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Kasznar Leonardos

Anderson Ribeiro, Priscila Kashiwabara and Aline Ferreira

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Personalised medicine in Brazil: IP and regulatory challenges

By **Anderson Ribeiro**, **Priscila Kashiwabara** and **Aline Ferreira**

With the development of techniques such as CRISPR and increasing knowledge in the 'omics', science can now provide what only a few years ago looked like science fiction: personalised medicine (sometimes referred to as 'precision medicine' or 'personalised healthcare'). Personalised medicine is an evolving field where a therapeutic treatment is tailored to an individual with a particular disease and is capable not only of avoiding or minimising harmful side effects caused by mass medicines and treatments (as well as ensuring a more successful outcome), but also helping reduce costs compared with a trial-and-error approach to disease treatment.

This chapter aims to discuss the current status of personalised medicine in Brazil from both a regulatory and an IP standpoint, as well as to underline the main challenges in this area.

General definition of 'personalised medicine'

The National Public Health Agency (ANVISA) provides no definition of personalised medicine. Nevertheless, there is a consensus in the scientific community that the definition of personalised medicine converges with the concept used worldwide.

Personalised medicine or precision medicine is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments and lifestyles. Personalised medicine's aim is tailored treatment – the right treatment, for the right patient, at the right time.

Personalised medicine identifies biological information (eg, genes, RNA/DNA and proteins) through diagnostics to provide a better understanding of the conditions in the patient to be treated. This approach aids the tailoring of a personalised medical treatment for the patient's molecular and genetic profile to increase the chances of the patient responding to a specific treatment. It represents a significant departure from the trial-and-error processes endemic in empirical medicine.

With whole genomic data sequencing, new disease pathways are being discovered, new therapeutic targets revealed, adverse drug effects evaluated and ideal treatment populations identified. Precision medicine treatments serve a very narrow population, making R&D investment enormous. In this context, we would like to highlight two Brazilian initiatives.

Brazilian Initiative on Precision Medicine

The first is the Brazilian Initiative on Precision Medicine, an initiative of five research innovation and dissemination centres supported by the Sao Paulo Research Foundation (FAPESP). The FAPESP is a public foundation, funded by the taxpayer in the state of Sao Paulo, with the aim of supporting research projects in higher education and research institutions in all fields of knowledge. The five centres engaged in this project are:

- the Brazilian Research Institute for Neuroscience and Neurotechnology;
- the Centre for Computational Science and Engineering;
- the Centre for Research in Cell Therapy;
- the Centre for Research on Inflammatory Diseases; and
- the Obesity and Comorbidities Research Centre.

The initiative is based on a software platform, built following the guidelines and principles of the Global Alliance for Genomics and Health, and observing the responsible sharing of genomic and clinical data. This platform is the first of its kind in Latin America and aims to offer public access to genomic and phenotypic data. It is intended to be used by clinicians and scientists all over the world, to share and obtain information about various aspects of genomic medicine and human health, as well as to support dissemination and training in the areas of human molecular genetics, computational biology and others.

Brazil's DNA project

The second initiative is Brazil's DNA project, led by a geneticist from the University of Sao Paulo in partnership with the Brazilian diagnostic medicine company 'Dasa' and Google Cloud. Brazil's DNA project aims to discover patterns in the Brazilian genome and make its findings available in global and public databases.

Current regulatory landscape

Despite the lack of a regulatory definition, personalised medicine involves a combination of steps:

- a diagnostic step (companion diagnostics); and
- an actual treatment step based on the results of the diagnostic step and the individual characteristics of the patient.

Companion diagnostic tests detect specific genetic mutations and biomarkers in those patients who are most likely to respond to precision medicine treatment. These tests reflect the true promise of personalised medicine – the provision of individually safe and effective treatment.

In that sense, precision medicine has the potential to make health systems more efficient by targeting treatments only at those who will benefit. In spite of these potential efficiencies, access and reimbursement remain a challenge in Brazil. Moreover, the promise of personalised medicine will remain unfulfilled without strong support for companion diagnostic testing.

The idea of tailoring medical treatment to the individual requirements of a patient has been accommodated by the existing regulatory framework for biological products since 2010. Immunotherapy treatments with some approved monoclonal antibodies under the existing regulatory framework for biological products are examples of targeting treatments.

More recently, ANVISA issued three important rules that aim to improve the regulatory landscape to accommodate tailoring medical treatment to the individual requirements:

- RDC 214/2018, which provides for good practices in human cells for therapeutic use and clinical trial;
- RDC 260/2018, which sets out rules for conducting trials with investigational advanced therapy products in Brazil; and
- RDC 338/2020, which sets out requirements for the registration of advanced therapy products.

According to RDC 338/2020, advanced therapy products subject to a marketing authorisation are:

- advanced cellular therapy products;

Anderson Ribeiro
Partner
anderson.ribeiro@kasznarleonardos.com

Anderson Ribeiro is a partner at Kasznar Leonardos, heading the team for transactional and regulatory matters affecting the life sciences industries and providing advice on strategic IP issues. He has an extensive background, ranging from dealing with leading cases discussing patents and strategies, to sensitive niches of the pharmaceutical sector such as rare diseases and government sales. His wide expertise embraces multifaceted challenges involving clinical trials, compliance, pharmacovigilance, economic regulation, technology transfer (related to the Productive Development Policy), health technology appraisals and government procurements.

Mr Ribeiro has an LLM in competition law and regulation from the University of Lisbon and an LLM in intellectual property from Queen Mary, University of London.

- gene therapy products; and
- therapeutic tissue engineering products.

ANVISA has already approved two gene therapy products:

- Luxturna (adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy); and
- Zolgensma (an adeno-associated virus vector-based gene therapy indicated for the treatment of paediatric patients under two years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene).

In Brazil, the Pharmaceutical Market Regulation Chamber (CMED) defines the price cap for most medicinal products after issuance of the marketing authorisation, as in the case of gene therapy products. However, under the CMED's current price regulation (Resolution 02/2004), gene therapy and biosimilar products are classified as *sui generis*, which creates legal uncertainty, bearing in mind that the price parameters are not set out in the current price regulation.

In the Brazilian health system, the Unified Health System (SUS) plays a paramount role in providing access to high-cost therapies within the largest public healthcare system in the world. Its management is decentralised at all levels (federal, state, Federal District and municipal)

Priscila Kashiwabara
Partner
priscila.kashiwabara@kasznarleonardos.com

Priscila Kashiwabara graduated in biology and has a master's in biotechnology from the University of Sao Paulo. She is a registered industrial property agent and works in Kasznar Leonardos' life sciences division focusing on patents, biodiversity and plant varieties. Ms Kashiwabara is co-coordinator of the Plant Variety Study Committee at the Brazilian Association of Intellectual Property (ABPI).

Aline Ferreira
Partner
aline.ferreira@kasznarleonardos.com

Aline Ferreira de Carvalho da Silva is an expert on litigation, legal counselling on patents, licence agreements, plant varieties and access to genetic resources. Ms Ferreira de Carvalho da Silva is a coordinator for the International Law of Intellectual Property Study Committee at the ABPI and she is also the chair of the Legal Committee of the Brazilian Network of Pharmaceutical Innovation within Sindusfarma (the union of pharmaceutical companies in Brazil).

She graduated in law from the State University of Rio de Janeiro and has a master's in IP law from the University of Cambridge and a postgraduate qualification in IP law from the Pontifical Catholic University of Rio de Janeiro.

"Although there is no legal definition of what constitutes personalised medicine, it is widely accepted that it involves a combination of diagnostic steps and subsequent treatment steps established by considering the results of the previous diagnostic steps"

of the federation. The SUS provides therapeutic assistance to all citizens, as well as pharmaceuticals, devices and other products appropriate for treatment. Treatment is provided in accordance with the SUS principles of universality, comprehensiveness and equity.

However, universal access to the public healthcare system (with full and free access for the population) does not mean access to all kinds of treatment. There are several medicinal products and treatments that the SUS does not provide (eg, the two approved gene therapy products).

The National Committee for Technologies Incorporation (CONITEC) performs health technology appraisals. CONITEC is responsible for advising the Ministry of Health on the incorporation or disinvestment of health technologies into the SUS and the development of clinical guidelines. It receives studies submitted by applicants and, after assessing aspects of health technology appraisal, it takes a position on inclusion or exclusion of health technologies. Health technology appraisals are a continuous process of analysing and summarising the potential health benefits and the economic and social consequences inherent in employing certain technologies, while considering the following aspects:

- safety;
- accuracy;
- efficacy;
- effectiveness;
- cost;
- cost effectiveness;
- equity; and
- any ethical, cultural and environmental impact involved in their use.

However, the existing health technology appraisal regime has some pitfalls and is often a barrier to citizens' access to healthcare. Health technology appraisal inadequacies have been considered a key factor in causing patients to seek court orders against the government to provide them with treatment not listed by the SUS.

This litigation trend is discussed widely in Brazil, as it often opposes the individual constitutional right to healthcare against public expenditure and health concerns.

Challenges for patenting personalised medicine inventions

Brazilian legal scenario for protection of diagnostic and treatment methods

Although there is no legal definition of what constitutes personalised medicine, it is widely accepted that it involves a combination of diagnostic steps and subsequent treatment steps established by considering the results of the previous diagnostic steps. This combination provides some challenges in terms of patent protection in Brazil.

In this context, the Brazilian Industrial Property Act 9,279/96 establishes that therapeutic and diagnostic methods performed on the human or animal body are not patentable subject matter (Article 10, item VIII).

Moreover, the Brazilian Patent and Trademark Office (INPI) still has no specific guidelines on personalised medicine. Therefore, general guidelines apply. When interpreting the current law provisions, INPI considers a method of treatment to be any therapy aimed at the cure or prevention of a disease or disorder of the human or animal body, or the relief of symptoms of pain, suffering and discomfort with the purpose of re-establishing or maintaining the normal health of an individual. Therapeutic methods carried out on or outside the body are not considered to be an invention and are not patentable. However, diagnostic methods carried out outside the human or animal body are eligible for patent protection.

Pursuant to these interpretations, INPI has been rejecting any claims bearing one or more

steps performed on the human or animal body. In this context, it is extremely important to pay attention to how claims are drafted to preserve the applicant's rights.

As a way of avoiding such a rejection, rights holders may use Swiss-type claims, which are accepted by INPI if written in a very specific format: use of compound X characterised as being for the manufacture of a medicament for treating disease or condition Y. It is also worth emphasising that the claims must be written in this exact format at the time of requesting examination, otherwise the rights holders may be precluded from making adjustments once the examination has been started.

When it comes to personalised medicine, one point of concern is the second medical use of a known therapeutic. An added complication is that this type of invention typically relates to the use of known therapeutics to treat the same disease as was treated previously, differing only in the dosage amounts, dosage regimens, population being treated and route of administration.

INPI has been adopting a restrictive understanding, in that novelty and inventive step in a Swiss-type claim are acknowledged only if the medical use has not been previously known in the state of the art. The selection of a sub-population, dosage, regimen and route of administration is also insufficient to confer novelty or inventiveness on the known medical use of a compound or composition, as well as not being considered patentable subject matter.

In light of INPI's understanding, it is of the highest importance that a careful review is made before requesting examination. As a practical tip, since the inclusion of any step carried out on the body is construed as being directed to non-patentable subject matter, it is advisable, whenever possible, to amend the claim to a pure diagnostic claim, further defining the patient being examined. It is also vital to ensure that all claim types surrounding the personalised medicine invention are pursued upon requesting examination (eg, tools, diagnostic methods, medical use claims and diagnostic kits).

Court discussions regarding personalised medicine

The main court case concerning personalised medicine was the motion for unconstitutionality brought by former Prosecutor General Cláudio Fonteles against the provisions of the Biosafety Act, which permitted research with human stem cells. According to Mr Fonteles, the provisions breached the right to life. The motion was dismissed by the Brazilian Supreme Court in 2008, which confirmed that research with human stem cells does not breach the Brazilian Constitution.

As for the patentability of personalised medicine, the matter is yet to be tackled by the courts. However, that Brazilian courts tend to deny patents for polymorphisms for lack of invention and also deny patents for dosage regimens, as both situations would fall within the prohibitions of Article 10 of the Industrial Property Act.

Comment

Brazil is yet to enact specific guidelines on personalised medicine, both from a regulatory and an IP perspective. Although INPI's guidelines were reviewed recently, they did not address the matter. Given that companies are likely to continue to invest in personalised medicine and to file patent applications for the new developments that arise from investment and research, it is perhaps inevitable that INPI's current approach will be challenged and reviewed. As for ANVISA, the agency partly addresses the matter by means of its guidelines on advanced therapies, but many issues remain unclear. The Brazilian courts decided on the constitutionality of stem-cell therapy, but matters related to patentability were not brought before the courts. The main issue relating to personalised medicine being dealt with by the courts is the price of treatment and whether SUS should pay for it.

Matheus Montecasciano, attorney at law, assisted in the preparation of this chapter.

Kasznar Leonardos
Teófilo Otoni st 63
5th to 7th floors
Rio de Janeiro RJ 20090-070
Brazil
Tel +55 21 2113 1919
Web www.kasznarleonardos.com

www.IAM-media.com