[www.reciis.cict.fiocruz.br]
e-ISSN 1981-6286

Original article

Patents of polymorphic forms in the pharmaceutical field in Brazil, and its impact on public health

DOI: 10.3395/reciis.v4i2.331en

Jaqueline Mendes Soares
Social Medical Institute, State University of Rio de Janeiro, National Institute of Industrial Property, Rio de Janeiro, Brazil
jsoares@inpi.gov.br

Marilena Cordeiro Dias Villela Correa
Social Medical Institute, State University of Rio de Janeiro, Rio de Janeiro, Brazil

Liane Elizabeth Caldeira Lage
National Institute of Industrial Property, Rio de Janeiro, Brazil

Abstract
The aim of this article is to show how the National Institute of Industrial Property (INPI) is examining the patent applications related to the polymorphic forms in the pharmaceutical field. In order to do so, there was a survey regarding the number of patent applications in this field. Such applications had already been examined by the INPI from January 2008 to March 2009. Results show that most of the patent applications neither meet some of the patentability requirements, nor some of the descriptive sufficiency condition requirements, in accordance with the legal provisions of Law 9279/96 (LPI) and the exam draft guidelines developed by the Institute.

Keywords
medications; polymorphs, crystal form

Polymorphs: definition, properties, and patent protection

The term polymorphism may be defined as the existence of alterations in the crystal packing of a substance without any changes in its molecular structure (molecular and spatial conformation). The chemical properties of different crystal forms of a substance are identical, but not their physical and physical-chemical properties, such as melting point, conductivity, volume, density, viscosity, color, refractive index, solubility, hygroscopicity, stability, and dissolution profile (GIRO et al., 2002).

The presence of different crystalline structures of an active ingredient may impair the performance of various operations in the production of medication such as filtration, washing, drying, milling, lyophilization, encapsulation, compression, and affect their properties of solubility and bioavailability (BOTTOM, 1999; BRITTAIN, 2006). For instance, according to Froehlic, samples of raw materials and mebendazole medication that are available in the market present different polymorphs in their composition, and that can affect their dissolution, and, consequently, their bioavailability (FROEHLIC et al., 2005).

A patent is considered a major incentive for technological development, both for being an official document that grants legal protection to the invention, and for being the greatest source of information on technological innovation in the world, with unpublished data added to its content, which are not available in any kind of technical and scientific publication. In order for a patent to protect an invention, some basic requirements of patentability must be met. These requirements regard the laws of industrial property: novelty, inventive activity, and industrial application (LONGA, 2007).

Usually, international office granted polymorphic form patents in the pharmaceutical field demand products and processes for the attainment of crystal forms of medication that are known in a "Markush Formula". Such patents end up becoming controversial, because their holders use crystal forms strategically to increase the protection of base molecule. It is important to notice that "Markush Formula" is a generic expression for several chemical entities functionally equivalent, allowed in one part or more parts of a chemical compound (JANNUZZI et al., 2008).

In fact, such an extension is made possible due to the scope of protection regarding patents that are being granted

in international offices. And because these patents are extensive and do not properly define the material supposed to be protected, they allow the extension of the matter that has been disclosed in the prior art. Consequently, access to medicine is affected, since the reproduction of generic products that are already out in the public will be prevented (PRO-GENERIC, 2009).

A great number of disputes over patent infringement involving crystal forms have been previously reported. Great examples of that are the issue of patentability of the crystal forms I, II and IV of Warner-Lambert's atorvastatin, and Smithkline Beecham's paroxetine chloride hemihydrate (LIMA, 2008).

In order to outline the position of several patent offices worldwide, in regard to the patenting of polymorphic forms, the laws and examination guidelines of the following countries were studied: United States, China, Japan, Argentina, India, Andean Community, and the European Patent Office. It was noted that for most countries there is no clear position in relation to the patenting of polymorphic forms, nor any legal impediment on such patenting. Regarding the Indian office, the polymorph is subject to patent protection if it meets the patentability requirements, and if it provides significant efficiency in relation to the previously disclosed form in the prior art (INPI, 2009).

In Brazil, the protection for pharmaceutical products and processes occurred until 1945. Henceforth, in order to strengthen the domestic industry, patenting of pharmaceutical products and processes was banned in the country. Law No. 5772 of 12/31/1971, which established the Industrial Property Code, maintained as non patentable matter substances, materials, mixtures or food products, chemical-pharmaceutical and medication of any kind, and their attaining or modification processes (BRASIL, 1971).

After great international pressure from developed countries in 1994, and after negotiations in the Uruguay round of GATT (General Agreement on Regional Development and Trade) / WTO, Brazil signed TRIPS - Agreement on Trade-Related Aspects of Intellectual Property Rights. In this agreement, all inventions in any field of technology should be entitled to patent protection, as the wording given in its article 27 (BERMUDEZ, 2000). Thus, it is understood that Brazil's inclusion in the TRIPS showed the country's intention to adapt its laws to those of other nations. Therefore, with the new Industrial Property Law (Law 9279 of 05/14/1996 - LPI), which entered into force on 05.14.1997, have become granted medication patents in the country (TACHINARD, 1993). It should be noted that this law does not mention the patentability or otherwise of polymorphic forms of medications, and due to the need of creating new examination guidelines that cover specific aspects of pharmaceutical patents, such as the polymorphic form ones, the National Institute of Industrial Property (INPI) started a round of technical discussions to deal with this matter (INPI, 2009).

In this context, to assess the current situation regarding the patentability of polymorphic forms in Brazil, we have worked on a survey regarding the number of applications examined by INPI from January 2008 to March 2009, and also on a critical evaluation of the results of INPI's examination guidelines application proposition.

It is important to note that INPI is a federal institution, under the Ministry of Development, Industry and Trade, that is responsible for the registration of trademarks, patent granting, registration of contracts of technology transfer, franchising, keeping computer records, industrial designing, and performing geographical indications, accordingly with LPI and Software Law (Law No. 9,609/98).

INPI round of technical discussions on the patentability of polymorphic forms

For INPI, the examination guidelines are intended to guide the examiner in the analysis of patent applications, in a way that there will be reconciliation of patent application analysis by different examiners. The current examination guidelines in the fields of biotechnology and pharmacy were published in 12/31/2002 in the Journal of Industrial Property (Revista da Propriedade Industrial - RPI) issue No. 1669. However, in order to conciliate these guidelines with more specific aspects of pharmaceutical patents, as, for instance, with polymorphic forms in mid-June 2007, INPI hosted a round of technical discussion on patents, with three meetings, in order to discuss the conditions for patentability of such forms to subsidize the new examination guidelines in the pharmaceutical field.

Technicians and authorities from other agencies participated on the round of discussions, the Health Surveillance Agency (Anvisa) and Oswaldo Cruz Foundation (Fiocruz), representatives of the Brazilian Association of Industrial Fine Chemicals (ABIFINA), Industry Association Pharmaceutical Research (Interfarma), and Research an Project Financing (FINEP), besides representatives of industrial property associations (INPI, 2009).

The first meeting was on June 11, 2007 at the INPI headquarters, and they mainly discussed polymorphism as an intrinsic property of the substance; the possibility of only patenting the polymorphous attainment process, instead of the product itself; and the lack of descriptive adequacy of

procedures for attaining polymorphs, observed on the great majority of patents that have been granted in international offices. We emphasize that the descriptive sufficiency is a condition of patentability in which the invention must be described so as to allow their manufacturing by someone who is skilled in the art (INPI, 2009).

The second meeting was on June 26, 2007. Initially they discussed aspects that were relevant to determining polymorphic form novelty, as well as the possibility of granting a polymorphic form through its attainment process. The necessity of setting important and essential parameters to the characterization of polymorphic form, and its attainment process were also issues that they discussed during the meetings (INPI, 2009).

At the last meeting held on July 10, 2007, they discussed the various parameters that were relevant to the characterization of the polymorphic form attainment process, which must be addressed to when filling in the patent application. Such parameters are essential for determining the crystalline phase of solid, which is pled to enable an technician to reproduce it. Among the criteria that are necessary for attaining the new polymorphic form, the following were mentioned: variation of concentration, mixture of reagents, addition of seed, cooling rate, torque, pressure, among others. Finally, as for the requirement regarded to the polymorphic form inventive activity, they had different opinions about the issue, however, they have not yet reached a definitive conclusion about it being obvious to technician, or otherwise (INPI, 2009).

Note that after the end of the round of technical discussions, and once the widespread participation of technicians from all areas was considered to be impossible, as well as aiming greater transparency, the INPI established an open channel of electronic communication.

In parallel to the round of discussions, INPI technician body on industrial property, formed by master and doctorate degree trained examiners in the fields of chemical engineering, chemistry, biology, and pharmacy, met at the headquarters of the institute to discuss polymorphic form technical patentability in the pharmaceutical field. After several meetings and technical consultations with members of the Brazilian Society of Crystallography, as well as with federal universities professors, a preliminary document on the patentability of polymorphic forms was drawn up, and displayed online on the INPI electronic page, to receive technical contributions about the subject. After the analysis of these technical contributions, the INPI published its proposed polymorphic form patent application examination guidelines on its online page.

The main items of these examination guidelines are briefly described below:

a) Polymorphic form

Analysis about the novelty requirement under Article 11 of the LPI

The comparison between the single crystal x-ray diffraction diffractograms in the required polymorphic form and the one that has already been disclosed in the prior art, is enough to measure the novelty of the required product. However, without such data it is necessary to compare them using the technique of x-ray diffraction through the method of indexing powder, besides other analytical methods, such as Nuclear Magnetic Resonance Spectroscopy of Carbon in Solid State, Spectroscopy in the Infrared Region, Raman Spectroscopy, Electron Microscopy, Thermal Analysis (Differential Scanning Calorimetry, Thermogravimetry, and Differential Thermal Analysis). Information about the purity of the sample is also important in determining polymorphic form novelty pled, since impurities in the sample may interfere in the quality of the results of the characterization of crystalline structure analysis. It is noteworthy that in order to determine the novelty of the required crystal form, only the characterization of crystalline form data disclosed in the prior art may be submitted after the pled form deposit date in the patent application.

Analysis regarding the requirement of inventive step under Article 13 of the LPI

The polymorphic form should solve a sufficiently differentiating problem of prior art, for instance, increasing in stability, solubility, and processability, which is not made so obvious from the prior art.

b) Procedure for attaining the polymorphic form

Analysis about the novelty requirement under Article 11 of the LPI

The process to attain the polymorphic form will be new when it is not described in the prior art.

Analysis regarding the requirement of inventive step under Article 13 of the LPI

The process of attaining the polymorphic form should not elapse so obviously from the state of the art. That is, the usual processes of crystallization, to begin with, would not be patentable, because their use to produce polymorphic forms in the chemical-pharmaceutical industry is obvious to any technician.

Analysis regarding the condition of descriptive sufficiency under Article 24 of the LPI

Once a simple change to a crystallization process can cause alterations in the crystalline form of the product, it

is necessary that every single parameter involved in the crystallization process is described in the patent application, to make it possible for a technician to reproduce them. Some examples of parameters are: solvent, temperature, concentration, cooling rate, addition of crystal seeds, among others.

Regarding the processes where the seeding of a particular crystal is carried out, the description of the process of attaining the seed is necessary to enable the technician to reproduce it.

c) Pharmaceutical composition containing the polymorphic form

Analysis about the novelty requirement under Article 11 of the LPI

Once verified that the polymorphic form is new, the composition containing it will also be considered new.

Analysis regarding the requirement of inventive step under Article 13 of the LPI

The inventive activity assessment should be performed independently, in other words, for the composition containing the new polymorphic form to present inventive activity, one should assess whether the effect is a differentiator, and if it is proven to solve a technical problem, based on its comparative specific parameters in relation to the prior art. Given that no effect of a composition can be derived from the independent actions of its ingredients, or even the interaction of its ingredients. In order for the examiner to be able to evaluate the effects from new polymorphic form in a composition, there should be comparative data of same quantity compositions as those contained in the prior art.

The protection of polymorphic forms and public health

The INPI round of discussions directly affected the deepening of discussions in the country regarding the impact of pharmaceutical patents on public health.

Thus, on November 28, 2007 there was the first public hearing on the Commission on Human Rights and Minorities of the House of Representatives where they discussed about the access to medications and how it could possibly be harmed by patents. The representatives raised questions related to compulsory licensing, pipeline patent unconstitutionality, and commitment to strengthening national policy on the access to medicines (DE OLHO NAS PATENTES, 2009).

The public hearing of June 25, 2008, requested by Rep. Dr. Rosinha (PT-PR), in the International Relations Committee of the House of Representatives, aimed to discuss the patenting of polymorphic forms in Brazil. The board of the hearing was attended by representatives of Anvisa, INPI, and the Interministerial Group for Intellectual Property (GIPI). According to Rep. Dr. Rosinha, multinational enterprises will be the only ones to benefit from the patenting of polymorphic forms, and if this measure is adopted in Brazil it will compromise the right of access to medicines, since patented medications are more expensive. According to Anvisa, the patentability of polymorphic forms can lead to the formation of monopolies that inhibit competition and limit the space of the national inventor. The representative of GIPI, who aims to conciliate the positions of the organs of executive authority on intellectual property, did not express his opinion on the patenting of new polymorphic forms. For the INPI president, the patenting of new polymorphic forms favors the country in the global network of technological innovation (CHAMBER OF DEPUTIES, 2009).

On October 30, 2008 a public hearing in the House of Representatives was held, and it included representatives from the Minstry of Development, Industry and Trade (MDIC), Ministry of Foreign Affairs, Ministry of Health, and the president of the INPI to discuss patenting in the pharmaceutical field, specifically in regard to new polymorphic forms, and medical use, in other words, new use of some medication that is already known. In this public hearing it was widely discussed that it is not up to the INPI to establish rules, and therefore its guidelines should be sent to be approved by the GIPI (ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS, 2009).

On December 1, 2008 the GIPI met in plenary session, with INPI representatives, and Anvisa, and the representative of the Ministry of Health (MS) claimed that the granting of patents for incremental inventions contradicts health public policies, and it also contradicts the country's health industrial complex development. However, the INPI representative warned that the proposed examination guidelines related to polymorphic forms created by the body is quite demanding and restrictive, and that its application has restricted the granting of patents in this field, to those who actually meet the legal requirements (novelty, inventive activity, and industrial application), and the condition of descriptive adequacy. The president of the INPI suggested legislative amendments that could legally assure the GIPI in the choice of not granting patents to polymorphic forms. Finally, the GIPI decided at its last meeting to limit the patenting of medicines in the country. Such decision is a response to the controversy regarding the applications given to the INPI that plead for protection for second medical use (INSTITUTO BRASILEIRO DE DEFESA DO CONSUMIDOR, 2009).

On September 23, 2008, a project was developed (PL 3995, 2008) by Mr Paulo Teixeira (PT-SP), and it proposed three amendments in Clause 10 of the IPL, namely: the prohibition of granting patents for new medical use of any medication, the banning on patents for new crystal forms of known substances, and, for last, the replacement of the term "operative methods" to "operative models". In the opinion of the authors of this project, the phenomenon of polymorphism is an intrinsic property of chemical substances with pharmaceutical properties, which may present themselves in different forms in its crystalline state. Thus, the proposed inclusion of a new clause to Article 10 of the LPI, according to the authors of the project, would meet the social requirements, and the technological and economic development of Brazil (DIÁRIO DA CÂMARA DOS DEPUTADOS, 2009).

Law 9279/96, Article 10, refers to matters that are not considered to be inventions, for instance:

I- discoveries, scientific theories and mathematical methods;
II- concepts that are completely abstract;
III- schemes, plans, principles or business methods, accounting, financial, educational, advertising, lottery and supervision;
IV- literary, architectural, artistic, and scientific works, or any aesthetic creation;
V- computer programs;
VI- reporting;
VII - game rules;
VIII - surgical techniques and methods, as well as therapeutic or diagnostic methods, for use on human or animal body, and
IX - all or part of natural living beings and biological materials found in nature or isolated therefrom, including the genome or germplasm of any natural living being and natural biological processes.

In accordance with the proposal of PL 3995, 2008, Article 10 of the IPL would have the following wording regarding polymorphic forms:

"Article 10 - Neither invention nor utility models are to be considered:
XI - chemically identical products, but with different crystalline forms, whether they are under patent protection, whether in the public domain. "

It is important to mention that the PL 3955, 2008, joined the PL 2511, 2007 by Mr Fernando Coruja, who refers to the prevention of patent protection for pharmaceutical products and processes which make new statement.

Thus, currently the patentability of polymorphic forms is under discussion involving several government agencies and civil society representatives, as well as the legislative chamber.

Patent applications related to polymorphic forms of medications that were being analyzed by the INPI from January 2008 to March 2009

There being no legal restrictions to the patenting of the subject matter, the INPI has been examining the applications for polymorphic forms in the pharmaceutical field based on current legislation.

While not decisive, a patent generates expectations of law, effectively functioning as blocking the use of pled material. Moreover, the longer a decision is delayed on the patentability of polymorphic forms, the longer will be the duration of a patent, if granted, in other words, more than 20 years from the date of filing, since according to Article 40 the LPI, the validity of a patent may not be less than 10 years after the granting date, there is the possibility that the INPI might be unable to examine the merits of the claim. Also, it is noted that if it takes time to decide about the material that has been claimed, it will prevent the entry of generics on the market, because while the patent application is pending there is the expectation of law.

The methodology of our study was to search for words such as modification, shape, polymorphic crystals and their variations in the title of patent applications related to polymorphic forms in the pharmaceutical field by the INPI, published in the Journal of Industrial Property (RPI) from January 2008 to March 2009. Therefore we have recovered the journal's issues n. 1930, 1939, 1941, 1942, 1946, 1967, 1968, 1972, 1975, 1983, 1986 a 1989, 1991 e 1995.

The RPI is an official publication of INPI, where all its acts are published, as well as orders and decisions regarding the industrial property system in Brazil. It is weekly published and it can be found at the INPI library, in police stations, outposts, and regional representation, as well as online (www.inpi.gov.br).

RPI journal has a code table of orders and each code comes with precise explanation of the procedural stage of applications, patents and industrial designs that proceed through the INPI, as well as measures to be adopted by their designated depositors or attorneys. Thus, it is possible to analyze the matter of the patent application and identify the progress of the application or patent through codes of order.

Now that we had the numbers of patent applications related to polymorphic forms, on the next step of this work we read the examination opinions with the purpose of analyzing which LPI articles, as well as the technical arguments that were used by technical examiners, who were responsible for the patentability or otherwise of the polymorphic forms. The examination opinions of each patent application can have its

photocopy requested to the INPI, this service is available to any person or entity.

When processing an examination of the patent application, the examiner shall issue a technical opinion (Article 35 of the LPI) setting out their conclusions, which can be: the granting of the patent, technical requirements for developing science, and opinion (if the matter does not meet the patentability requirements), and by rejecting the request.

If the decision is made to grant the patent, in other words, for the patentability of the application, the creation of technical requirements, the fact that the application meets the requirements for protection (awareness notification) and the request being refused.

If the decision is for the patentability of the application, ie. the granting of it (published as code of order 9.1), it means that previously hindered documents have not been found, and that the request meets the patentability requirements and Normative Acts of the INPI.

If technical requirements are formulated (published as code of order 6.1) for the reformulation of the request, so that they may receive the pending patent, the applicant will have 90 days to comply with them. When the requirement is not responded within the deadline, the application is filed final (Article 36 of the LPI Once the requirement has been responded to, but not yet met, the examiner may arrange new technical requirements in order to solve the irregularities of the patent application (second examination) and, again the depositor will have 90 days to comply with them.

If a patent application has evidence of non patentability, then an awareness notification will be issued (published order with code 7.1) and the depositor will have 90 days to respond and present his arguments about it. If the examiner considers the arguments presented by the applicant as pertinent, the application will be accepted. However, if the arguments are not enough to fully resolve the evidence of non-patentability of a new notification or requirement may be issued. If the applicant fails to submit reply to the notification, then the application is filed. If the arguments are deemed rejected, the application will be also rejected.

The rejection of an application (published order with code 9.2) means that it does not meet the patentability requirements and conditions expressed in the LPI. It is important to note that the patent application cannot be rejected on first examination, in other words, it may only be refused if requirements are not met.

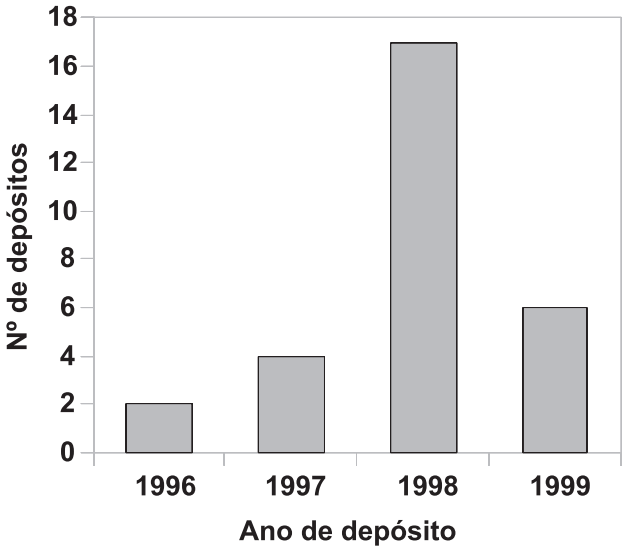
In a second moment, the depositor will have the opportunity to speak before a final decision by lodging an appeal against the dismissal, within sixty days of notification of the rejection in the RPI. On the appeal phase, the patent application is examined by a technician other than that who refused it, and also after the analysis of the board, a new technical notification is issued and it may decide to maintain the dismissal or the reversal thereof. If the report is said to keep the rejection, for now, the administrative phase is closed, and the discussion about the patentability of the application can still be questioned in court. If the board decides to overturn the rejection, the examination follows the standard procedure, it is referred to ANVISA for prior informed consent in accordance to Art.229-C, LPI. If it is granted, the INPI publishes its report of approval.

The following Table shows the results of the survey, highlighting the number of patent application, the depositor, subject and situation in the INPI, as well as the numbers of patent applications related to polymorphic forms reviewed by the Division of Chemistry II (DIQUIMII) of INPI during the stated period.

RESULTS AND DISCUSSIONS

On the applications examined by DIQUIM II from January 2008 to March 2009, regarding polymorphic forms, it is observed in the graph that the largest number of applications are from 1998.

Graph - Breakdown of patent applications examined by the INPI between January 2008 and March 2009 on polymorphic forms in the pharmaceutical field.



(Vertical – Number of Filings. Horizontal – Year of Filing)
Source: authors.

Table - Applications reviewed by the INPI regarding the polymorphic forms from January 2008 to March 2009.

N° of Application	Depositor	Subject	Situation in INPI
PI9603540-4	Tioga Pharmac.	New form thermodynamically stable to heat the N-methyl-N-[(1s)-1-phenyl-2-((3s)-3-hydroxy-pyrrolidine-1-yl) ethyl] -2,2-difenilacetamida	7.1 (RPI 1975 de 11/11/2008)
PI9611229-8	Merck & Co Inc.	Polymorphic form of the compound methanesulfonate N-[1 (R) - [(1,2-dihydro-1-metanossulfonil spiro [3H-indole-3, 4'-piperidine] 1-yl)-carbonyl] -2 - (phenylmethyl-oxy) ethyl]-2-amino-2-metilpropanamida.	9.2 (RPI 1941 de 18/03/2008)
PI9711151-1	G.D. Searle & Co	Crystalline form of 4 - [5-methyl-3-4-IL-fenilisoxazol] Benzenossulfonamida	9.2 (RPI 1942 de 25/03/2008)
PI9712072-3	Meiji Seika Kaisha Ltd.	Crystalline substance of Cefditoren pivoxil and production process.	9.2 (RPI 1968 de 23/09/2008)
PI9714059-7	Astrazeneca AB	S-omeprazole in a neutral, process of preparation and pharmaceutical composition.	7.1 (RPI1989 de 17/02/2009)
PI9714081-3	Sanofi-Aventis	Process for the crystallization of the hydrochloride of 1 - [2 - (2-naphthyl) ethyl] -4 - (3-trifluorometilfenil) -1,2,3,6-tetrahydropyridine (SR 57 746 A).	9.2 (RPI 1967 de 16/09/2008)
PI9804946-1	Novartis Ag	Crystal modification of a pharmaceutical agent	9.2 (RPI 1972 de 21/10/2008)
PI9804947-0	Novartis Ag	Crystal modification of a pharmaceutical agent	9.2 (RPI 1972 de 21/10/2008)
PI9816234-9	Sanofi-Aventis	New crystal form of N-(4-trifluormetilfenil)-5-metilisoxazol-4-carboxamide.	7.1 (RPI1986 de 27/01/2009)
PI9806784-2	Viatris GMBH & CO. KG	Modifications of 2-amino-4-(4-fluorobenzilamino)-1-Etoxicarbonil-aminobenzeno and preparation process	9.2 (RPI 1983 06/01/2009)
PI9810360-1	Merck & CO, INC	Polymorphic form of the compound 2 - (R) - (1 - (R) - (3,5-bis (tri-fluorometil) phenyl) ethoxy) -3 - (S) - (4-fluoro) phenyl-4 (3 - (5-oxo-1H, 4H-1 ,2,4-triazole) Methylmorpholine and preparation process.	9.2 (RPI 1983 de 06/01/2009)
PI9810483-7	Astrazeneca AB	Form B of omeprazole-sodium and preparation processes.	7.1 (RPI 1939 de 04/03/2008)
PI9810776-3	Roche Dignostics Gmbh	Thermodynamically stable modification of 1 - (4-carbazolilóxi) -3 - [2 - (2-metoxifenóxi) ethylamine] 2-ol and the preparation process.	9.2 (RPI 1995 de 31/03/2009)
PI9810920-0	Novartis AG	Modification of crystal form of a derivative of N-phenyl-2-pirimidinoamina and preparation process	7.1 (RPI 1988 de 10/02/2009)
PI9816198-9	Novartis AG	Crystalline form of acid addition salt monometanossulfônico	7.1 (RPI 1988 de 10/02/2009)
PI9810956-1	Novartis AG	Macrolides crystal and process for its preparation	9.2 (RPI 1995 de 31/03/2009)
PI9811061-6	Astrazeneca AB	11 - (4 - [2 - (2-hydroxyethoxy) ethyl] -1 - piperazinyl) - dibenzo [b, f] [1,4] Thiazepines crystalline processes for the preparation and pharmaceutical composition	9.2 (RPI 1930 de 02/01/2008)
PI9812866-3	Schering Corporation	Crystalline antifungal polymorph	9.2 (RPI 1995 de 31/03/2009)
PI9813213-0	Orion Corporation	Polymorphic form of Levosimendan	7.1 (RPI 1946 de 02/04/2008)
PI9814476-6	Sigma-Tau& Medosan	New crystalline form of an acid guaiacyl ester 5-methyl-p-2-toluilpirrol acetamidoacético.	7.1 (RPI 1986 de 27/01/2009)
PI9814496-0	Bayer Yakuhin	Form thermodynamically stable Ramatroban.	7.1 (RPI 1962 de 12/08/2008)
PI9816067-2	Astrazeneca AB	The form of omeprazole, omeprazole, the preparation process.	7.1 (RPI 1939 de 04/03/2008)
PI9816198-9	Novartis AG	Crystalline form of acid addition salt monometanossulfônico	7.1 (RPI 1988 de 10/02/2009)
PI9911219-1	Sanofi-Synthelabo	Polymorphic form of clopidogrel hydrogensulfate, preparation process and pharmaceutical composition.	7.1 (RPI 1991 de 03/03/2009)
PI9911523-9	Bristol-Myers Squibb Pharma	New crystalline forms of Efavirenz and pharmaceutical composition.	7.1 (RPI 1987 de 03/02/2009)
PI9912842-0	Menarini International Op. Lux. S.A.	Process for preparing crystalline form of calcium salt of zofenopril	7.1 (RPI 1995 de 1/03/2009)
PI9912622-2	Basf Aktiengesellschaft	Acid R-or S-lipoic pure crystalline enantiomers.	7.1 (RPI 1995 de 31/03/2009)
PI9915669-5	Bayer Aktiengesellsch	Modification of the crystalline acid 8-cyano-1-ciclopropyl-7-(1s, 6s-2 ,8-diazabicyclo-[4.3.0] nonane-8-yl)-6-fluoro-1 ,4-dihydro-4- oxo-3-qui-nolinocarboxilico	7.1 (RPI 1987 de 03/02/2009)
PI9915682-2	Bayer Aktiengesellsch	Modification b crystalline acid 8-cyan-1-ciclopropyl-7-(1s, 6s-2 ,8-diazabicyclo-[4.3.0] nonane-8-yl)-6-fluoro-1 ,4-dihydro-4-oxo-3-quinolincarboxilico	7.1 (RPI 1987 de 03/02/2009)

From studying the Table it is possible to conclude that the filing of applications for patents of polymorphs began in the 1990s and that out of 29 reviewed applications, 15 were rejected, 14 received an awareness notification, none was rejected and there was no filing by any national company regarding this matter.

By reading the expertise of patent applications that make up the framework, it was found that the vast majority could not assess the novelty of the claimed polymorphic form, as provided in Articles 8 and 11 of the LPI, since it was not properly marked according to the analysis techniques mentioned in the proposed guidelines for examination of the INPI on the matter. It is noteworthy that most patent applications listed in the table, ie 95%, claims the product (polymorph), the preparation process, pharmaceutical composition, and use of the polymorph.

For approximately 90% of the patent applications which claim a polymorphic form the state of the art is the closest patent application of the chemical compound, usually in a "Markush formula", where the solid was not characterized. In these cases, to measure the novelty of the pled polymorphic form that the depositor is essential to distinguish the crystalline state of the disclosed compound in the prior art and compare it with the form that is now being claimed in the patent application, through the X-ray diffraction method and other complementary techniques, besides the evidence of the purity of the sample. The issue of the requirement of proving the purity of the polymorphic form lies in the fact that impurities in the sample may jeopardize the outcome of the review, and resolve any doubt that there is no mixture of polymorphic forms. It is noteworthy that none of the applications that have been already reviewed by the INPI presented comparative data from X-ray diffraction of single crystal; this technique is enough to ascertain the novelty of the pled polymorphic form. Thus, for polymorphic forms in which it was not possible to assess the novelty, there would still be a possibility of protecting its attainment process.

It was observed in most of the reports that the obviousness of claimed polymorphic form was questioned, since most patent applications do not have any different technical effect, which is not predictable in relation to the forms described in the prior art. There was no application for patent in which the polymorphic form present greater bioavailability than the already disclosed one in the prior art, and much of the technical solutions resided in the area of pharmaceutical technology, in other words, greater physical or chemical stability, better processability and flowability, among others.

As for the process of attaining polymorphic forms, in most technical reports it has been pointed out that the essential parameters of a crystallization process were not described in order to allow their reproduction by a skilled technician (Article 24 of the LPI For instance, the cooling rate used in the crystallization process, the solution concentrations of crystallization, the temperature used, and how the crystal seed that was used in the planting process was attained, none of those were described on the application. Thus, according to the INPI draft examination guidelines of polymorphic forms, such processes to attain a polymorph as described do not meet the requirements described on Article 24 of the LPI, and therefore are not patentable.

In addition to questioning the lack of descriptive adequacy of procedures for attaining a polymorphic form of the table patent applications, the INPI examiners argued that such are obvious results to a skilled technician who understands about organic synthesis of purification and crystallization of a chemical compound and thus, they do not meet the requirement of inventive step under Article 8 and Article 13 of the LPI.

It is noted that 96.7% of applications are still being analyzed at first instance, awareness notification and rejecting, and therefore no final decision at the administrative stage has yet been made.

Regarding the pharmaceutical compositions containing a polymorphic form in all patent applications of the Table, there was no comparative data to justify a differentiating effect between a composition containing a polymorphic form and one that had already been described in the prior art, and thereby pled to the pharmaceutical compositions was alleged that they have no inventive activity, and thus are not patentable.

Conclusion

Currently in Brazil, the patenting of polymorphic forms in the pharmaceutical field is housed within ministries and civil society and is a very controversial issue especially with regard to access to medicines. In this scenario, the INPI has decided on the round of technical discussions regarding this subject and, after analyzing it, the INPI made public its proposal for examination guidelines for patent applications of polymorphic forms.

As presented in the text, patent applications related to pharmaceutical polymorphic forms which were examined by the INPI from January 2008 to March 2009 are not entitled to patent protection since they do not meet some of the requirements for patentability, in addition to the descriptive adequacy condition, when examined under the

legal considerations of LPI, and its proposed examination guidelines.

This paper gives awareness about the importance of the INPI proposed examination guidelines for patent applications of polymorphic forms, with the purpose of conciliating the examinations in meeting the requirements for patentability, and in guiding patent depositors when writing them.

Bibliographic references

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS. **Discussão sobre patentes de polimorfos e segundo uso terapêutico polariza a posição de Ministérios e parlamentares de um lado e do INPI do outro.** Disponível em: <http://www.abiaids.org.br>. Acesso em: 20 jan. 2009.

BERMUDEZ, J.A.Z. *et al*. **O acordo trips da OMC e a proteção patentária no Brasil:** mudanças recentes e implicações para a produção local e o acesso da população aos medicamentos. Rio de Janeiro: Editora FIOCRUZ/ENSP, 2000.

BOTTOM, R. The role of modulated temperature differential scanning calorimetry in the characterisation of a drug molecule exhibiting polymorphic and glass forming tendencies. **International Journal of Pharmaceutics**, v.192, n.1, p.47-53, 1999.

BRASIL. Lei nº 9279, de 14 de maio de 1996. Regula direitos e obrigações relativos à propriedade industrial.

BRASIL. Lei nº 5772, 21 de dezembro de 1971, Institui o novo código da propriedade industrial e dá outras providências.

BRASIL. Projeto de Lei n° 3.995, de 2008. **Diário da Câmara dos Deputados**, Brasília, 23 set. 2008. Disponível em: <http://imagem.camara.gov.br/diarios.asp>. Acesso em: 20 jan. 2009.

BRITTAIN, H.G. Polymorpism and solvatomorphism. **Journal of Pharmaceutical Science**, v.96, n.4, p.705-728. 2006.

CÂMARA DOS DEPUTADOS. **INPI**: patente de polimorfos favorece inovação tecnológica. Disponível em: <www.camara.gov.br>. Acesso em: 20 jan. 2009.

DE OLHO nas patentes: a inconstitucionalidade das patentes pipelines. Disponível em: <www.deolhonaspatentes.org.br>. Acesso em: 20 jan. 2009.

FROEHLIC, P.E.; GASPARATTO, F.S. Mebendazol: identificação das formas polimórficas em diferentes matérias-primas e medicamentos (referência e genéricos) disponíveis no mercado nacional. **Revista de Ciências Farmacêuticas Básica e Aplicada**, v.26, n.3, p.205-210, 2005.

GIRO, D. *et al*. Solid-state characterizations of pharmaceutical hydrates. **Journal of Thermal Analysis and Calorimetry**, v.68, p.453-465, 2002.

INSTITUTO BRASILEIRO DE DEFESA DO CONSUMIDOR. **Patentes de medicamentos**: decisão do grupo interministerial prioriza saúde pública. Disponível em: <www.idec.org.br>. Acesso em: 20 jan. 2009.

INPI. **Proposta de diretrizes para exame de pedidos de patentes de novas formas polimórficas**: metodologia usada e os dados coletados sobre patentes de formas polimórficas em outros países. Disponível em: <www.inpi.gov.br>. Acesso em: 20 jan. 2009.

INPI. Diretrizes para o exame de pedidos de patente nas áreas de biotecnologia e farmacêutica depositados após 31/12/1994. **Revista da Propriedade Intelectual,** 2002. Disponível em: <http://www.inpi.gov.br>. Acesso em: 20 jan. 2009.

INPI. Proposta de diretrizes para o exame de pedidos de patentes de novas formas polimórficas. Disponível em: <http://www.inpi.gov.br>. Acesso em: 20 jan. 2009.

INPI. Reunião do Grupo de Estudos sobre Polimorfismo, 1., 2007. Disponível em: <www.inpi.gov.br>. Acesso em: 20 jan. 2009.

INPI. Reunião do Grupo de Estudos sobre Polimorfismo, 2., 2007. Disponível em: <www.inpi.gov.br>. Acesso em: 20 jan. 2009.

INPI. Reunião do Grupo de Estudos sobre Polimorfismo, 3., 2007. Disponível em: <www.inpi.gov.br>. Acesso em: 20 jan. 2009.

JANNUZZI, A.H.L.; VASCONCELLOS, A.G.; SOUZA, C.G. Especialidades do patenteamento no setor farmacêutico: modalidade e aspectos de proteção intelectual. **Cadernos de Saúde Pública**, v.24, n.6, p.1205-1218, 2008.

LIMA, D.M.M. **As estratégias de extensão da proteção e/ou bloqueio da concorrência da indústria farmacêutica:** o caso das patentes de polimorfo. 2007. (MBA em Políticas Públicas - Enfase em Inovação e Propriedade Intelectual) – Centro de Ciências Jurídicas e Econômicas, UFRJ/INPI, Rio de Janeiro, 2007.

LONGA, L.C.D. **O gerenciamento da informação tecnológica contida na literatura patentária:** uma proposta para a FIOCRUZ. Dissertação (Mestrado) - Escola Nacional de Saúde Pública Sérgio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro, 2007.

PRÓ-GENÉRICOS. Barreiras relacionadas à patente para entrada de medicamentos genéricos no mercado da União Européia. Disponível em: <www.progenericos.org.br>. Acesso em: 17 jan. 2009.

TACHINARDI, M.H. **A guerra das patentes:** o conflito Brasil x EUA sobre propriedade intelectual. Rio de Janeiro: Editora Pa e Terra, 1993.