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Legal possibility of marketing authorization and commercialization of advanced therapy medicinal products in Brazil

Possibilidade jurídica de registro e comercialização de produtos de terapias avançadas no Brasil

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ABSTRACT

In view of the provisions of the Constitution of 1988, of the Federative Republic of Brazil, article 199, paragraph 4, which prohibits any form of marketing of organs, tissues and human substances for transplants, research and treatment, the possibility of commercialization and marketing authorization of human origin products in Brazil has been questioned. With the advent of advanced therapies, legal uncertainty on the subject has reached regulatory issues and permeated scientific and investments concerns over the sector. Such perception based the detailed analysis on the matter by Anvisa´s Federal Attorney's Office, which was expressed on the Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU and exposed in this article. Outline, in this article, the main aspects concerning the legal possibility of marketing authorization and commercialization of advanced therapy medicinal products in Brazil, based on the Legal Opinion n° 12/2016/PF-Anvisa/PGF/AGU. Assessment of the Legal Opinion content and extraction from the document of its main issues. The document concluded for the possibility of a marketing authorization of the advanced therapy medicinal products, considering the principle of human dignity and fundamental rights to life and health, and conditioned it to the elaboration of a strict regulatory framework.

KEYWORDS: Advanced Therapies; Stem Cells; Regulation; Marketing Authorization; Constitution

RESUMO

Em vista do disposto no parágrafo 4° do art. 199 da Constituição Federal Brasileira, de 1988, que veda todo tipo de comercialização de órgãos, tecidos e substâncias humanas para fins de transplante, pesquisa e tratamento, a possibilidade de registro sanitário e comercialização dos produtos de origem humana no Brasil passou a ser indagada. Com o advento das Terapias Avançadas, a insegurança jurídica sobre o tema alcançou as questões de caráter regulamentar e permeou preocupações de ordem científica, tecnológica e financeira relacionadas ao setor. Tal percepção ensejou a análise detalhada da matéria pela Procuradoria Federal junto à Anvisa, expressa no Parecer Cons. n° 12/2016/PF-Anvisa/PGF/AGU. Expor, no presente artigo, os principais aspectos concernentes à possibilidade jurídica de registro e comercialização de produtos de terapias avançadas no Brasil, com base no teor do Parecer Cons. n° 12/2016/PF-Anvisa/PGF/AGU. Descrição do conteúdo do respectivo parecer, considerando os aspectos principais emanados no documento. Por meio da releitura constitucional, o Parecer concluiu pela possibilidade do registro e comercialização dos produtos de terapias avançadas, com fundamento no princípio da dignidade da pessoa humana e nos direitos fundamentais à vida e à saúde, e condicionada a um arcabouço regulatório rigoroso, a ser elaborado.

PALAVRAS-CHAVE: Terapias Avançadas; Células-tronco; Regulamentação; Comercialização; Constituição

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INTRODUCTION

Scientific and technological progress has provided countless advances in the field of medicine. In this context, since the advent of Advanced Therapies occurred especially in the last decade, stem cell research has been regarded as a promising area to improve the healthcare offered to the population[1,2,3]. Worldwide research efforts play their role in conducting studies to treat a variety of diseases – from common to rare to those oftentimes neglected – for which there is no current treatment available or the only therapeutic solution is organ or tissue transplantation. In addition to the objective of saving lives, other clinical conditions studied in the field of Advanced Therapies also presuppose the desire to obtain improvement in quality of life.

Europe and the United States published regulations on advanced therapy medicinal products (ATMP) in the mid-2000s, respectively: Regulation (EC) n. 1394/2007 of the European Parliament and of the Council[4] and Cellular & Gene Therapy Guidance Documents published by the Food and Drug Administration (FDA)[5]. According to these standards, advanced therapy medicinal products consist of three categories: advanced cell therapy products, tissue engineering products and gene therapy products.

In Brazil, according to the definitions described in Public Consultation n. 270, of November 4, 2016, of the Brazilian Health Surveillance Agency (Anvisa) – Board of Directors Resolution Proposal on Good Cell Practices for therapeutic use and clinical research[6] –, advanced therapy medicinal products, derived from human substances subjected to extensive handling, have the purpose of obtaining therapeutic or preventive properties, through their main modes of action of metabolic, pharmacological and/or immunological natures, for use in humans. Extensive handling is understood as the processing of cells during, for example, laboratory cultivation for the purpose of expansion or differentiation – with the potential to change any of its relevant biological characteristics, including level of differentiation and activation, potential proliferation and metabolic activity.

With the objectives of entering the field of stem cell research and change from a technology-absorbing country to a country that produces technological innovation, Brazil has taken important initial steps:

- In March 2005, after the enactment of Law 11.105, of March 24 (Biosafety Law)[7], the country came to have a regulation that, among several other measures, allowed, in its art. 5, the use of human embryonic stem cells (ESC) for research and therapy purposes. In November of the same year, the Biosafety Law was regulated by Decree n. 5.591, of November 22, 2005, granting Anvisa the authority to establish norms for procurement, processing, testing, storage, transportation, quality control and use of ESC. Art. 5 of Law 11.105/2005 was challenged by direct action on unconstitutionality (ADI) n. 3.510/DF[8], which was dismissed by the majority of the court, in accordance with the vote of the rapporteur, Justice Carlos Ayres Britto. In an emblematic decision, the Brazilian Supreme Court (STF) understood that although there is life in the frozen embryo, it would not yet be under the custody of the State in the same dimension of the human life of the child. The STF declared, thus, the constitutionality of art. 5, because the precept would confirm that contained in articles 199 and 218, §1 of the Federal Constitution of 1988 (CF/88), allowing science to work for the benefit of human health.

- In 2008, the federal government began to make financial investments in the sector through the creation and structuring of the National Cell Therapy Network (RNTC). As of 2010, it has been performing robust promotion activities in the areas of cell therapy and regenerative medicine through the Department of Science and Technology (Decit) of the Ministry of Health, the National Council for Scientific and Technological Development (CNPq) and the Funding Authority for Studies and Projects (Finep) – in partnership with the Ministry of Science, Technology, Innovation and Communications (MCTIC), the Coordination for the Improvement of Higher Education Personnel (Capes) of the Ministry of Education and the National Bank for Economic and Social Development (BNDES). In total, the federal government has already allotted about 120 million BRL for infrastructure, scientific research carried out by the public and private sectors and for the training of highly qualified human resources for the area[9].

- In 2011, the following documents were published: Anvisa's RDC n. 9, of March 14, which provided for the operation of the Cell Technology Centers (CTCs)[10], Resolution of the National Health Council (CNS) n. 441, of May 12, which approved the guidelines for ethical analysis of research projects involving the storage of human biological material[11], and Ministry of Health act n. 2.201, of September 14, which establishes the national guidelines for biorepositories and biobanks of human biological material for research purposes[12].

In view of the investment in the sector, both governmental and private, some companies, especially multinationals that have advanced therapy medicinal products registered and currently commercialized in foreign countries[13], showed interest in making such therapeutic strategies available in the Brazilian domestic market. In this scenario, it is presumed that financial gains are required to sustain the investment in research and technology for the development of these products.

With that, the various stakeholders – academic, business and government – began to discuss the possible discontinuation of domestic and foreign investments, due to the thus far prevailing understanding that the rule contained in the final part of §4 of art. 199/CF/88 would be an obstacle to the marketing of advanced therapy medicinal products and, *a fortiori*, to their market authorization under the terms of Law n. 6.360, of September 23, 1976[14].

Some legal uncertainty arose due to the lack of a specific regulatory framework that addressed the matter in response to the

current international regulation. It was also argued that we could expect some loss of interest in the development of new technologies in the sector and the difficulty for the public sphere to thrive and remain robust without heavily depending on continued governmental investments. These barriers would result in the lack of access to innovative therapeutic treatments that could benefit the Brazilian population and keep Brazil in a condition of dependent country that merely absorbs foreign technology.

In view of the foregoing, a consultation was made to the Federal Attorney's Office at Anvisa about a possible reinterpretation of the constitutional provision, with the objective of promoting effective legal compliance permeated by the situation presented and to begin, in accordance with the legal system, the preparation of a Brazilian regulatory framework on the subject. The consultation also took into account the risks involved in the use of new technologies and the institutional purpose of Anvisa – as coordinator of the National Health Surveillance System (SNVS) – to promote the protection and improvement of the health of the people, through the sanitary control of the production and marketing of products and services subject to sanitary surveillance, including the facilities, processes, materials and technologies related to them[15]. The response to the consultation addressed to the Anvisa's Federal Attorney's Office was expressed in Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU[16]. In this article, it is explained in detail during the discussion and conclusions.

DISCUSSION

Based on the entire content of Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU, the main aspects of its rationale are set out below and support our respective conclusions.

Constitution as a "living organism"[17]

To understand the meaning and scope of the rule established in art. 199, §4, of CF/88, some preliminary observations on the concept of Constitution are necessary.

José Afonso da Silva starts from the notion of Constitution as:

> a system of legal norms, either written or customary, which regulates the form of the State, the form of its government, the mode of acquisition and the exercise of power, the establishment of its bodies, the limits of its action, the fundamental rights of men and the respective guarantees. In short, the constitution is the set of norms that organizes the constitutive elements of the State.

This classic idea of the Constitution, however, is often criticized, as José Afonso da Silva himself notes, for expressing only part of the concept, "because it treats it as something separated from social reality, when it must be conceived as a normative structure, a meaningful connection, which involves a set of values". Thus, after a very brief analysis of the theories developed by Hans Kelsen (legal sense), Ferdinand Lassale (sociological sense) and Carl Schmitt (political sense), the prominent Brazilian jurist concludes:

> We seek, therefore, to formulate a structural conception of constitution that considers it in its normative aspect, not as pure norm, but as a norm in its connection with social reality, which gives it factual content and axiological meaning. It is a complex that is not made of parts that are added, but of elements and members that are intertwined in a unitary whole. The legal sense of constitution will not be obtained if we judge it to be estranged from the totality of social life, without connection with the whole community. Well, certain ways of acting in society become human behaviors valued historically and constitute the basis of community existence, forming the constitutional elements of the social group, which the legislator understands and reveals as fundamental normative precepts: the Constitution.
>
> The Constitution is something that has, as a form, a complex of rules (written or customary); as content, human conduct motivated by social relations (economic, political, religious, etc.); as an end, the accomplishment of values that point to the existence of the community; and, finally, as its creating and recreating force, the power that emanates from the people. It cannot be understood and interpreted if one does not keep this structure in mind, considered in connection of meaning, as is everything that integrates a set of values. This does not prevent the scholar from giving preference to a given perspective. We can study it from a predominantly formal angle, or from the content side, or from the assured values, or from the interference of power[18].

Along the same lines, Uadi Lammêgo Bulos asserts that "constitutions are living organisms, real documents open in time, in intimate dialectic connection with the surrounding environment and with the forces of transformation of the society"[17]. Anna Cândida da Cunha Ferraz affirms that "the Constitution as a set of norms does not, however, distance itself from the social substratum that gives it life, nor from the system of values that the norm intends to achieve". She also refers to Karl Loewenstein when she explains that:

> every Constitution, when it is born, comprises only the moment, that is the *status quo* existing at the moment of its birth; it is not able to predict the whole future; at best, it may try to take into account future needs through carefully placed provisions and mechanisms, although overly elastic wording may undermine legal certainty[19].

Therefore, it is inferred that, although the *Magna Carta* reflects the objectives pursued by the people at the moment in which it is positioned, after its enactment it begins to suffer the influence of new values that are incorporated into the society. That is to say, constitutional reality is constantly affected by changes in ethical, economic and political standards arising from technological, scientific and social relations. In this sense, it is undeniable that the progress made in medicine, notably the modern Advanced Therapies technologies, are capable of causing impact in the constitution.

Consequently, the conciliation of political and social reality with legal reality demands the constant updating of the norms of the constitution, as a tool for survival and revival of its normative force, either through constitutional reforms or through informal processes of constitutional change, which many call constitutional mutation.

Constitutional mutation enables the harmonious and progressive evolution of the Constitution, giving a renewed meaning to the constitutional text, without contradicting it. For better understanding, we appeal to the reasoning of Anna Cândida da Cunha Ferraz:

> Thus, in short, constitutional mutation alters the meaning, sense and scope of the constitutional text without violating its letter or spirit. This is the fundamental characteristic of the notion of constitutional mutation that deserves, for the moment, to be emphasized. It is, therefore, a constitutional change that does not contradict the constitutional text, that is, that indirectly or implicitly is accepted by the Constitution.
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> These constitutional changes, operated outside the organized modalities of the exercise of the established or derived constituent power, are warranted and have a legal basis: they are, in fact, work or manifestation and an unorganized type of Constituent Power, the so-called diffuse constituent power, in Burdeau's accurate definition.
>
> This is the second characteristic to be pointed out.
>
> The diffuse constitutive function is destined to complete the constitution, to fill constitutional voids and to continue the work of the legislator. It stems directly from the Constitution, that is, its foundation flows from the Fundamental Law, albeit implicitly, in a diffuse and unorganized fashion.
>
> It is a logical consequence of the Constitution, inasmuch as it is a text that is created to be effectively enforced, especially in what is essential about it, and the essential is sometimes incomplete, requiring further action to define it, precise it, clarify obscurities, give it continuity and application, without violating the written constitutional work.
>
> As an exercise of an implicit constitutive function, it is necessarily limited. Its limits are necessarily broader and more definite than the limits imposed on the constituent party, that is, on the power of constitutional reform, insofar as, with the express permission of the Constitution, it acts precisely to reform it and amend it, modifying the constitutional text and content. Because it is not expressly authorized and because it is born implicitly and logically, the diffuse constituent power cannot reform the text and the content of the Constitution. Its action is restricted to clarifying or modifying the meaning, the sense and the scope, without ever violating the constitutional text[19].

Uadi Lammêgo Bulos does not disagree and states that:

> constitutions, as the living organisms they are, accompany the evolution of social, political, and economic circumstances, which, if they do not alter the text in its wording and form, modify it in substance, meaning, reach and sense of its provisions[17].

It should be noted that the material limits imposed on the reforming constituent power apply to the so-called diffuse constituent power. In fact, for informal processes of constitutional change, such limits must be understood even more broadly, in order to avoid the violation of the spirit of the constitution, the depletion of its normative force and the corrosion of the Democratic Rule of Law.

In spite of the absence of a doctrinal consensus in the systematization of the informal processes of constitutional amendment, it is certain that the constitutional interpretation is more often listed as its main mechanism of action.

Modern constitutional hermeneutics

Every normative act establishes general and abstract rules, and it is up to the law enforcer to interpret them, determining their meaning and scope in each specific case. The Constitution, as the "Law of Laws," is not immune to interpretation. On the other hand, because it is not composed of traditional archetypes such as "occurrence of the hypothesis - juridical consequence", but primarily of formulations about juridical goods and fundamental values, its exegesis is indispensable and extremely complex, demanding greater hermeneutic effort. Alexandre de Moraes states that:

> the Federal Constitution must always be interpreted, because only through the comparison of the text with the historical, political, and ideological characteristics of the moment will one find the best meaning of the juridical norm, in comparison with the socio-political-economic reality, aiming at its full efficacy[20].

Moreover, as Uadi Lammêgo Bulos adds,

> no constitutional text dispenses interpretation at the risk of failing to adapt its norms to the inflow of social, historical, political, religious and economic events at a given moment. Extracting the ultimate purpose of constitutional precepts and making them effective and harmonious among themselves is key to the exegesis of the constitutions[17].

Thus, interpretation represents much more than a mere assumption for the application of constitutional norms, but rather plays an important role in the constant renewal of the legal system, in order to accommodate, within the formal and material limits established by the original constituent, the new social inflows.

With that in mind, the emergence of Advanced Therapies raises questions that lead to the need for a deep and invigorated reading of §4 of art. 199 of CF/88, in order to interpret it in an evolutionary manner, in view of the current context significantly marked by scientific and, consequently, social progress.

In the performance of this task, in addition to the classic hermeneutical elements, among which the teleological and logical-systematic ones stand out for the present debate – which understands the constitution as a logical and coordinated system of principles and rules that should be consistent among them – modern methods of constitutional interpretation must be taken into account, namely: a) problematic topic, starting from a concrete problem for the norm, where the interpretation has a practical nature in the search of the solution for the concrete problems; b) hermeneutic-concretizing, that goes from the constitution to the problem, using the interpreter's previous understanding of the subject; c) scientific-spiritual, which analyzes the constitutional norm elastically and flexibly, to accompany the dynamism of social relations, in constant change; d) normative-structuring, which seeks to create a norm for each conflict, lacking identity between the norm and the normative text; and e) constitutional comparison, which combines the elements of traditional hermeneutics with comparative law.

Principles commonly pointed out by the jurists should also be considered, namely: a) principle of unity of the constitution, according to which constitutional norms should not be seen in isolation, but interpreted in their entirety to avoid contradictions; b) principle of practical agreement or harmonization, which considers that constitutional legal goods should exist harmoniously, in the case of any conflict between them, thus seeking to avoid the sacrifice of one principle to the benefit of another; c) the principle of integrative effectiveness or integrative effect, which prioritizes the political and social integration of the State, leading the interpreter to develop a critical and global reasoning of the constitution in order to extract the true purpose of its norms; d) principle of maximum effectiveness, whose objective is to give the broadest social effectiveness to the constitutional norm, extracting the greatest content possible, especially in matters of fundamental human rights; e) principle of the interpretation according to the constitution, according to which, in view of norms that have more than one interpretation, preference must be given to the one that comes closest to the constitutional interpretation; and f) the principle of reasonableness and proportionality, which states that norms should be interpreted according to criteria of fairness, common sense, and ideas of justice, prudence and moderation.

In the combined use of the elements, methods and principles mentioned above, it is essential to go beyond the literal provision of §4 of art. 199 of CF/88 and achieve the constitutional principles directly related to it, since they synthesize the values embodied in the legal system, true vectors or interpretative paradigms that impart unity and harmony to the system, requiring greater concretion. There is no denying its relevance in the interpretation and application of norms of any nature, including the constitutional rules themselves. It is in the principles that lies the value justification of the rules, helping operationalize their interpretation and, consequently, their suitability to concrete cases.

The constitutional principles are like lights for the constitutional exegesis, providing the interpreter with axiological elements for a reasonable interpretation capable of imparting a systemic logic to the constitutional order[21]. Undoubtedly, they represent the objectification of certain sociopolitical values that existed when the constitutional power was constituted by legal formality and, therefore, they reflect in the procedures of interpretation of the Constitution and are responsible for the stabilization of the constitutional text. In other words, we can say that, due to the need for permanence, the constitution has a principiological character that covers most of its norms, allowing the updating of its dictates in the face of changes occurred in society. Therefore, the constitutional principles are the foundation of legitimacy to the legal system of the society, possessing, as well, a hermeneutic, supplementary and argumentative function.

We are not saying that principiology allows one to say "anything about anything," but rather that, among several possible interpretations of a norm, the one that best fulfills such principles should prevail, in order to contribute to maintaining the integrity and consistence of the regulatory framework.

Therefore, one might wonder: what do we intend to protect with the prohibition contained in the final part of §4 of art. 199? Which fundamental principles lie in the origin of the declined constitutional rule and how to make them as effective as possible? What legal assets are involved and how to reconcile them?

Undeniably, what drives the rule under analysis, that is, what gives it its reason-to-be, is the protection of the dignity of the human person, from which the fundamental rights to life and health derive. This is the guiding principle embodied in §4 of art. 199 of CF/88, which should inform the interpretation of the provision and guide the preparation of future and possible regulatory acts on the matter.

Interpretation of §4 of art. 199 CF/88 based on the fundamental principle of the dignity of the human person and on the fundamental rights to life and health

The Federal Constitution of 1988, in its art. 1, III, listed the recognition and consideration of the dignity of the human person as a fundamental principle of the Democratic Rule of Law, which is binding for all actions of the State and for life in society. As such, it functions as a criterion of interpretation and integration, conferring general consistence to the constitutional order.

The value of dignity has multiple dimensions, which is why there is great difficulty in outlining its concept. For Guilherme Wünsch, the principle of the dignity of the human person constitutes a general clause of protection of the human being, represented by the value of the person, which must be protected without limits, except for the interest of other human beings[22]. José Afonso da Silva, in turn, classifies the dignity of the human person as a supreme value that attracts the content of all fundamental rights[18].

Alexandre de Moraes goes in the same direction when he states that the foundation of dignity of the human person grants unity to the fundamental rights and guarantees, explaining that it is:

> a spiritual and moral value inherent in the person, which manifests itself singularly in the conscious and responsible

> self-determination of life and which bears the pretension to respect by other people, constituting the invulnerable minimum that every legal status must ensure, so that limitations can only exceptionally exist in the exercise of fundamental rights, always without neglecting the necessary esteem that all people deserve as human beings[20].

In view of the above, it becomes clear that the rule established in §4 of art. 199 of CF/88 has the principle of the dignity of the human person as its axiological support. This principle says that the human being is not an object of law, but a considerable value in itself. With the prohibition of practices such as the trade of organs, tissues, blood, sperm and other human substances, Brazilians and foreigners resident in the country are protected from the commercialization of the human body. This is the *mens legis* that is checked in a teleological interpretation of the provision.

Furthermore, it should be noted that although the original legislators could have foreseen some progress in the field of biotechnology, which can be deduced from the text of §4 of art. ("Paragraph 4. The law shall provide for conditions and requirements that facilitate the removal of human organs, tissues and substances for transplantation, research and treatment..."), they could not imagine that research would unleash the enormous potential of cell therapy and raise it to the level of a new paradigm in medicine today, since the first lineage of human embryonic stem cells was only developed by researcher James A. Thomson in 1998[23].

It so happens that the era of biotechnology has irreversibly arrived, bringing many expectations of breakthroughs that can be applied to the cure of serious chronic diseases or to the improvement of the quality of human life. Therefore, the evolution of juridical categories in the face of scientific advances is forced, or else a great mismatch between social desires and law will appear, thus weakening the normative force of the Constitution.

Given these premises, the ensuing analysis will depend on the following reflection: is it reasonable for the fulfillment of the principle of the dignity of the human person by means of the rule established in the final part of §4 of art. 199 of CF/88, in addition to preventing the remunerated collection of organs, tissues, blood, etc., to also prohibit the trade of advanced therapy medicinal products produced in laboratories through extensive handling, using modern and elaborate technologies, using parts of human cells, tissues and genes, originally obtained through free living or *post mortem* provision?

The answer is no. If an absolute interpretation of §4 of art. 199 of CF/88 was perfectly justifiable back then – even because there were no prospects of creating products from human substances with such an impact on the health of a large number of people – today an exegesis that *a priori* precludes the commercialization of therapeutic solutions from or containing human substances (since they were originally obtained by donation in life or *post mortem*) seems incorrect, inasmuch as such a ban would limit and substantially delay the development of biotechnological products by reducing the supply of such alternatives for promotion and protection of health of the population. This is contrary to the provisions of articles 6 and 196 and following of CF/88, which address the fundamental right to health and ultimately violates the very principle of the dignity of the human person.

In fact, prohibiting the commercialization of "medicines" or "products" of human origin (harvested free of charge, it should be emphasized) would limit this healthcare sector to the State and discourage the private initiative from investing in these studies, since the objective of private companies is to make profit. And, of course, the fewer research fronts are open, the lower the availability of treatments, and the longer it will take them to become available to the population. It should be noted in particular that the introduction of the provision in question states that "healthcare is open to private initiative". It does not make sense, therefore, to understand its §4 so rigidly that it discourages private healthcare from supplying biotechnological products, especially when we take into account the right to health, designed in a broad and universal way, as one of the facets of the same principle of the dignity of the human person.

We can therefore observe that an aspect of the fundamental principle of the dignity of the human person can be translated into the guarantee of respect for the psychophysical integrity of the human being. Such a bias prevents the denial of the human being as entitled to rights to the point of allowing the "sale" of parts of his or her body, which justifies the prohibition established in §4 of art. 199 of CF/88. At the same time, however, it is the source of the fundamental social right to health, which imposes on the State direct action and incentive/regulation of the private initiative to provide services that lead to the effective promotion of health, well-being and dignified life of human beings, as widely and universally as possible.

"Health" (to which Section II, Chapter II, Title VIII, CF/88, where Article 199 itself is located is fully dedicated), is recognized in art. 6 as a social right of a fundamental nature, and, in art. 194, as the first of all social security rights. In accordance with art. 196,

> health is a right of everyone and the duty of the State, guaranteed by social and economic policies aimed at reducing the risk of disease and other disorders and universal and equal access to actions and services for its promotion, protection and recovery.

Art. 197 also rules that:

> health actions and services are of public relevance and it is the responsibility of the public administration to ensure, under the terms of the law, their regulation, supervision and control, and their execution should be done directly or through third parties, and, also, by individuals or companies of private nature.

Health is a prerequisite for the quality of life and human dignity of any person. Without health, it is pointless to speak of the right to life or of human dignity, since the human being will be incapable of enjoying his or her life as he or she wishes. In other words, the principle of the dignity of the human person imposes

on the State, in addition to the duty of respect and protection, the obligation to promote the conditions that remove all kinds of obstacles that prevent people from living with dignity.

As known, thousands of Brazilians suffer from diseases and consequences of trauma that significantly reduce their quality of life, preventing them from enjoying a decent life (some types of cancer, neurological diseases like Parkinson's, spinal cord injuries, diabetes, heart diseases and others). For them, the results already published in stem cell research bring comfort and the hope of improving their health.

In view of this situation, considering §4 as a constitutional prohibition applicable to the trade of advanced therapy medicinal products would represent a substantial obstacle to the full enjoyment of the broad and universal right to health. It is worth repeating that this right entails for the State the duty to act directly in the development of biotechnological products and also the obligation to foment and regulate the performance of the private initiative in this area.

It should be emphasized, furthermore, that the best interpretation of the constitutional text does not abstain from the systemic analysis of the legal framework. In this context, it is important to invoke arts. 218 and 225 of CF/88. We can verify that art. 218 of CF/88 assigns to the State the responsibility not only to promote, but also to encourage private initiative to carry out research as a priority with a view to the scientific progress of humanity and the improvement of living conditions for everyone. Additionally, art. 225 of CF/88 ensures the fundamental social right of men to an ecologically balanced environment and establishes the principle of solidarity between the generations, in order to guarantee the dignity of human existence, and it is incumbent upon the State to act in order to ensure its effectiveness.

In the judgment of the aforementioned ADI n. 3.510/DF, by means of which art. 5 of Law 11.105/2005 (Biosafety Law) was challenged, the Brazilian Supreme Court considered that, although embryos cannot be produced in order to obtain stem cells for research purposes – because in such a situation the embryo would be instrumented from the beginning, which would represent serious damage to the dignity of the human person – once respected the positive requirements, considered as reasonable and proportionate to the legal goods involved, frozen embryos could be scientifically categorized as not viable and subsequently be used to obtain stem cells. In this respect, the legislative choice, far from signifying contempt for human life (of the embryo), denotes, in fact,

> a stronger disposition to shorten the paths that may lead to overcoming the misfortune of others. This is within the framework of a constitutional system which, from its preamble, describes 'freedom, security, well-being, development, equality and justice' as the supreme values of a society that is, above all, 'fraternal'. This means incorporating the advent of fraternal constitutionalism into human relations, to translate true communion of life or social life in a climate of overflowing solidarity for the benefit of health and against possible traumas and even adverse conditions of nature itself.

In her vote, Justice Carmem Lúcia pointed out that the principle of the dignity of human life is to be observed not only in relation to the embryo, from which the embryonic stem cell would be obtained, but also in relation to those afflicted with misfortunes that hinder life with health and dignity.

A close look at the entire contents of the emblematic sentence shows that the highest court in the country has accepted the challenge of interpreting the provisions of the Constitution is an evolutionary, consistent, prudent and balanced manner, re-signifying the constitutional system to face the challenges of modernity.

CONCLUSIONS

The understanding of the Brazilian Constitution as a living organism, whose meaning and scope must conform to social and political dynamics, validates and reinforces the inference of Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU that the statement contained in the final part of §4 of art. 199, considering the evolution of science and the new methods of treatment of diseases and health promotion that emerged after its promulgation in 1988, deserved to be reconsidered, interpreted and thus updated, in order to allow concrete enforcement of the constitutional norm and the maintenance of its normative force.

This time, through the research done in Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU, it was concluded that the value justification of the rule set forth in the final part of §4 of art. 199 of the CF/88 lies in the dignity of the human person, a fundamental principle of the Democratic Rule of Law, a supreme value from which fundamental rights to life and health derive. For this reason, the instrument in question could not be subjected to an absolute interpretation that would impose disproportionate obstacles to the effective achievement of the right to health in a comprehensive and universal way, at the risk of violating the very principle of the dignity of the human person.

Therefore, Legal Opinion n. 12/2016/PF-ANVISA/PGF/AGU defended that the fundamental principle of the dignity of the human person can be achieved through teological, systematic and integrative exegeses of §4 of art. 199 of CF/88, according to which the collection or procurement of human material must always be voluntary and unselfish, without prior classifying as goods out of trade the medicines or products obtained in the laboratory by means of substantial manipulation, with the employment of modern technologies, from or using substances of human origin, originally obtained through donation in life or *post mortem*.

Considering that the decision favorable to the possibility of marketing authorization by Anvisa and the commercialization of advanced therapy medicinal products is based on the principle of the dignity of the human being, Legal Opinion n. 12/2016/PF-Anvisa/PGF/AGU remarked that these products

deserve protection of the legal system only if and as long as they serve to promote health, well-being and, consequently, a dignified life without degrading human beings to the condition of objects to be commercialized.

The Legal Opinion stressed that a rigorous infra-constitutional regulatory framework must be built to ensure that substances of human origin to be used in the manufacture of advanced therapy medicinal products are collected for free and in conditions of voluntary, spontaneous and informed donation, in order to avoid the risk of any abuse. The Legal Opinion also found it necessary to establish rules to delimit the assumptions and requirements for the manipulation of substances of human origin and their transformation into products for therapeutic purposes to be commercialized with the aim of dignifying the lives of those who may be treated by them[16].

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.