medicines, through the edition of DRC n. 28. However, it was from the edition of DRC n. 205/2017 that the regulatory procedure started to be more similar to the one currently practiced by the American governmental body Food and Drug Administration (FDA), known as fast track.

The most important change introduced by the Resolution concerns the permission to submit the registration request with the presentation of completed phase II clinical studies and phase III in progress; or without Phase III presentation, when its

achievement is not feasible, according to Article 14 (4) of DRC n. 205.

As a condition for receiving accelerated registration, provides DRC n. 205 that the medicinal product should treat, diagnose or prevent rare disease; be used in a serious debilitating condition; and propose clinically significant changes in the evolution or remission of the disease.

In accordance with Article 15 of the Standard, additional evidence may be provided after the registration has been granted through the signature of a term of engagement between ANVISA and the requesting company.

Still under the differentiated regime, the agency edited the DRC number 338/2020, defining rules for registration of products of advanced cellular therapies, genetic and tissue engineering. The flexibility of clinical trial phases has been shown to be more intense in this regulation than in DRC n. 205/2017, allowing exceptional registration of products requiring data and clinical efficacy tests, by presenting a schedule of clinical studies to be performed after registration.

According to Article 30, items II and III, of DRC n. 338/2020, ANVISA may grant exceptional registration for advanced therapy requiring additional data and evidence of efficacy, provided that there is no comparable medicine for the

respective stage of the disease or when the new drug offers greater therapeutic advantage in relation to it (item II). it is also necessary that the benefit-risk balance of the immediate availability of the product overcome the need for additional evidence of its efficacy (item III).

In the Term of Commitment, the applicant must attest to the clinical uncertainties and legal uncertainty that may arise from the accelerated health record of the product, taking responsibility for possible civil and criminal risks and responsibilities, if it turns out, after clinical use, to be unsafe or ineffective.

The applicant for the exceptional registration also requires highlighting in the medicine packages that the product is authorized for use under conditions of monitoring and production of additional evidence of efficacy.

Therefore, since 2020 Brazil adopts much more flexible rules than those originally fixed in DRC n. 205/2017, detaching from the health registry for gene therapies the prior execution of specific stages of clinical trials and no longer requiring significant outcomes, the circumstances that Articles 4º, item II, and 14 §4º of DRC n. 205/2017 explicitly adopted as essential to the registry.

It is noted that Article 30, item II, of DRC n. 338/2020 allows the granting of the exceptional untied record of proof of efficacy when there is no therapy or greater therapeutic advantage compared to the existing one on the market. In the two hypotheses the significance of the effect is neglected, either for improvement of the quality of life of the patient, or for remission of the disease.

However, as pointed out by the Ministry of Health (General Coordination of Management of Judicial Demands in Health/MS, 2019, p. 4 and 6), the existence of new therapy to treat a rare disease, which as a rule is incurable and poses a challenge to medicine, does not necessarily imply a significant increase in the quality of life or a reduction in the stage of the disease. In this sense, it is notable that Anvisa, in the original fast track regulation (DRC n. 205), was careful to stress the requirement regarding the significance of the results and to safeguard early stages of clinical trials (phases I and II).

With regard to the benefit-risk assessment, a requirement of Article 30, item III, of DRC n. 338, there is clear inaccuracy and generality, which does not sound compatible with the necessary systematization required by science. If Evidence-Based Medicine represented a water divider for medical sciences and health systems, bringing safety and effectiveness

to scientific research and decision-making by health managers, by preventing abuses of pharmaceutical market strategies, there is also an urgent need for the regulation of pre-established methods of evaluation of evidence, certainly special and less rigid than the classic methods of Health Technology Assessment (ATS), in view of the difficulties inherent in conducting clinical trials with patients with rare diseases, but which ensure at least scientific plausibility and do not neglect the significant benefits.

As Nascimento explains, the adoption of specific criteria harmonized to the current model of ATS is a possible path to be followed in the context of rare disease medicines (2022, p. 51).

The value of rare disease medicines is very high and it cannot be ignored that it represents a valuable commodity in the current system. Like all merchandise, it is the object of advertising and business, thus clear, fair, non-generic and systematic rules are necessary for the safety of the patient and for the fair and equitable maintenance of the Brazilian health system.

2. The difference in market and Brazilian healthcare system relative in relation to the United States

As the main object of this research is the reflection on the impact of fast track on the judicialization of the health of medicines of high cost, and consequent distortion of the primary purpose of the introduction of accelerated registration in Brazil in the field of the judicialization of health, it is necessary to explain the differences in the market and health system existing between Brazil and the United States, since the latest inspired the new Brazilian registration model.

2.1 Fast track features implemented by the FDA

Although generally known as Fast Track, the FDA has organized four types of procedures in the United States to speed up access to medicines: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review.

The medicine that is intended to treat a serious condition with a medical need not yet addressed may be submitted to the Fast Track approach. If the therapy is intended to treat serious condition and medical need already met, and the new medicine has preliminary studies that demonstrate a substantial clinical improvement compared to the existing one, the special registration procedure is called Breakthrough Therapy.

According to the FDA (2018), the definition of a serious condition is somewhat subjective, but it has parameters of correspondence with factors such as survival, functionality or probability that the condition, if not treated, progresses from less severe to more severe, in circumstances that there is no therapy or is a potentially more effective therapy than the existing one.

The FDA (2018) considers as more effective the therapies that provide: improved effect on serious outcomes; exclusion of serious side effects in therapy already available; improves the diagnosis of a serious condition where early diagnosis results in a better outcome; decreased significant clinical toxicity of an available therapy that is common and causes discontinuation of treatment; and meeting emerging or anticipated public health needs.

The interested manufacturer requests the designation of Fast Track from the FDA, which will decide whether the medicine meets an unmet medical need in a serious condition. If the FDA defers the designation of Fast Track, the medicine becomes eligible for some or all of the special procedures listed below: meetings with the FDA to discuss the drug development plan; more frequent written communications with the FDA on proposed clinical trials; accelerated approval eligibility and

priority review, if relevant criteria are met (Accelerated Approval and Priority Review); and rolling review permission, a procedure for early submission of documents (Biologic License Application or New Drug Application) that allows partial analysis before submission of all mandatory phases of the application for approval, not needing to wait for each section to be completed before the entire process can be reviewed (FDA, 2018).

Already in the "Breakthrough Therapy" approach, it should be determined whether the improvement over the available therapy is substantial, so that the magnitude of the treatment effect and the importance of the observed clinical outcome will be assessed in order to assess whether clinical evidence demonstrates a clear advantage over the available therapy.

To receive the designation of "Breakthrough Therapy," the clinically significant outcome measures whether there is an effect on morbidity, irreversible mobility or symptoms representing serious consequences of the disease, as well as findings suggesting an effect on a substitute endpoint; at an intermediate clinical endpoint considered reasonably likely to predict a clinical benefit; in pharmacodynamic biomarker that does not meet the criteria for an acceptable substitute outcome, but strongly suggests the potential for a clinically significant effect on the underlying disease; and significantly improved

safety profile compared to therapy available and with evidence of similar efficacy (FDA, 2018).

After receiving the breakthrough therapy designation, the medicine is eligible for all available resources in the Fast Track approach.

2.2 The significant change of accelerated approval by the FDA and its disconnection with the context of Brazilian market

Specifically on accelerated approval, a tool implemented to reduce analysis deadlines and that can be applied in Fast Track and Breakthrough Therapy, it should be clarified that it has received significant change in U.S. legislation. The FDA originally instituted, in 1992, an accelerated approval regulation, which allowed rapid registration based on a replacement endpoint (outcome) for drugs intended to treat serious conditions and unmet medical needs. In 2012, the Food and Drug Administration Safety Innovations Act (FDASIA) was passed, allowing approval to be also carried out on an intermediate endpoint (FDA, 2018).

According to information available on the FDA website (2018), a substitute endpoint used for accelerated approval is a marker (laboratory measurement, radiographic imaging,

physical signal etc.) that indicates clinical benefit, but is not in itself an effectively proven measure of benefit. Also according to information made available by the FDA itself, an intermediate endpoint is a measure of therapeutic effect considered reasonably likely to predict clinical benefit.

Since 1992, thanks to the establishment of the accelerated registration mechanism in American legislation, important drugs received accelerated approval in the 2000s, such as Kaletra, intended for HIV treatment, and Pegasys, for treatment of hepatitis C. Such processes represented advancement in the cure of neglected diseases, since allowing accelerated approval (average in four months) of medicines for serious diseases based on substitute outcome, increased access to health and pharmacological care was promoted.

However, with the change of American legislation in 2012, in which the outcomes were further relaxed, admitting intermediary endpoint, combined with the new technological horizon in pharmaceutical production, there is a change of scenario, in which the opening of the instrumentalization of the registration process to economic and marketing strategies is promoted.

In this context, it is interesting to note that the World Health Organization (WHO) calls neglected diseases the ones that are

typically from developing countries, or are unique to them, such as leishmaniasis, Chagas disease (CD), trachoma, hanseniasis, malaria and parasitosis. The WHO differentiates neglected diseases from orphan diseases, clarifying that both cannot generate sufficient incentives for drug development. The first, because of the potential buyer's lack of recourse; and the second, by the small size of the potential consumer market (MORAIS, 2013, p 35).

Morais (2013, p. 11/13), when researching models of pharmaceutical promotion, explains that the least developed or developing countries, such as Brazil, in addition to the budgetary, structural and logistical problems of access to treatment, represent an uninteresting market for large private conglomerates, since there is no attractiveness for international industry to invest in treatment research for diseases typical of such countries, a situation known as a 10/90 imbalance, where only 10% of world health research is devoted to diseases that account for 90% of the global burden of disease.

Considering this context, it should be stressed the vital importance of conducting public research and incentives to official medicine production laboratories. Therefore, the accelerated health registration procedure in this context would represent one of many other measures to be taken by the State

to make access to technologies more efficient in countries with neglected disease.

In the light of the socio-economic context of Brazil, explains Morais (2013, p. 10) that neglected diseases should be widely interpreted, such as tropical diseases, childhood diseases and other basic diseases that predominantly affect poor countries, such as tuberculosis and AIDS, and also vaccine-containing diseases, diagnoses and treatments available for developed countries but not suitable for use in poor countries.

It is noted, then, that the fast track in Brazil should not only meet the technologies for orphan diseases that are approved by the FDA, since these aim to meet its specific consumer audience, not fitting the predominant epidemiological profile in Brazil, which has typical incidence of neglected diseases.

The automatic application of American fast track in Brazil, without the metrics of minimal evaluations treated above and without agreements to encourage scientific research equally priority in relation to neglected diseases, leads to emptying the differentiation proposed by the WHO, since the need to combat neglected diseases is also important to promote socio-economic development for countries such as Brazil.

The application of Brazilian fast track, based on the premises of the FDA and disconnected from the concomitant

institution of extended access program to Brazilian patients, under conditions of reimbursement or co-financing with the manufacturer of the medicinal product, as it occurs in countries paradigm of the fast track, facilitates a scenario that generates the consequent withdrawal of funds from the Brazilian health system (SUS) without analysis of the cost-effectiveness. As a consequence, even more inequalities in relation to neglected diseases are promoted.

Thus, instead of fast track being a mean of simultaneously encouraging research about neglected and orphan diseases, there is currently a tough battle between economic interests and social interests in the course of the judicialization of health, as will be explained below.

In the Organization for Economic Cooperation and Development (OECD) classification for healthcare systems, the Adam Smith model, characterized by access to health through private insurance and funding from voluntary contributions from individuals and employers, applies in the United States. In this system, the State does not assume the responsibility of guaranteeing and protecting the health of the population, merely protecting the most vulnerable social groups (SERAPION and TESSER, 2019, p. 45).

Therefore, it is compatible with the American system the investments in fast track for orphan diseases, since the country is developed and has no epidemiological profile of neglected diseases, as well as it is natural the carelessness with less strengthened beacons of scientific evidence, since the funding is not essentially public, so that trade agreements are made with manufacturers precisely because of the stage of absence of scientific certainty of the medicines approved in fast track.

Brazil, on the other hand, has a mixed or segmented health system, with *beveridgean* characteristics regarding the Unified Health System (SUS) and *smithianists* in relation to the private sector (supplementary health).

The SUS has classic features of the Beveridge model, since it is financed exclusively by public resources and available to the entire population. Thus, instead of replicating an accelerated registration model developed in a country with a health system essentially financed by private capital and with no neglected diseases typical of countries with great social inequality, why not consider joint measures with developing countries to build an innovation plan and fair and equitable access to neglected and orphan diseases?

The proposal sent to WHO in 2009 by the governments of Bolivia, Suriname and Bangladesh on the use of prizes as a

mechanism to encourage innovation in new treatments against cancer and vaccines, with the aim of meeting the needs of epidemiological segments in poor countries and sharing the costs of clinical trials, is an example of an innovation initiative more in line with countries marked by extreme social inequality (MORAIS, 2013, p. 53).

The compulsory licensing mechanism can also be cited as one of the possible outputs for innovation in countries with neglected diseases. According to Morais (2013, p. 55-56), the compulsory licence represents the possibility for a government to ensure that its population has access to essential medicines at reasonable prices, as a bargaining tool for developing countries to obtain considerable discounts from laboratories, and exemplifies the episode in which Brazil, threatening to resort to compulsory leave, obtained discounts on various medications for the treatment of AIDS.

3. The context of the ANVISA's accelerated registration of the drug and the immediate judicialization of the respective approved technology

The evaluative premise of ANVISA in a fast track regime is different from that adopted by the National Commission for the Incorporation of Technologies (CONITEC), the federal agency

responsible for the incorporation of medicines in the Public Health System.

In order to analyze requests for incorporation into the SUS, the requirements set out in art. 15 of Decree n. 7646/2011, such as scientific evidence demonstrating that the guided technology is at least as effective and safe as those available in the SUS for a given indication, and economic evaluation study comparing the new technology with those available in the system.

If there is a therapeutic substitute in the SUS, CONITEC evaluates the studies of the two therapies in order to assess whether in fact there is superiority of the technology object of the request for incorporation (significant difference in the primary outcomes) and performs a formal cost-effectiveness analysis.

In this context, registration of the drug at ANVISA is just one of the requirements for starting the process of analysis of incorporation by CONITEC, in accordance with paragraph 1º of article 15 of the Decree n. 7646/2011, and does not generate presumption of incorporation in the SUS, nor certainty of evidence superior in relation to the other drugs already incorporated.

In light of current legislation, it is observed that there is no political articulation between the fast track and the requirements for incorporation into the SUS. In the interval between ANVISA registration and CONITEC analysis, there is high judicialization for access to the drug that received the accelerated registration, with the costs necessarily being covered by the SUS as if they were incorporated, but granted without any public criterion of harmonization with the System of Health, without analysis of the cost-effectiveness, without comparison with the technology already incorporated, and without the definitions of the technical and clinical criteria that would indicate the public administration of the medicine, because there is no Protocol of Guidelines elaborated by CONITEC in this stage of recently registered medicine.

In the judicialization of health, the orders contemplate an individual for the specific case, as if they were specific exceptions to the system, disregarding the vision of collective health and cost-effective planning structured in the area of health economics. There is no collective purchase and there are numerous court orders for importation in dollars, and in many cases there is not even respect for the maximum value set by the Medicines Market Regulation Chamber (CMED).

These cases are not exceptional. On the other hand, as will be analyzed below, the increase in the judicialization of high-cost drugs arising from Anvisa's fast track has been exponential.

The absence of an extended access policy concomitant with the fast track, with clear rules of financial compensation by the manufacturing company, inclusion of Brazilian patients in the course of clinical trials, reimbursement conditions and respect by the industry for ethical imperatives of access to health technologies, is disastrous for the structure and equity of the SUS.

If judicial orders are provided individually and based on the budget gathered by the plaintiff, it is evident that abuses can be perpetrated, since the public purchase and the consequent national availability, based on pre-established criteria and price negotiation together manufacturers, would represent greater equity for the public health system.

Judicial orders to provide new medicines based solely on the plaintiff's medical report disregard all the requirements that should be analyzed by a Commission of doctors and health professionals, such as the CONITEC, which has expertise in technological analysis and cost-effectiveness. The principle of integrality is, under the terms of art. 19-Q of Law nº 8.080/90,

subject to the verification of safety, efficacy, effectiveness and cost-effectiveness, aspects that are important not only for equity and structuring of the public health system, but also for the safety of the patient himself, avoiding the use of the judicial route to access million-dollar drugs, often with a marketing bias.

It should be considered that the judicial orders to the federal government are often granted in circumstances that the manufacturing company still would not have the technical conditions to request the incorporation before CONITEC, since the accelerated registration with ANVISA is done in the light of criteria of generic effectiveness, while for CONITEC it is necessary to produce robust technical material on cost-effectiveness, setting the necessary discount for incorporation and/or sharing costs with the manufacturer.

The judicial granting of a drug recently approved by Anvisa entails profit margins for the production chain involved on a scale that is greater than that of incorporation into the public health system, and this margin is financed with public resources from the SUS, without any counterpart or financial liability of the manufacturing company, a scenario that would not occur if the incorporation analysis procedure takes place at a stage prior to the judicialization.

3.1 The Zolgensma case

The gene therapy Onasemnogeno Abeparvovequexio (Zolgensma®), indicated for children less than 2 years old with a certain type of spinal muscular atrophy (SMA), received accelerated registration from ANVISA in 2020. Before, when the therapy received registration in fast track of FDA, it was hailed as a 'cure' for this debilitating and life-threatening condition, and evaluated at US$2 125 000 for a one-time infusion (at BRL 11.3 million at the time). The manufacturing company undertook to annually send data from ongoing studies to Anvisa and ensure the carrying out complementary follow-up studies of Brazilian patients.

Ivama-Brummell, Wagner, Pepe and Naci explain that Anvisa's conditional approval for Zolgensma was based on the same data as those used by the FDA, but, after approval, relevant uncertainties hovered over the long-term safety and efficacy of the medication. Therefore, in the absence of relevant therapeutic benefit in relation to existing alternatives on the market, the Brazilian Chamber for Regulation of the Medicines Market (CMED), in line with other agencies from high-income countries, which also reduced the price in view of the uncertainty of evidence, approved, in December 2020, a provisional maximum price of BRL 2.9 million (US$531 173.2;

£396 516.4), which was set at a level 77% lower than the price established by the manufacturer. The manufacturing company filed an administrative appeal against the CMED decision, refusing to market the medication in the country. (IVAMA-BRUMMELL, Adriana Mitsue *et al*, 2022, p.1).

According to technical information presented by the Ministry of Health in a judicial process (Technical Note n. 431/2022-DAET/CGAE/DAET/SAES/MS, p. 9), Germany's Health Technology Appraisal Institute, after the FDA, evaluated the results of studies that compared this therapy with other drugs, and came to the conclusion that the medication did not prove to be more effective than nusinersen (a drug offered by the SUS). According to the German dossier, the results of Zolgensma for patients who received the medication before 12 weeks are comparable to the ones of patients who received nusinersen later, which would change the comparative results found in the main scientific study of the therapy.

In February 2022, CMED adjusted the maximum value of the drug to BRL 6.5 million, and in December 2022, during the 115th Ordinary Meeting, CONITEC recommended the incorporation of the drug for the treatment of pediatric patients up to 6 months of age with type I SMA who are off invasive ventilation for more than 16 hours a day, criteria much more

restricted than those set out in the drug package leaflet, in Anvisa's fast track register, and in supply court decisions, given the uncertainty of the therapy's scientific evidence in relation to significant long-term results.

So far, the medicine has not yet been supplied in the SUS network, nor is there any concrete news regarding the sharing of costs with the manufacturer and the price at which zolgensma will effectively be purchased to comply with court decisions, so the uncertainties and the large expenditure of resources by the SUS in improper marketing conditions will still remain within the scope of judicialization.

The concrete fact is that, since its approval by Anvisa in 2020, until at least February 2022, in view of the refusal by the national marketing company and the impasse generated with the cost of medication, the Ministry of Health operated in the international market, through the purchase of the drug in dollars, to comply with court orders for supply of zolgensma, at US$2 125 000 for a one-time infusion, whose conversion was, on average, at BRL 11.3 million per ampoule (IVAMA-BRUMMELL, Adriana Mitsue *et al,* 2022, p. 4).

Ivama-Brummell, Wagner, Pepe and Naci (2022, p. 4) explain that by October 2021, court decisions forced the Ministry of Health to finance treatment of 46 patients with

onasemnogene abeparvovec, at a total cost of $79 million. The average cost of the drug ($1.7 million) per patient is more than triple the originally maximum price approved by the Brazilian CMED.

Lawsuits against states and private health plans resulted in additional pay orders, including children over 2 years of age, for whom the therapy is not indicated in Brazil by ANVISA, and under administration conditions that were not later endorsed by CONITEC, which incorporated it for patients only up to six months of age, given the weak evidence in the older age group (Biblioteca Virtual em Saúde/MS, dez.2022).

It should be considered that these amounts were deposited in the patient's account – for him to carry out the importation – or purchased directly by the Ministry (if the judge in the case allowed the importation by the Federal Government and did not determine the immediate deposit). Thus, millions of reais (BRL) were spent by the SUS without any planning or respect for bidding rules, collective purchasing, administrative inspection, or sharing costs with the manufacturer, since the resources are spent on judicialization on an urgent basis, an environment in which bidding administrative rules are not regularly applied, nor is there ample room for monitoring the probity and rationality of the use of public funds by the parties (PGU, 2021, p 27/31).

Four worrying scenarios stand out for the equity of the use of public funds in the Unified Health System, punctuated by Ivama-Brummell, Wagner, Pepe and Naci (2022, p.4/5), and which indicate instrumentalization of the Judiciary for profit purposes market and the need for attention from social actors to the critical panorama that is being formed:

a) large number of judicial decisions to supply zolgensma to children over 2 years of age or using mechanical ventilation (circumstances in which the therapy is not indicated in the package leaflet or in the conditional registration of Anvisa);
b) if the preliminary CMED decision had been adopted as a parameter by the Judiciary since 2020, the resources spent by the Ministry of Health on the treatment of 46 authors of lawsuits would have been more than sufficient to treat babies born with SMA type 1 in the Brazil in one year (189 patients), highlighting that this initial age group is the one that has studies with scientific evidence;
c) dangerous articulation of patient advocacy groups and law firms, often supported by the pharmaceutical market, attracting families to provoke individual (and not collective) judicialization to individually obtain the

financial coverage of therapies by the federal government, specifically when it is very high cost;

d) benefit of the drug manufacturer, given the combination of strong media appeal and pressure on society that financial issues related to policies are responsible for restricting patient access to innovative drugs, producing an environment that facilitates a media strategy in exploiting vulnerabilities of the country's governance.

3.2 The federal government's expenses with the judicialization of health

Comparison of the table of federal expenses with judicial demands of health in the years 2007 to 2018 (Consultoria Jurídica da União, 2019) with the table of federal expenses with the judicialization of health in the year 2021 (prepared by the author based on the " Indicators CGJUD 2021"), illustrated below, indicates that judicial health benefits have been increasing significantly in recent years, especially after the introduction by ANVISA, through RDC nº 338/2020, of the accelerated health registration mechanism for gene therapies for rare diseases.

ANO	VALORES GASTOS
2007	R$ 23.961.006,10
2008	R$ 70.742.807,83
2009	R$ 102.339.121,70
2010	R$ 99.755.832,86
2011	R$ 175.919.318,20
2012	R$ 324.453.256,20
2013	R$ 431.403.708,70
2014	R$ 698.831.712,49
2015	R$ 1.008.203.845,30
2016	R$ 1.226.559.609,64
2017	R$ 979.001.580,60
2018*	R$ 1.139.767.181,00

	Ano	Valor	Número de Pacientes
Gastos da União com Judicialização da Saúde[1]	2021	R$ 2.009.144.822	5.736

The amount spent by the Ministry of Health in 2021 to comply with court decisions in health claims was BRL 2,009,144,822 (two billion, nine million, one hundred and forty-four thousand, eight hundred and twenty-two reais) to cover 5,736 patients. It should be considered that this amount is equivalent to the budget of the Popular Pharmacy Program, which, according to data from Ibsfarma, the Ministry of Health, Fiocruz and the Budget Panel (apud Globo, 2022), served approximately 20 million people in the year, with the budget allocation of R$ 2.5 billion.

Therefore, the data and circumstances highlighted above seem to indicate the need for governmental institutional articulation with the Judiciary and clarification with Brazilian society about the technical weaknesses of many of the scientific studies related to these drugs that receive, or are candidates to receive, accelerated registration, mainly in relation to cases in which there is no significant increase in quality of life or cure; or when there are no studies that scientifically prove an outcome relevant to the form of manifestation of the disease that affects the plaintiff.

When it comes to access to very expensive new technology medicines, individual lawsuits do not seem to solve the problem in a profound and equitable way. It is worth reflecting on the ways to provide medicines with safe evidence to all individuals who suffer from the same pathology, through conditions delimited by scientific evidence, with the participation of the legally competent agency, which is CONITEC; adjustment of the price of medication for collective purchase, with adjustment of reimbursements or sharing of costs, following rules in extended access programs that treat with more rationality and care the funds that structure the SUS; and that criteria of scientific plausibility, significance of outcomes and cost-effectiveness are not neglected.

However, the way in which these technologies are currently granted in court, individually, within the scope of the judicialization of health, without financial and budgetary planning and with a focus on the parameters of scientific evidence and cost-effectiveness adopted by CONITEC (which plans them to provide equitable access to health for all Brazilians who use the SUS – more than 150 million people), ignoring the sanitary model that formed the SUS and favoring the medical-hegemonic model – characteristic of technical decision-making in private practices of medicine, indicate to assert iniquities in the SUS, harming the social health programs and, even, the effective expansion of the programs destined to the treatment of rare diseases.

Conclusion

Resolution of the Collegiate Board (RDC) n. 205/2017, of ANVISA, introduced into the Brazilian system the accelerated health registration mechanism for drugs intended for the treatment of rare diseases, by reducing deadlines for analysis of submission of registration and flexibility of clinical trial phases presented in the safety and efficacy reports.

ANVISA's special accelerated registration procedure for drugs intended for orphan diseases has contributed to a

significant increase in judicial concessions of very high-cost technologies, many of which are still being evaluated by scientific studies to discover evidence regarding significant outcomes.

Still under the differentiated regime, the agency edited RDC nº 338/2020, defining rules for the registration of advanced cell, gene and tissue engineering therapy products. The flexibility of clinical trial phases was shown to be more intense in this regulation than that carried out in RDC nº 205/2017, allowing exceptional registration of products that require data and evidence of clinical efficacy, upon presentation of a schedule of clinical studies to be carried out after registration.

This new model is inspired by the accelerated registration mechanism practiced in the United States by the FDA. In the OECD classification of the health system, the Adam Smith model is applied in the United States, characterized by access to health through private insurance and funding from voluntary contributions by individuals and employers. In this system, the State does not assume responsibility for guaranteeing and protecting the health of the population, limiting itself to protecting the most vulnerable social groups (SERAPION et al, 2019, p. 45).

Thus, investments in fast track, primarily for orphan diseases, are compatible with the American system, since the country is developed and does not have an epidemiological profile of neglected diseases, as well as it is natural to be unconcerned with less strengthened benchmarks of scientific evidence. Since financing is not essentially public, commercial agreements are made with manufacturers precisely because of the stage of lack of scientific certainty for drugs approved under accelerated registration.

The SUS, in turn, presents classic characteristics of the Beveridge model. It is financed exclusively by public resources and available to the entire population, which is why the establishment of the fast track in Brazil ignored the differences in relation to the country's paradigm health system.

Morais (2013, p. 11/13), in research on models of pharmaceutical promotion, explains that the least developed or developing countries, such as Brazil, in addition to the budgetary, structural and logistical problems of access to treatment, they represent an uninteresting market for large private conglomerates, since there is no attractiveness for international industry to invest in treatment research for diseases typical of such countries, a situation known as a 10/90 imbalance, where only 10% of world health research is devoted

to diseases that account for 90% of the global burden of disease.

Considering this context, it should be stressed the vital importance of conducting public research and incentives to official medicine production laboratories. Therefore, the accelerated health registration procedure in this context, would represent one of many other measures to be taken by the State to make access to technologies more efficient in countries with neglected disease.

The high-income countries that implemented the fast track and that served as a model for Brazil do not have a mixed health system like the Brazilian one, nor an epidemiological profile of coexistence of neglected diseases, as Brazil has, in which the public and private system health conditions coexist according to the social inequality in the country. In the US, there is no drug access policy that covers the entire population of the country, as is the case with the SUS in Brazil.

The application of the Brazilian accelerated registration, disconnected from the concomitant institution of an extended access program for Brazilian patients and without fixing reimbursement or co-financing with the drug manufacturer, as occurs in fast track paradigm countries, facilitates the scenario of judicialization of these drugs before public entities and the

consequent withdrawal of funds exclusively from SUS without analysis of cost-effectiveness; without market compensation; without pre-established effectiveness evaluation methods; without attention to the epidemiological differences of poor countries; no equity in facilitating access to neglected diseases; and without the adoption of other innovation support mechanisms, such as compulsory licensing.

It should also be considered that the evaluative premise of ANVISA in the fast track regime is different from that adopted by CONITEC, but in the judicialization of health there is no distinction or greater caution with the drugs approved in the fast track regime compared to the drugs that received registration by the ordinary procedure (in which more advanced stages of scientific studies are analyzed).

The amount spent by the Ministry of Health in 2021 in compliance with court decisions handed down in health claims was BRL 2,009,144,822 (two billion, nine million, one hundred and forty-four thousand, eight hundred and twenty-two reais) cover 5,736 patients. It should be considered that this amount is equivalent to the budget of the Popular Pharmacy Program, which, according to data from Ibsfarma, the Ministry of Health, Fiocruz and the Budget Panel (apud Globo, 2022), served

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