

Monitoring of technological horizons for patents on chronic kidney disease

Edmara Thays Neres Menezes (Corresponding author)

PhD student in Intellectual Property, Federal University of Sergipe,
Sergipe, Brazil.

José Wendel dos Santos

Dept. of Production Engineering, Federal University of Sergipe,
Sergipe, Brazil.

Luciano Fernandes Monteiro

Dept. of Production Engineering, Federal University of Sergipe,
Sergipe, Brazil.

Mairim Russo Serafini

Dept. of Pharmacy, Federal University of Sergipe,
Sergipe, Brazil.

Gabriel Francisco da Silva

Dept. of Petroleum Engineering, Federal University of Sergipe,
Sergipe, Brazil.

Abstract

Worldwide, the lack of resolution of the current pharmaceutical arsenal to heal some diseases, including chronic kidney disease, opens space for further research in the field of health. Technological horizons monitoring actions are highlighted in the tracking of relevant technologies to solve certain health issues that are still considered incurable. In this perspective, it is proposed in this study to monitor technological horizons on chronic kidney disease to investigate whether any of the technologies found is incorporated into SUS, with effective use and social impact. For this purpose, a survey was conducted on the International Platform for Clinical Trials Records (ICTRP) of WHO, National Institute of Industrial Property (INPI) and patent database linked to the ORBIT intelligence system. The searches allowed the identification of 32 clinical trials and 375 patents filed worldwide, 33 in Brazil. However, no new technology has been incorporated or is being analyzed for incorporation by the Brazilian Unified Health System (SUS).

Keywords: Monitoring of technological horizons, chronic kidney disease, patents.

1. Introduction

To achieve economic development with equity, academia, government and society understand that this growth depends on the strengthening, expansion and consolidation of science, technology and innovation

(CT&I) activities. The economic development of countries is ensured in innovation based on scientific and technological development. It is no coincidence that several countries, such as the United States and China, have placed innovation as the central line of their strategies for resuming growth after the 2008 crisis (BRAZIL, 2016).

Associated with the scenario of needs of strategic solutions to program innovation in the context of health, Brazil, through the Brazilian Unified Health System (SUS), created in 2006 the commission for the incorporation of technologies (CONITEC) in the scope of the SUS and Supplementary Health (SS), by means of decree No. 3,323 of December 27, 2006 (BRAZIL, 2006). In 2008, he created the Brazilian Network for the Evaluation of Health Technologies (REBRATS) and a Working Group (WG) was established for the development of a Monitoring Technological Horizon (MTH) system. In summary, it can be inferred that the gradual implementation of the WGMTH together with health technology assessment (HTA) actions is considered as an important aspect to establish priorities and provide innovations relevant to the health system, still in the initial phase of the life cycle of health technologies (BRAZIL, 2011).

However, according to the World Health Organization (WHO, 2011), despite the important achievements recorded in the health area in recent decades, there are still several uncured diseases that surround the world population, such as chronic kidney disease (CKD).

CKD is characterized by decreased glomerular filtration rate (GFR) function or presence of kidney injury markers, or both, for duration longer than one trimester, regardless of etiology. In which in its most advanced phase the kidneys can no longer maintain the normality of the patient's internal environment. The cause of CKD is complex and uncertain and progression is multivariate, which leads to different prognoses (WANG et al., 2019).

According to the Brazilian Society of Nephrology (SBN, 2017), approximately 13 million Brazilians have some degree of kidney problems. Of this total, 126,583,000 are in a serious condition with hemodialysis dependence or transplant dependence. In Brazil, cases increase at a rate of 10% per year and kidney disease already kills more than breast cancer. Of these deaths, 70% occur before diagnosis, according to data from the Ministry of Health (BRAZIL, 2015).

In this perspective, it is proposed in this study to perform the MTH on CKD to investigate whether any of the technologies found are incorporated into the SUS, with effective use and social impact. Thus, it can be emphasized the fundamental role of technological innovation as an important instrument for the evolution of disease treatment and driving a healthy and stable quality of life with reduced suffering in the population. In addition, the social role of the use of knowledge is featured, being able to provide preventive aspects that privilege public health.

2. Chronic kidney disease

The kidneys are organs that have the function of eliminating toxic substances from the body through urine. In addition, they participate in the excretion of water and mineral salts and in controlling the pH of the blood. When the individual is affected by a chronic disease that leads to the loss of their functions, they say that there is CKD (RUDNICKI, 2014, p. 107).

The kidneys are fundamental organs for the maintenance of homeostasis of the human body. Thus, it is not

surprising to find that, progressive decrease in renal function, implies in the impairment of essentially all other organs. Renal function is assessed by glomerular filtration (FG) and its decrease is seen in CKD, associated with loss of kidney regulatory, excretory and endocrine functions. When FG reaches very low values, below 15 mL/min/1.73 m², what is called renal functional failure (FFR) is established, that is, the most advanced stage of progressive functional loss observed in CKD (BASTOS; BREGMAN; KIRSZTAJN, 2010, p. 250).

CKD is currently defined as the presence of abnormalities in the structure or function of the kidneys, present for more than three months, with health implications. The new Improving Global Outcomes Guidelines (KDIGO) recommend to classify CKD based on the cause, on the category of glomerular filtration rate (GFR) and on albuminuria, which makes it possible to identify the risk of adverse outcomes, such as progressive CKD, end-stage kidney disease, acute kidney disease, all-cause mortality and cardiovascular mortality (PORTO et al., 2015).

CKD is increasingly recognized as a global public health problem. According to the WHO, kidney and urinary tract diseases are the most common cause of death and the twelfth most common cause of disability. In Brazil, available statistics are alarming, as they emphasize that approximately 100,000 people are undergoing dialysis in Brazil. The cost of the dialysis and kidney transplantation program in Brazil is around R \$ 1.4 billion per year (MENEZES et al., 2017, p. 1060).

The increase in the number of cases has been reported in the last decade in different contexts, associated with aging and the demographic transition of the population, as a result of the improvement in life expectancy and the fast urbanization process. Arterial hypertension and diabetes are the main causes, while socioeconomic, racial and gender disparities are also determining factors (MARINHO et al., 2017, p. 381). CKD does not contemplate an expectation of cure, but the maintenance of a chronic state by subjecting the patient to renal replacement therapy modalities. The treatments available for terminal kidney diseases are: hemodialysis, peritoneal dialysis and kidney transplantation, which are complex, varied modalities and represent a health problem of wide magnitude and relevance, especially when its complexity, risks, diversity of operations and cost are recognized (CASTRO; GROSS, 2013).

It is known that hemodialysis as a treatment for CKD replaces the main functions of the kidney, but is not able to fully replace the organ. It is a high-cost/complex procedure that involves highly specialized assistance, advanced technology, highly complex actions and requires coordination between the secondary and tertiary levels of assistance. In addition, over the past few years, there has been a growing demand, which has resulted in considerable consumption of financial resources (COSTA; VASCONCELOS; TASSITANO, 2010, p. 463).

SUS expenses with renal replacement therapy (RRT) are very high, such information can be observed in the study by Silva et al. (2016), in which they highlight that in 2012, SUS financed 84% of patients undergoing treatment in some type of RRT, spending 2 billion reais.

The federal government stated in 2017 that over the years, expenditure on these procedures has evolved in percentage terms more than the amount realized. Between 2014 and 2015, federal spending on TRS increased by 3.84%, from R \$ 2.6 billion to R \$ 2.7 billion, while the number of procedures grew 3.7% in the period, ranging from 13.5 million to 14 million (BRAZIL, 2017).

As with kidney transplantation, for Silva et al. (2016), innovations related to dialysis can also bring

favorable changes in the costs of this intervention.

3. Monitoring of technological horizons

MTH is not about making predictions, but about conducting a methodical investigation of evidence that ensures adequate and resilient preparation for future opportunities and threats. This tool emerged in the early 20th century with the British Defense Committee of England. Since then, it has been used in several other areas, especially in the business area since the 1960s, with increasing application in supporting political decisions (BRAZIL, 2017).

Still in the 1990s, discussions started on the importance of developing a network for collaboration and exchange of experiences on the theme, which was intensified at the conference organized by the Danish Hospital Institute in 1995, with the participation of representatives of the Denmark, Finland, France, Luxembourg, the Netherlands, Sweden and the United Kingdom. From these discussions, the first international MTH network called European Information Network on New and Emerging Health Technologies (EuroScan) was established in 1999, initially composed of agencies from countries participating in the Danish Hospital Institute conference and one agency from Canada. In 2006, with the growing interest and participation of agencies from other continents, the network was renamed EuroScan International Network (PACKER; SIMPSON, 2005).

In 2017, members of the EuroScan international network founded the legal scientific association of the EuroScan International Network in Cologne, Germany. The knowledge provided must support the areas of evaluation and decision-making at the local, regional, national and international levels (EUROSCAN, 2017).

In Brazil, one of the first activities for the development of MTH was the realization, in 2010, of the MTH workshop. In the initial proposal, issues related to the stages of the MTH were defined, such as the definition of the customer, the type of technology to be explored and the time horizon of the technology life cycle. Thus, the body responsible for the incorporation of health technologies in the SUS was identified as the main customer for information generated by the MTH (BRAZIL, 2011).

Due to the importance of MTH in the elaboration of policies and in the decision-making process, its application can be thought of in order to subsidize the actions of the main actors involved in the management of technology in the health system. Thus, MTH in the health system can support decision-making processes throughout the technology's life cycle (BRAZIL, 2017).

These processes are part of the National Policy on Health Technology Management (PNGTS), approved in 2009 and whose objective is to maximize the health benefits to be obtained in view of the available resources, ensuring the population's access to effective and safe technologies, under conditions of equality. In Brazil, SUS is a major incorporator of technologies. The Ministry of Health alone purchases approximately R \$ 8 billion in medicines, equipment and health products per year. At the same time, managers of all SUS instances are constantly under pressure to incorporate new and emerging technologies (SILVA; PETRAMALE; ELIAS, 2012).

As a result, there was a need to develop guidelines to program MTH within agencies and institutions. The development of an MTH guideline was motivated by the fact that the agencies present a wide variety of

ways to carry out MTH activities. Thus, the guideline proposed by the network aims to systematize these experiences in the form of a general structure that allows other agencies to develop their MTH systems, adapting this guideline to their realities.

The process of monitoring new and emerging technologies will anticipate for the manager the priority technologies for the health system, which will allow the planning of the incorporation agenda, as well as the direction of health technology research and evaluations, making the time and resources for investment in research. In addition, the planning of the incorporation agenda will result in a better allocation of health system resources (VIDAL et al., 2013).

4. Methodology

This is a quantitative, exploratory and cross-sectional research, conducted on the International Platform for Clinical Trials Records (ICTRP) of WHO, National Institute of Industrial Property (INPI) and patent database linked to the ORBIT intelligence system.

The research universe included technological products related to CKD deposited in Brazil and in the world in the last 20 years.

Data collection was carried out from February 2018 to February 2019 using patentometry techniques. Initially, the keywords were defined from the consultation with Health Sciences Descriptors (DeCS): Chronic Kidney Disease; Kidney Disease and Kidney. In the INPI database, the advanced search strategy was used with the Boolean operator "and" combined with the descriptors, to maximize the possibilities of finding patent documents about CKD.

In the ORBIT intelligence system, the search expression was created, which was formed from Boolean operators "and" and "or", in addition to the logical connectives of ORBIT and International Patent Classification (IPC): "TI" title; "AB" summary; "OBJ" objective of the invention; "ICLM" independent claims; "IC" international patent classification; "EC" European classification; "CPC" cooperative patent classification. These operators were used combined with the established keywords. Equation (1) refers to the search term for patents about CKD.

Table 1. Equation used for search

Equation (1)	(+ KIDNEY DISEASE + OR + CHRONIC RENAL DISEASE + OR + NEPHROPATHY CHRONIC +) / TI / AB / OBJ / ICLM AND (A61K OR A61P OR A61M OR A61N OR A61B) / IC / EC / CPC).
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The table contains the equation used to perform the searches in ORBIT intelligence.

The ICTRP was used to verify the number of potential ongoing clinical trials for developing patents. For this purpose, it was used the advanced search combined with the conditions or problems studied and the time frame of 20 years. After the selection of technological products, the MTH was carried out. At this stage, the technologies were tracked in the databases of the National Health Surveillance Agency (ANVISA) based on the search for the International Classification of Disease (ICD) N180, which refers to CKD.

To analyse the collected data, descriptive statistics techniques were used, using the Microsoft Office Excel

2016 for Windows® program.

5. Results

5.1 Clinical trials registered in ICTRP/WO related to CKD

According to the search strategy associated with the keywords, the results reported in the ICTRP were 32 clinical trials related to CKD in the last 20 years. In Figure 1, there is a prevalence of more recent trials having the highest number of records in 2018.

According to Camacho (2013, p. 5), in a scenario of innovation in a certain field, clinical trials are indispensable, because they constitute an essential prerequisite for the licensing of drugs and immunobiologicals by the regulatory agencies of several countries.

Berwanger (2009) emphasize the importance of clinical trials in its study, stating that they became a process of choice for evaluating interventions, aiming to protect against ineffective or harmful procedures to human health.

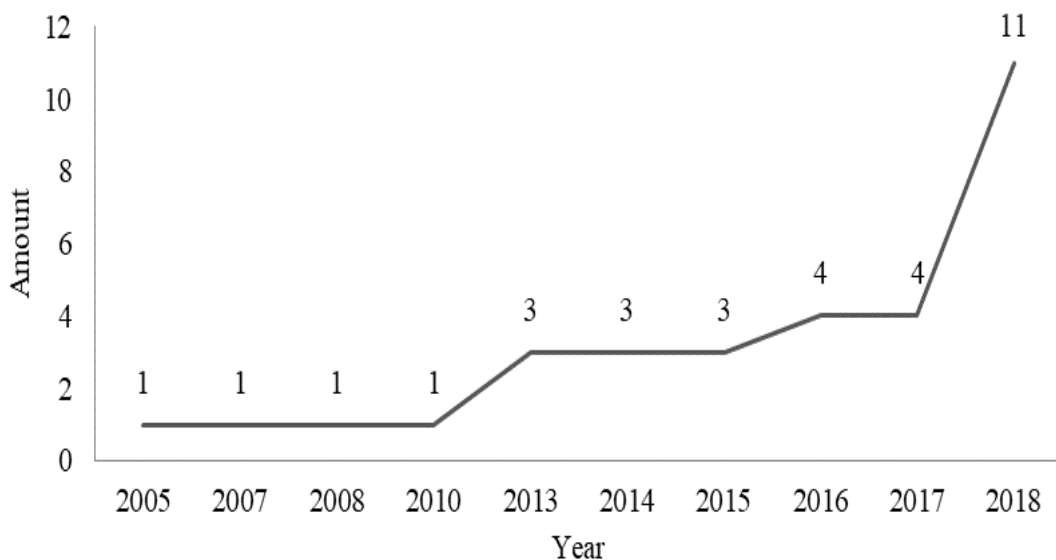


Figure 1. Year of registration of clinical trials on CKD.

Self elaboration (2019).

One of the challenges in the CKD area is to increase the availability of medications and therapeutic procedures that can enable patients to live longer with less suffering, providing a better quality of life for these people. This leads to the search for resources, the professional training of researchers and the conduct of research in the country that generates consistent scientific evidence and contributes to the process of incorporating technologies by SUS.

ANVISA (2017) describes that clinical trials are studies conducted with humans to measure the parameters of safety and efficacy of new drugs, being essential for the arrival of new therapeutic alternatives on the market. These trials are divided into phases I (the first studies to be conducted in humans, usually in a small number of healthy volunteers), II (through these trials, it is confirmed if the new drug has a therapeutic effect and toxicity is assessed allowing the selection of the therapeutic regimen (the dose and frequency of

administration of the new drug) for the Phase III trials), III (comparative studies, usually multicentric) and IV (studies carried out after obtaining the marketing authorization and related to the approved indication), Figure 2 shows the clinical trials under analysis, separated by year and phase. In percentage terms, it can be observed that clinical studies that are in phase I comprise 6.24%, those in phase II represent 3.12%, in phase III there is 9.36% of clinical studies, phase IV represents 6, 24% of these studies. It is noted that 75.04% of the tests were not precisely identified, as they are represented by the category N / A (not applicable). Here it is also showed that 15.6% of the tests are in an advanced stage, comprising the junction of the categories of phases III and IV.

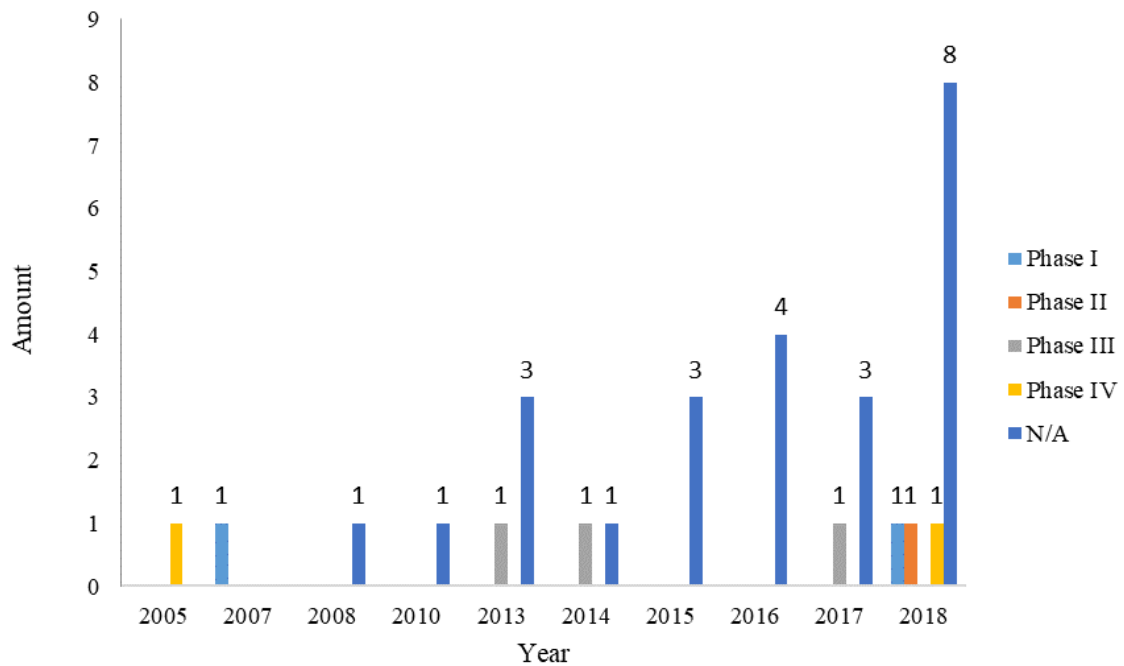


Figure 2. Phases of clinical trials registered for the CKD field of study. Self elaboration (2019).

Figure 3 shows the countries that register clinical trials about CKD, with emphasis on Australia, which in the studied scenario, had 29% of the trials, followed by China with 16%, the United Kingdom with 13%, Canada with 10% and Brazil occupying the 5th position with 7%. The number of clinical trials in Brazil showed a growth rate of 26% in the period 2001 to 2011. However, according to information from the Center for Innovation and Pre-Clinical Trials (CGE, 2017) it is below the average shown in the other BRICS countries that is 39%. Official companies and laboratories are responsible for the smallest part, approximately 27% (in 2010) and about 50% of these tests are concentrated in phase III, in which there is less density and technological risk.

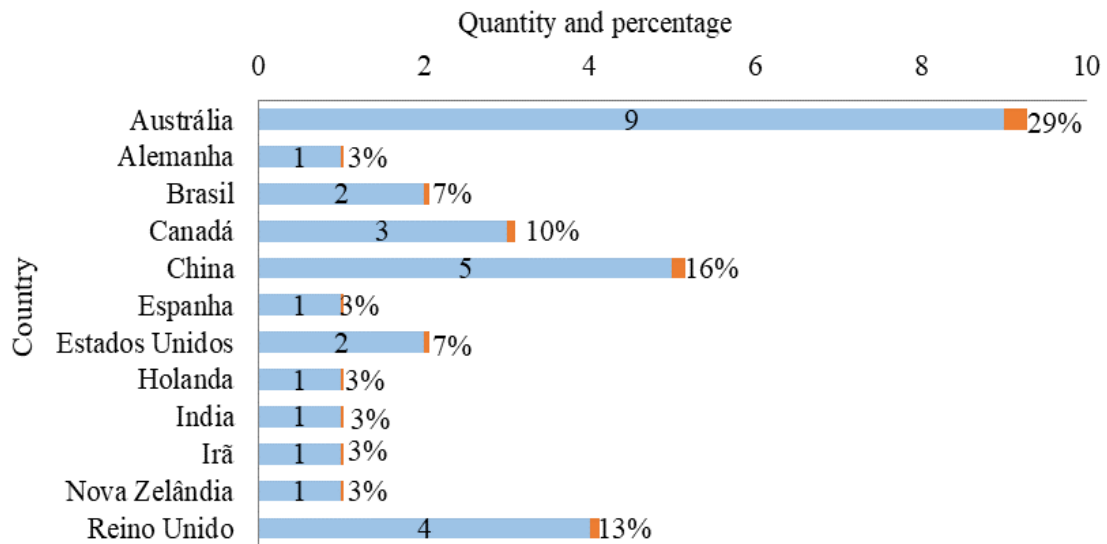


Figure 3. Countries that have registered clinical trials on CKD.
Self elaboration (2019).

Brazil does not have a large volume of private sector investments in RD&I, but despite that, according to Moraes (2016), the country had 0.55% of the Gross Domestic Product (GDP) applied by private companies, even so, remaining distant countries like South Korea (2.68%) and China (1.22%). Also according to the author, comparing the GDP of investment in RD&I in Brazil with the numbers of nations of the Organization for Economic Cooperation and Development (OECD), with other countries in Latin America and the BRICS, Brazil only appears above Mexico, Argentina, Chile, South Africa and Russia being very distant from China and South Korea, nations that started the leap in industrial development very recently. In 2011, China became the world's second largest investor in RD&I.

What stands out is the large private investment in innovation in the world's major economies. In Brazil, this investment is still hesitant. The government should look for strategies to encourage these investments, simplifying the processes, providing attractive tax benefits to investment in RD&I for companies, valuing the companies that make this investment.

5.2 Patents filed with the PTO and ORBIT intelligence related to CKD

The analysis of patents on the world stage is made to monitor the countries where protection was used for purposes of market reserve or as an incentive strategy for international trade. From a technological perspective, this information about the trends of technologies in world markets can bring scenarios of the current relevance of a given area (FERREIRA; FERREIRA; HASNER, 2016, p. 4).

In Figure 4, it can be seen that in the world there are 375 patents related to CKD, while in Brazil only 33. Current patents have been protected in several national offices. What can be seen is a consolidated scenario in China (CN), followed by Japan (JP) and the patents of the European Patent Organization (EPO). Another expressive scenario that stands out is the USA. China is a great power when it comes to innovation, according to which WIPO (2018) shows in its report that China in 2017 filed 1.38 million patent applications, which is more than double the number received by States United. Furthermore, the report

shows China's fast rise in patent issues over the past 15 years.

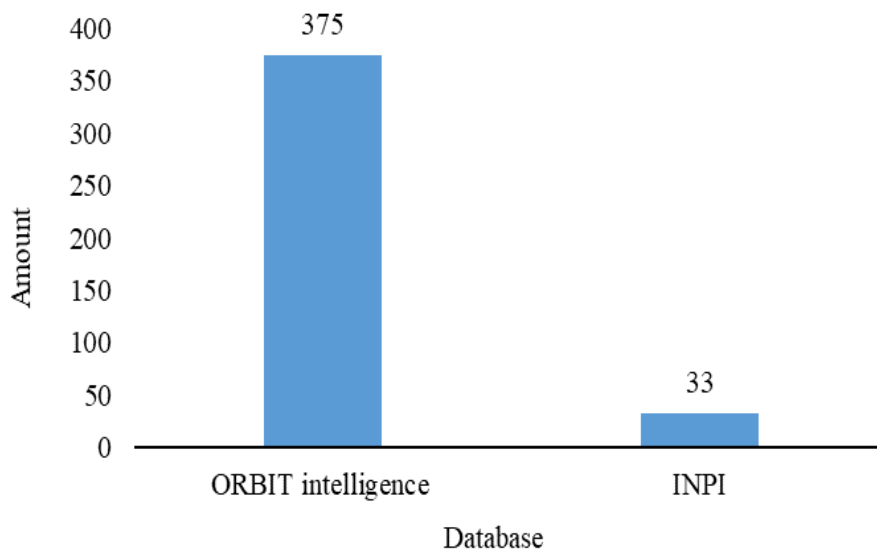


Figure 4. Number of patents on CKD. Self elaboration (2019).

The top 30 DRC patent depositors were pharmaceutical companies and universities. In the first five positions, pharmaceutical companies lead the ranking of patent deposits in the world. The pharmaceutical industry and new drug development process is largely linked to the patent system. This is also a relevant sector characterized by great dynamism and constant need for innovation, requiring high investments in RD&I (OLIVEIRA et al., 2018).

In Brazil, the INPI (2018) released its yearbook for depositing technological products, the ranking of patent deposits, in this case, the top position occupied by universities stands out, with eight of the top ten positions occupied by federal and state universities. As occurred in 2016, only one company appears among the ten largest depositors.

The reason why Brazil is not among the best is that, unlike the economies that aim to achieve prominence on the world stage, Brazil does not yet have public policies and does not make the necessary investments to leverage innovation in the country. In addition, as revealed by Akkari et al. (2016) the development of new drugs and pharmaceutical formulations for other countries are seen as the focus of economic progress and innovation, which makes them stand out worldwide.

5.3 The MTH in the CKD scenario

After collecting the patent information, we tried to identify whether these technologies are being analyzed by the agencies for their market introduction. In the ANVISA database, the search for CID N180 regarding DRC did not return any records.

Analyzing the patents found with the clinical trials found in the ICTRP, no relationship was found between the technologies selected in the study for CKD, stating the results that more than 75% of the trials were registered in the category does not apply. In this category, the studies do not aim to analyze the efficacy of drugs, but rather some alternative therapy, such as music therapy.

From this, it was observed that there are no emerging technologies that can bring effective results and that

are different from those currently applied. The predominance of drugs for factors related to CKD was noted, but not technologies related to better substitute therapies.

Thus, it is emphasized that investments must be made in order to finance research that has quality and can be effectively used, considering that the investment is large so that research does not leave the paper to benefit society.

It is important that the Brazilian MTH system seeks to conduct studies at specific diseases such as CKD, in addition, it is important that HTA activities consider intelligent data systems and international collaboration to improve the efficiency of the MTH system. In this way, the institutions will also be able to measure the quality of the patents produced within their scope.

6. Conclusion

In view of the objectives outlined in the study, the use of the MTH methodology for the analysis of emerging technologies is emphasized. The main point of emphasis in the application of the methodology is the importance of using collaborative work for the effectiveness of the system. In addition, the need to strategically bring together several actors is highlighted so that there is a real success in HTA activities.

The reason is that world patent scenario reveals that the area of CKD still has little research, despite the fact that the disease is currently considered a public health problem. 375 patents have been filed worldwide, 33 of them in Brazil. Within this scenario, China stands out as one of the main countries to develop research in the area, with the pharmaceutical industry being the one that most deposits patents on CKD.

When is about clinical trials, the main reason for studying them is the possibility of identifying other emerging technologies that are already under analysis. In the context of CKD, 32 trials were found in the last 20 years, however, 75% of them seek to analyze alternative therapies for patients with the disease, not applying the category of new products or processes.

The MTH revealed that in the scenario in study, none of the technologies found is in the maturity stage to be incorporated into SUS, considering that their incorporation depends on the analysis of several factors, among them being a new and effective therapy and results.

However, pioneering research in Brazil uses stem cells to allow the return of kidney function. Although Brazilian law prohibits the protection of patents on this type of material, research is at an advanced stage, it is an emerging technology with the possibility of effective use. Thus, its processes must be widely monitored by the HTA teams in order to accelerate the research process, seeking mainly to implement it in SUS. This research can promote a better quality of life for patients with CKD, as well as reducing the costs of treatment with hemodialysis.

The MTH methodology proved to be effective in the application for analyzing the quality of the technologies produced and identifying those technologies. ATS systems need to be attentive to act effectively in the use of emerging technologies, monitoring, fostering for faster development and seeking more quickly to implement novelties that promote improvements for patients and health systems.

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