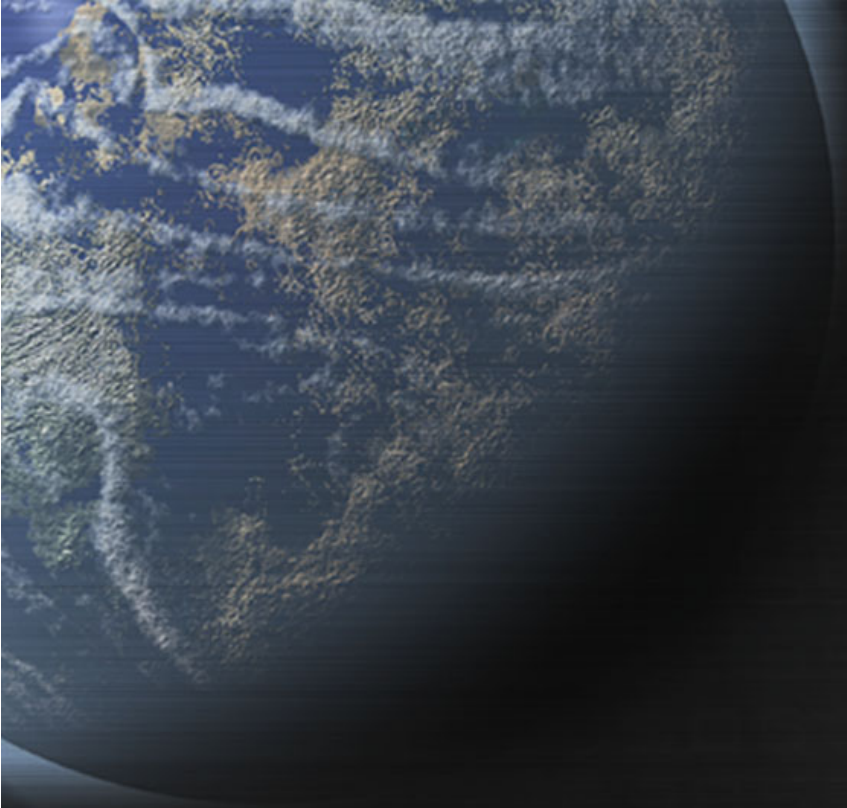

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Biopharma IP issues in Brazil

João Luis Vianna
Gabriel F. Leonardos

18 January 2012

New Jersey Intellectual Property Law Association

Agenda

- Brazilian biopharmaceutical market
- Different types of marketing approvals
- Status of patent linkage legislation
- ANVISA's role in the examination of patent applications
- View of INPI on the patentability of bio/pharma inventions
- Exclusive Marketing Rights
- Data Package Exclusivity
- Patent infringement and invalidity actions
- Citizen's petitions against approval of substandard "generic" and "similar" drugs

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Brazilian Biopharmaceutical Market

- Largest country in Latin America.
- 5th largest population in the world.
- $2,5 trillion economy – 6th largest (CEBR, 2011).
- The most steady democracy in Latin America.
- Foreign direct investment highly stimulated.

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Brazilian Biopharmaceutical Market

- Science fostered as well.
- More than 1% of the GDP goes into R&D.
- Brazil accounts for over 60% of all research spending in Latin America.
- Between 1997 and 2007, Brazilian papers in indexed, peer-reviewed journals more than doubled to 19,000 a year.
- Brazilian scientists write half of the papers in Latin America.
- Number of patents yet to grow.

Source: *Nature Medicine,* 2011, 17(10):1169

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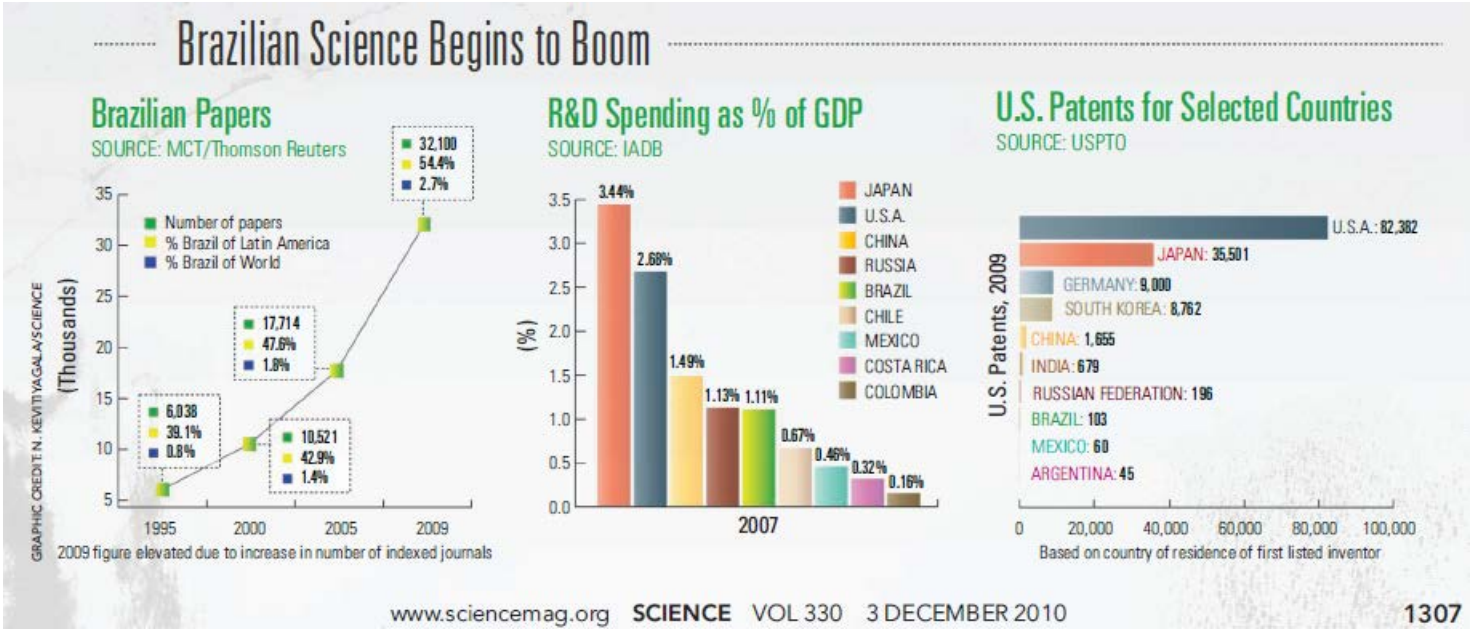
Brazilian Biopharmaceutical Market



Brazilian Biopharmaceutical Market

- Brazil's life science industry begins to boom.
- Private sector concentrated in the Southeastern region (SP, MG and RJ). Among activity areas, human health stands out.
- Roughly 9% of the GDP spent on health care, and about one-sixth of that goes towards pharmaceuticals.
- One of the main countries in most big drug companies' emerging market strategy.
- Sanofi-Aventis acquired top leading generic company Medley in 2009; Pfizer has a 40% stake in Laboratório Teuto (2010); and Amgen bought Laboratório Bergamo in April 2011.

Brazilian Biopharmaceutical Market

- Novartis is entering into a partnership with the Brazilian Government. It includes technology transfer agreements in the field of manufacture of medicaments for use in oncology, transplantation and neuroscience.
- The company plans on setting up a biotech plant for the manufacture of vaccines in Pernambuco (costs: US$ 400-500 million).
- Novartis will also boost research for the development of products for the treatment of tropical diseases, including Dengue fever and Chagas disease, besides broadening its program for fighting Hansen's disease in the country.

Source: Valor Econômico - 9 Jan 2012

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Main Types of Marketing Approval

New/Originator Medicine
Merck's Propecia®

Generic

Branded copy – "similar"

Other Types of Marketing Approval

- Radioactive medicines
- Herbal medicines: Active ingredients are of plant origin.
- Industrialized dynamized medicines: Made from substances subjected to successive triturations/dilutions followed by succussion or other form of rhythmic agitation.
- Simplified notification medicines: Those medicines which use or to which exposition offer low risk of causing health consequences and/or damages.
- Specific medicines: Do not fall into any of the other categories and bear an active substance that cannot be subjected to bio-equivalence assay.
- Biological medicines: Vaccines, hyperimmune serums, hemoderivatives, medicines obtained from biological fluids, animal tissues or biotech processes, monoclonal Abs, medicines containing live, attenuated or dead MOs, probiotics and allergenics.

Other Types of Marketing Approval

New Biological Products and Biosimilars – Resolution ANVISA No. 55/2010

- For new biological products, the classical pathway, based on a full dossier submission by the applicant, is required.

- For copies, two regulatory pathways: comparative and individual development.

- Individual Development Pathway

- Comparative Pathway

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Status of Patent Linkage Legislation

- No patent listing required
- No public database listing patents for given products, such as the US Orange Book.
- No certification requirement
- Medicaments: prices are controlled by the Government
- "Linkage" – Only possible during pricing proceedings before the CMED*
- ANVISA does not prevent or delay registration of generic/similar drugs because of possible patent rights
- Section 43, VII, Law 9,279/96 – Bolar Exemption
- Bill 6,654/2009: When applying for MA, the applicant must prove that it is the owner of the patent for that given active ingredient/drug, or is authorized to use it. Status: shelved, after being rejected by one of the commissions within the HR.

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ANVISA's Role in Examination of Patent Applications

- Patents claiming pharmaceutical products and processes might only be issued after receiving **prior consent** from Brazilian FDA (Section 229-C*, introduced in Brazilian Patent Law by Law No. 10,196 of February 14, 2001)

> ***Section 229-C** - The granting of patents in connection with pharmaceutical products or processes shall be dependent on prior consent from the National Sanitary Surveillance Agency (ANVISA).*

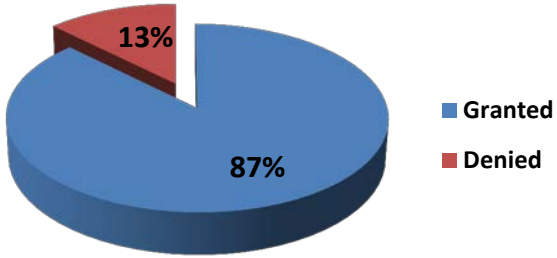
- Resolution RDC No. 45 of June 23, 2008: ANVISA's administrative proceedings for prior consent

  → Section 4, caput: Analysis of **patentability requirements** and other criteria established by the legislation in force

ANVISA's Role in Examination of Patent Applications

Total of decisions issued by ANVISA (June/2001 - December/2011)

	No. of applications	%
Granting of prior consent	1256	87
Denial of prior consent	181	13
Total	1437	100

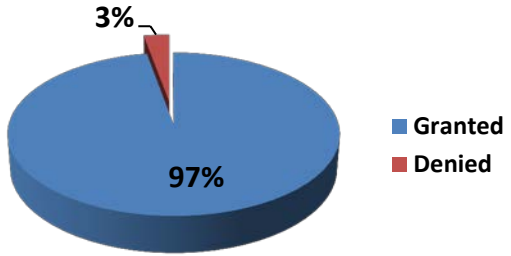


* Source: Oficial Federal Gazette / ANVISA's website (updated until October 31, 2011)

ANVISA's decisions

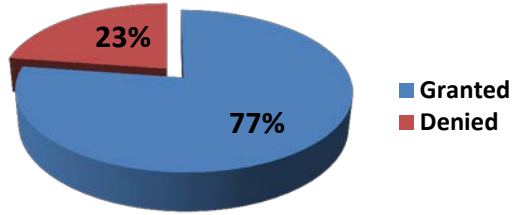
Before RDC No. 45 (June 23, 2008)

	No. of applications	%
Granting of prior consent	711	97
Denial of prior consent	21	3
Total	732	100



After RDC No. 45 (June 23, 2008 – December 31, 2011)

	No. of applications	%
Granting of prior consent*	545	77
Denial of prior consent	160	23
Total	705	100



* Denial of prior consent reviewed in 31 applications

* Source: Oficial Federal Gazette / ANVISA's website (updated until October 31, 2011)

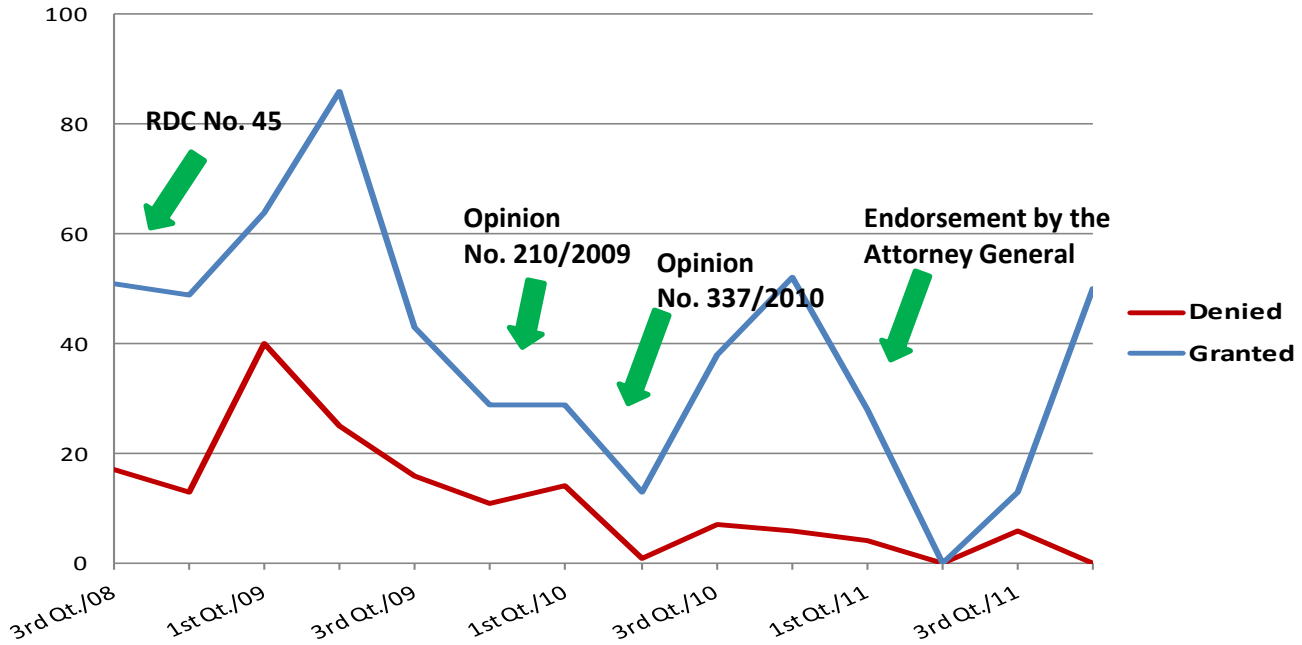
Opinions from the Attorney General's Office

- **Legal Opinion No. 210/PGF/AE/2009** (October 16, 2009)
  - ✓ ANVISA should be limited to examination of public health factors

- ANVISA requests the Attorney General's Office to reconsider the opinion

- **Legal Opinion No. 337/PGF/EA/2010** (March 4, 2010)
  - ✓Reiterates previous opinion
  - ✓Endorsed by the Attorney-General Hon. Luis Adams on **January 7, 2011**
  - ✓ Final and non appealable
  - ✓Decrease in number of decisions

ANVISA's decisions after Resolution RDC No. 45



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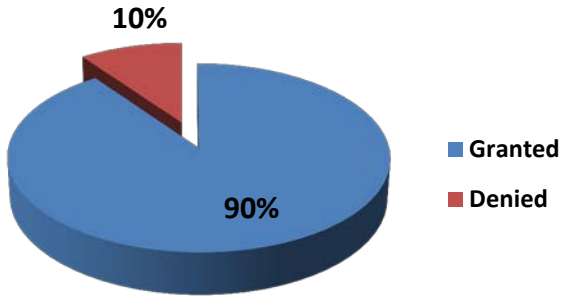
ANVISA's decisions

After endorsement of Opinion No. 337 by the Attorney General on January 7, 2011

	No. of applications	%
Granting of prior consent*	91	90
Denial of prior consent	10	10
Total	101	100



* Denial of prior consent reviewed in 6 applications

* Source: Oficial Federal Gazette / ANVISA's website (updated until October 31, 2011)

Recent Developments

- Interministerial Admin. Ruling No. 1,956, of August 16, 2011: Working group* to discuss the application of Section 229-C → 60-day term for issuance of a final report

- Interministerial Admin. Ruling No. 2,584, of November 1st, 2011: extra 60 days
  - ✓ Time-limit: **January 2, 2012**

- No further developments published

*Interministerial working group formed by representatives from Ministry of Health, Ministry of Development, Industry and Foreign Trade, Attorney General's Office, Brazilian Patent Office, and ANVISA

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Second Medical Use Inventions

- The claim format currently accepted by the Brazilian PTO for pursuing second medical use inventions, according to the Examination Guidelines now in force is:

"Use of Compound X characterized in that it is in the preparation of a medicament for treating disease Y."

- According to the PTO's understanding, second medical use claims are regarded as process claims, not product claims.

- In 2007 the PTO launched a cycle of public debates for discussing the patentability of controversial subject matter, including second medical uses, which resulted in non-official Examination Guidelines that are being applied thenceforth by the Examiners at the PTO.

Second Medical Use Inventions

- **Novelty**: the claimed second use must be substantially distinct from the use disclosed in the state of the art.

- **Inventive activity**: the new mechanism of action, the structure-activity relationship of the compound and the etiology of the newly targeted disease shall not derive in an obvious and evident manner from the teachings of the state of the art.

- **Descriptive Sufficiency**: the specification should, most preferably, disclose *in vivo* tests, in order to be enabling.

- Use inventions based on the mode of administration, and/or dosage regimen are considered as **therapeutic methods (Section 10, VIII)**.

- **ANVISA** : Second medical uses would not be novel and consist of mere discoveries.

Polymorphs

- There are no any legal hindrances in the IP Law for the patentability of polymorphic forms.

- A draft of Examination Guidelines was proposed during the cycle of discussions which took place in 2007. Such Guidelines, though non-official, are being applied by Brazilian Examiners. Examination criteria stand quite restrictive.

- **Novelty**: There should be presented a complete set of experimental data in order to demonstrate that the obtained polymorph is distinct from the parent compound and/or other polymorphic forms disclosed in the state of the art. Comparative test data with the state of the art being required.

- **Inventive activity**: The obtained polymorph must solve a "sufficiently distinct" problem of the art. Comparative data is frequently required.

Polymorphs

- **Descriptive sufficiency**: The parameters related to the process for the obtainment of the polymorphic form must be clearly and sufficiently described within the description of the specification.

- Applications directed to the **process for the obtainment of polymorphic forms** must fulfill the standard patentability requirements of novelty and inventive activity. Concerning the descriptive sufficiency, the PTO considers that it is vital that several parameters, such as, concentrations of the different used solutions that are critical for the process, solvents, cooling rate, time, temperature of the different process stages, torque or addition of seeds* of the desired crystalline form are disclosed so that the specification is enabling.

*When the crystallization process is conducted with seeding, the process for seed preparation must be also clearly and sufficiently described in the application.

Polymorphs

- **ANVISA**: Has publicly shown a contrary position as to the patentability of polymorphs, under the grounds that the granting of patents for this type of subject matter would be detrimental to public health and contrary to the development of National industry*.

- **PL 3995/2008**: Aims at amending the IP Law, to specifically, exclude from patentability new therapeutic uses of known compounds and novel polymorphic forms

*Source: SOARES, *et al*, R. Eletr. De Com. Inf. Inov. Saúde. Rio de Janeiro, v.4, n.2, p.43-52, Jun., 2010 [www.reciis.cict.fiocruz.br]

Biotech inventions

Not considered as invention, e.g.:

- Nucleic acid molecules, even if artificially obtained or isolated/purified from nature
- Plant / animal extracts
- Chemical compounds which have a natural counterpart, even if obtained by synthetic means
- Polyclonal antibodies
- Naturally occurring microorganisms, and plant and animals

Non-patentable inventions, e.g.:

- GM animal or plants, including cells

Biotech inventions

Bill n° 4961 / 2005: Brazilian Industrial Property Law changes proposal

Aims at changing the IP Law so that substances or materials isolated from nature which meet the patentability requirements and do not consist of mere discoveries shall be patentable.

Patentable inventions, e.g.:

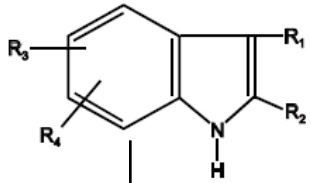
- Recombinant DNA/polypeptides
- Monoclonal/humanized/chimerized antibodies and hybridoma
- Vaccine, compositions, formulations
- Processes for producing transgenic organisms
- Modified microorganisms (transgenic, recombinant, mutants).

Markush and Selection Patents

Markush Patents

- No specific guidelines issued by the Brazilian PTO.
- Critical patent requirements: Unity of Invention and Sufficiency of Disclosure/Enablement.
- Unity of Invention: All members of the Markush group need to belong to a common or recognized class and share a common property, activity or function.
- Sufficiency of Disclosure/Enablement: The description must comprise sufficient data allowing the skilled person to obtain all compounds generalized by the claim.

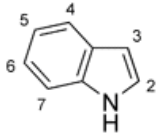
Claim 1: A Compound of the formula:



Wherein R_1 is selected from the group consisting of phenyl, pyridyl, thiazolyl, triazinyl, alkylthio, alkoxy and methyl; R_2 - R_4 are methyl, benzyl or phenyl. The compounds are useful as pharmaceuticals for the purpose of enhancing the capacity of the blood to absorb oxygen.

In this case the indolyl moiety is the significant structural element which is shared by all of the alternatives. Since all the claimed compounds are alleged to possess the same utility, unity is present.

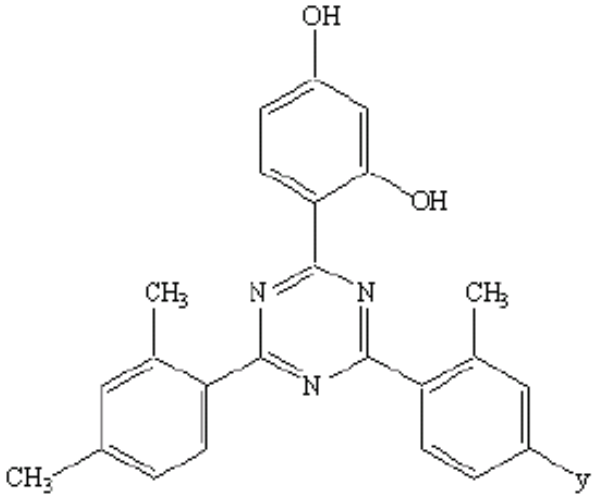
UNITY OF INVENTION



Indolyl

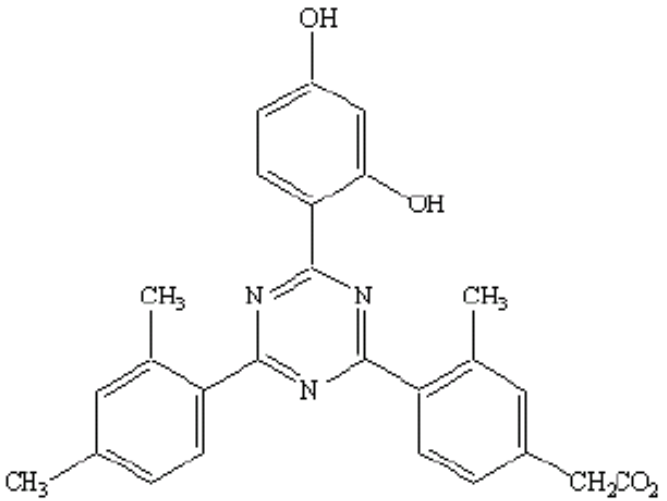
Markush and Selection Patents

PRIOR ART



wherein y is alkyl or alkyl-alkoxyl
Specification only enables compounds in which y is methyl. Used as UV absorber in aqueous solutions.

SELECTION



UV absorber with a 200-fold decrease in the required amount, which can be used in organic solutions.

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Exclusive Marketing Rights – EMRs

- Not expressly foreseen in any Brazilian Statute
- Transitional rule based on Art. 70.9 of the TRIPS Agreement, which set forth that an exclusivity of 5 years should be granted to products which were not patentable under local laws, in the date of entering into force of the TRIPS Agreement in such country
- TRIPS entered into force in Brazil on Jan. 1st, 1995 and in Brazil an international treaty is incorporated into the national laws automatically upon its approval by the Brazilian Congress, without the need of additional implementing legislation to be passed
- The new Patent Act entered into force on May 15, 1997 (Law No. 9.279, of 1996)
- All pending patent applications filed between Jan. 1st, 1995 and May 14, 1997 were subsequently examined in accordance with the new Patent Act (as per Section 229 of the Patent Act), and for this reason the Government understands that there was never the need to create EMRs in Brazil
- There is no final decision yet, but the trend of the Courts is to understand that EMRs did not, and do not exist in Brazil

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Data Package Exclusivity

- Article 39(3) of TRIPS
- Data Package Exclusivity (DPE) Act: Law No. 10,603, of 2002: “pharmaceutical products for veterinary use, fertilizers, pesticides, and their related components”
- Congressional debates: pharmaceutical drugs for human use were expressly excluded
- Drugs for human use enjoy data package protection based on general trade secret Law (Section 195, XI of the Patent Act)
- Presidential Decree 3,209, of 1999 requires that ANVISA keep all information confidential, but creates some exceptions – these exceptions have not yet been scrutinized in a law-suit

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Patent Infringement and Invalidity Actions

- Infringement Cases: State Courts
- The invalidity of a patent may be requested within 6 months of granting, by means of a petition of revokation filed with the BPTO; or anytime during the validity term of a patent, by means of an invalidity action filed before a Federal Court
- Patent infringement is both a criminal and a civil offense
- In both types of law-suits, preliminary injunctions (PIs)and TROs are available and dependant upon the Judge's discretion
- Criteria for PIs and TROs are: the likelyhood of success of the complaint and the need for an urgent decision; and the Judge must weigh the hardship caused by the decision granting the PI or TRO, as opposed to the hardship caused by not granting it. Public interest considerations always play an important role in a Judge's decision

Patent Infringement and Invalidity Actions

- In both types of law-suits the Judge decides with the help of a technical expert he appoints, and whose fees must be paid by the plaintiff. The cooperation of the parties with technical experts is very important, not only to impress the Judge, but also to positively try to influence the Court's Expert

- Damages are available, and the Patent Act has criteria for minimum damages that must be awarded to the patent owner. However, there are no punitive damages in Brazil

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Citizen's Petitions Against Approval of Substandard "Generic" and "Similar" Drugs

- Brazilian Constitution gives to every person "the right to health" (Art. 196)

- Brazil has universal health care coverage

- Consumer protection is also a constitutional commandment, and the Consumer Rights' Act (CRA) gives to indivual consumers and to consumers roganizations legal standing to file several types of law-suits for the protection of consumers' interests. The protection of a consumer life and health is also foreseeen in the CRA.

- The Unified Health System – SUS was created in 1990 and combines the Federal, State and Municipal administrations

Citizen's Petitions Against Approval of Substandard "Generic" and "Similar" Drugs

- List of essential medicines which are distributed for free: RENAME – one of its main principles is the cost/benefit ratio of a pharmaceutical drug

- Several types of law-suits are possible: by companies which want to have their drugs included in RENAME; by companies which do not want that their competitors are included in RENAME; by consumers' organizations of by individual patients who want to by provided with a certain drug etc. The result of these law-suits depend heavily on the factual circumstances of each case.

- Such cases can be very complex, with several stakeholders participating in the case. For example:

Citizen's Petitions Against Approval of Substandard "Generic" and "Similar" Drugs

- Class Action nº 0011053-91.2009.4.02.5101:

Filed by the Federal Prosecutor against the Union and the State of Rio de Janeiro requiring the inclusion of medicines Bosentan ("TRACLEER", manufactured by Actelion Pharmaceuticals) and sildenafil ("REVATIO", manufactured by Pfizer) in the RENAME list. Both drugs are used in the treatment of pulmonary arterial hypertension. The Defendants alleged that the medicines Digoxin (manufactured by GSK), Warfarin, Amlodipine (manufactured by Pfizer) and Verapamil (manufactured by Nordisk), among others, were already listed in RENAME for the treatment of such disease, and the choices of the Public Administration were based upon the National Drug Policy. They also presented a report showing evidence that the cost-benefit of including Bosentan ("TRACLEER") and sildenafil ("REVATIO") in the RENAME list was not worth. Although the Plaintiff eventually got an injunction, this decision was later overruled by the Federal Court of Appeals for the 2nd Circuit. The case was subsequently dismissed since the Public Administration established adopted a protocol for the treatment of pulmonary arterial hypertension which included the use of sildenafil ("REVATIO") and iloprost (manufactured by Bayer Schering Pharma AG) – but not Bosentan ("TRACLEER").

Thank You

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