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**Opportunities and Challenges for Innovation in
Pharmaceuticals: Now or Never!****Barreiro, E. J.;*** **Pinto, A. C.***Rev. Virtual Quim.*, 2013, 5 (6), 1059-1074. Online publication: 6 September 2013<http://www.uff.br/rvq>**Oportunidades e Desafios para a Inovação em Fármacos: Agora ou
Nunca !**

Resumo: O artigo apresenta um histórico sobre a descoberta de novos fármacos e alguns dos cientistas pioneiros dessas descobertas. Descreve a cadeia de inovação em fármacos, os desafios e as contribuições do INCT-INOVAR para que o Brasil, a exemplo dos países do grupo G-8, seja um *player* no desenvolvimento de fármacos.

Palavras-chave: Inovação em fármacos; fármacos inovadores; a cadeia de inovação em fármacos.

Abstracts

The article describes the discovery of new drugs and presents some of the pioneer scientists of these findings. It also shows the innovation in pharmaceuticals and the contributions of INCT-INOVAR that will help Brazil to be one of the players in drug development.

Keywords: Pharmaceutical innovation; new drugs; process of drug discovery.

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Opportunities and Challenges for Innovation in Pharmaceuticals: Now or Never!

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1. **Historic Chronology**
2. **Pharmaceutical technological innovation: Pasteur's Quadrant**
3. **The capacity for innovation in the Pharmaceutical Industry (PI)**
4. **Contemporary innovative pharmaceuticals**
5. **Contribution of the National Institute of Science and Technology in Drugs and Medicines (INCT-INOVAR)**
6. **Final Considerations**

Preamble

Innovation is a complex process which is based on the application of scientific knowledge into processes leading to products and goods with a high technological level (e.g. pharmaceuticals, computers, scientific instruments, airplanes, etc.). These products were responsible for 25% of the world trade in the beginning of this century, and its production is mainly restricted to developed nations, the ones that make up the G-8 Group. As this is a wide topic, it will be dealt

in a concise way and will be limited to the issue of innovation in pharmaceuticals.¹

Industrialized drugs, more so than any other technological good, demand high scientific and technological knowledge in their invention /creation, in all the steps of this translational process, starting from the research laboratory bench to the chemical-pharmaceutical industrial factory. High sums of resources are necessary until the medications reach drugstore shelves. The reward for pharmaceutical companies who develop new pharmaceuticals is the profit they provide. For countries like Brazil, with

no tradition in the development of new pharmaceuticals, and in the current stage of our pharmaceutical industry, if invention is difficult, innovation is possible.

For making easier the understanding of the topic of drug innovation, we will consider the following items

1. Historic Chronology

The pharmaceuticals as industrial products and goods began with acetylsalicylic acid (ASA) in the latter days of the XIX century when Felix Hoffman successfully obtained it in 1897, in its pure form, reproducing what French chemist Charles Gerhardt had obtained in 1853, as an impure product, in the acetylation of salicylic acid. In

the early XX century, several pharmaceuticals with various therapeutic indications were created.²

Figure 1 illustrates the timeline for the discovery / invention of certain drugs.

In a careful analysis of Figure 1, one observes that many of the listed drugs have represented great therapeutic innovations, although many of these pioneer molecules have been for the most part supplanted in terms of safety and efficacy. The lack of knowledge of the pharmacological mechanism of action (MOA) is a common important aspect to note in the drugs created in the first two decades of the XX century, as it was the case with salvarsan³ and penicillin, both being included in the class of chemotherapeutics. This reality persisted until the second half of the century, when pharmacology started to stand as a subject.

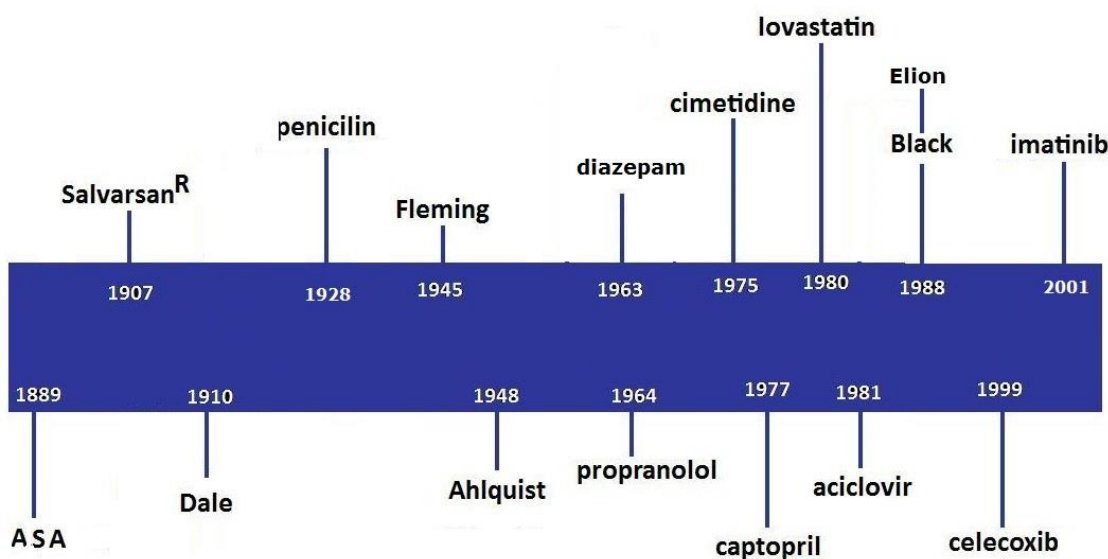


Figure 1. Timeline of the discovery of pharmaceuticals until the XX century

The reports by Henry Hallett Dale (1875-1968; Figure 2),⁵ in 1942 on the cholinergic receptors, and later, the description of subtypes of adrenergic receptors by Raymond Ahlquist (1914-1983; Figure 2)⁶ can be considered important marks that have allowed for the later discovery of a typically innovative molecule, propranolol (Figure 3).

Invented by *Sir* James W. Black (1924-2010; Figure 4),⁷ at the industrial research laboratories of the Imperial Chemical Industries (ICI), in London, England, in 1965, this pharmaceutical, the first antihypertensive acting as a β -blocker, is a significant example of the application of the so-called basic research, recognized by the

genius of Black who was awarded the Nobel Prize in Physiology and Medicine, in 1988, after having invented cimetidine, another innovative pharmaceutical. Cimetidine (Figure 3)⁸ was the first selective antagonist

of the sub-type 2 of histaminergic receptors with an indication for the treatment of peptic ulcer, also being the first blockbuster in the history of pharmaceuticals, reaching US\$ 1 billion in yearly sales in the 1980s.⁹

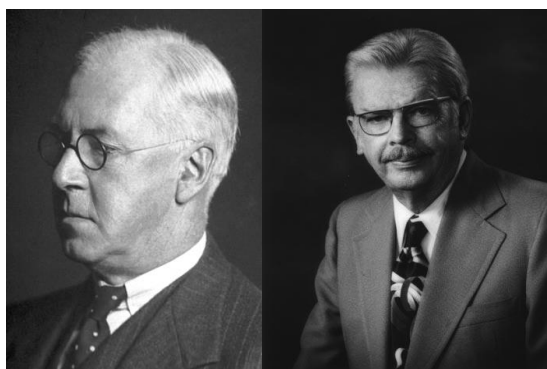


Figure 2. Henry H. Dale & Raymond P. Ahlquist

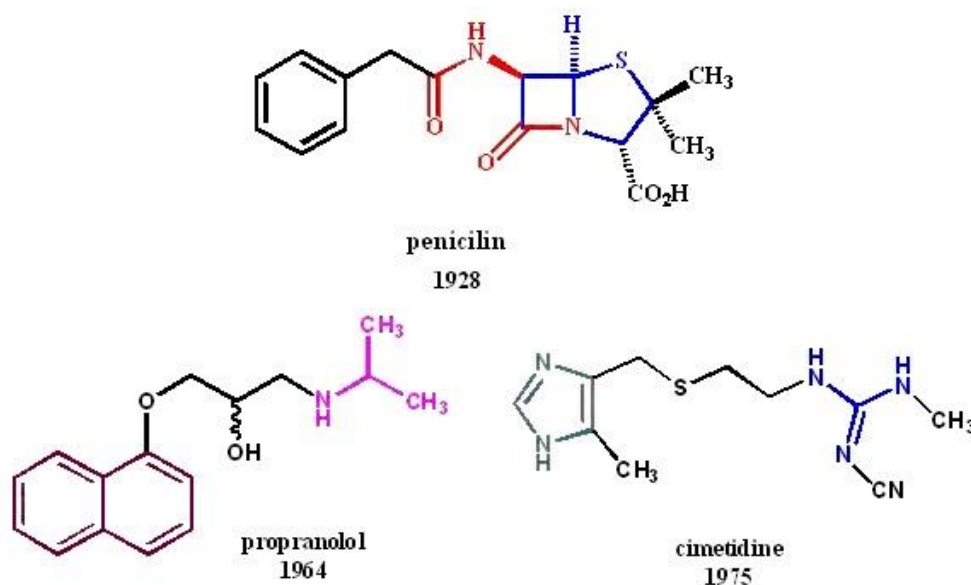


Figure 3. Penicillin, propranolol and cimetidine structures, indicating the years of their discoveries

There are many successful examples resulting from the research capacity of universities,^{10,11} allowing for deep and significant advances in scientific knowledge, coupled with the opportunities for scientists working in research laboratories in the R&D departments of pharmaceutical industries. The careful reading of the history of penicillin (Figure 3) will show that this fact is repeated,

and that the wit and intellectual background of Scottish doctor Alexander Fleming (1881-1955; Figure 5), awarded with the Nobel Prize in Medicine in 1945, shared with Ernest Boris Chain (1906-1979; Figure 5) and Sir Howard W. Florey (1898-1968; Figure 5), were not enough to assure that, when the first half of last century was over, the first antibiotic represented by G-penicillin was released for

therapeutic use. This was a medicinal mark that would revolutionize the treatment of bacterial infections. Without the initiative of pharmaceutical industries to fund, at that time under risk, the necessary studies for the isolation, purification, and production of the active principle of a microbial nature

described for the first time in 1928, by Fleming, would remain as an academic curiosity. The discovery of penicillin, unstable when administered orally, allowed for the studies in the pharmaceutical use of its injectable form.



Figure 4. Sir James W. Black, Gertrude Belle e Elion & George H. Hitchings

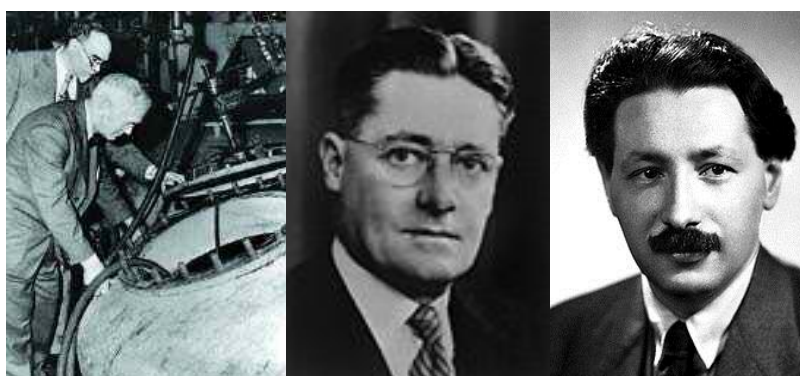


Figure 5. Alexander Fleming, Sir Howard W. Florey & Ernest B. Chain

In the few examples mentioned herein (Figure 3), it is observed that all three drugs were the first ones of their therapeutic classes, inspiring other incremental innovations, which joined these pioneers drugs.¹² There are several β -lactamic antibiotics, β -blocker antihypertensive or H-2 antagonists that are now available.¹²

Considering that only these drugs (Figure 3) are truly innovative, being the first ones of natural origins and the following ones synthetic, it is impossible to quantify their therapeutic impact in terms of number of saved lives ever since. The cure of infections that were previously lethal and the control

and reduction of morbidity of arterial hypertension, a chronic non-communicable disease, silent and sneaky, treated by penicillin and propranolol could be symbols for the impact of innovative drugs for the improvement of the quality of life for humankind.¹³

Carefully inspecting the timeline of the discovery of pharmaceuticals of Figure 1, we can observe several examples of truly innovative pharmaceuticals that have revolutionized therapies throughout the XX century. Benzodiazepines represented by diazepam (Figure 6), released in 1963; captopril (Figure 6) in 1977; lovastatin (Figure

6) in 1980, a statin precursor, which is the most important class of antilipemic medications used so far; aciclovir (Figure 6) invented by Gertrude B. Elion (1918-1999; Figure 4) in 1981, who was awarded with the Nobel Prize in Medicine in 1988 alongside with Sir James W. Black and George H. Hitchings (1905-1998; Figure 4); celecoxib

(Figure 6), the first selective cyclooxygenase-2 inhibitor non-steroid anti-inflammatory drug, in 1999; and imatinib (Figure 6), in 2001, the first multiple tyrosine kinase (TK) inhibitor, with important anticancer properties, acting through a new mechanism of action.

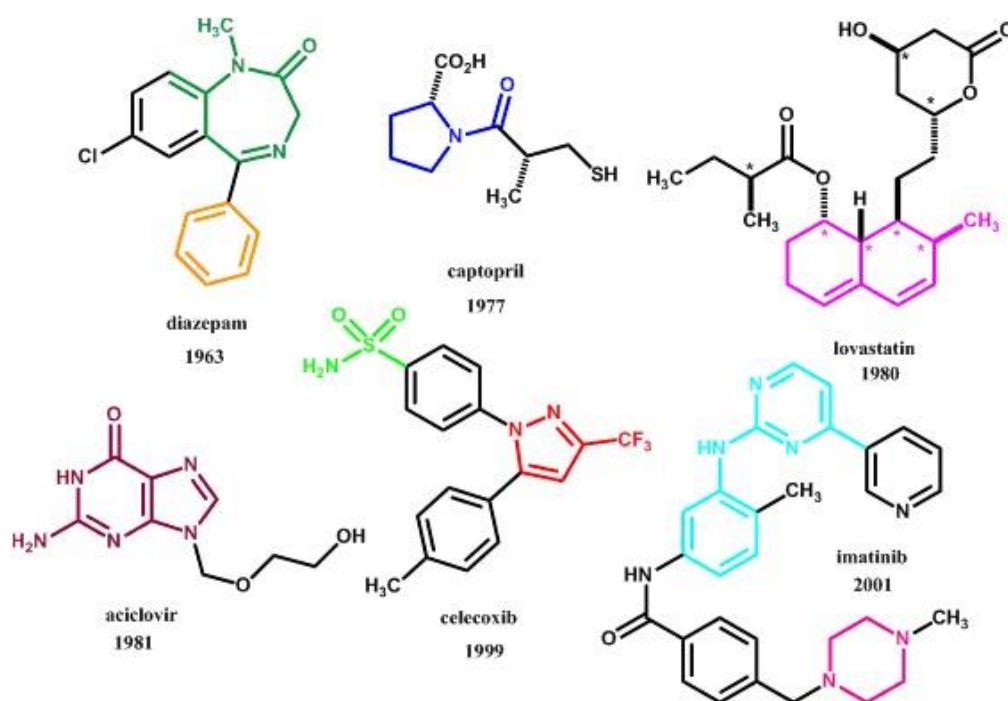


Figure 6. Structures of the pharmaceuticals mentioned in the timeline of Figure 1

2. Pharmaceutical technological innovation: Pasteur's Quadrant

Throughout the years, after the World War II, there were many studies carried out for attempting to improve the social profits of investments in science and technology (S&T). Among the authors who have devoted about this question is Donald Stokes (1927-

1997),¹⁴ an American political scientist from the University of Princeton, USA, who published, in 1997, the book "Pasteur's Quadrant: Basic Science and Technological Innovation" (Figure 7).¹⁴ In his book he established a dialogue between basic and applied sciences. He has named the quadrant that results from the effective application of scientific knowledge as the Pasteur's Quadrant (Figure 7).

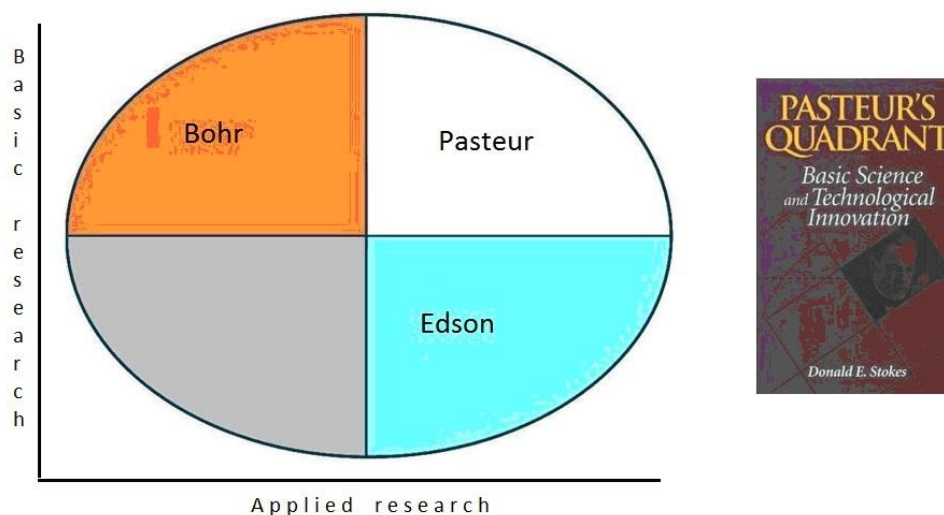


Figure 7. The Stokes quadrants, illustrating the applicability of science

The reading, even if brief, of the quadrants illustrated in Figure 7, allows to understand that drugs might be the most significant example of the importance of basic knowledge to be applied in industrial products that might significantly benefit the society, and which occupy the quadrant named Pasteur, where the so-called basic sciences were coupled with the applied sciences.

Recent published works have indicated that the current conception guiding the scientists thoughts involved in the processes of discovery / invention of new innovative drugs, that have high market impact, is based on technologies that stimulated new local developments and in the application of basic scientific concepts, not rarely coming from universities, which allow the election or choice of original therapeutic targets, resulting in effective and valuable therapeutic innovations.¹⁵

In this context, it is worth noting that the world pharmaceutical sector has surpassed US\$ 890 billion in sales in 2011,¹⁶ out of which, according to innovative pharmaceutical companies, 10 to 15% a year is invested in R&D. These Big Pharmas have in their portfolio, under patent processes, authentic billionaire molecules with yearly gross profits of sums up to 2 digit in the

billion dollar category, thanks to the large funding for research that allows these significant therapeutic innovations to come to fruition, coupled with the effective and continuous marketing and advertising work, which might be responsible for another 15% of their yearly gross profits.

3. The capacity for innovation in the Pharmaceutical Industry (PI)

Figure 8 exemplifies the ability of the PI to create new drugs.¹⁷ Between 1998 and 2011, 475 new pharmaceuticals were released, averaging *ca.* 25 new drugs annually. In that period, the best years were 1999 and 2000, with 35 new chemical entities released, while the worst, in terms of innovation, with only 15, was 2009, followed by 19 in 2004.¹⁸ The USA is the main market for medication innovation, which also has the greatest volume of sales throughout the world. We have identified, each year, those which have become authentic blockbusters in terms of world sales, like esomeprazole, released in 2000, which has not only supplanted the all time best-selling drug, atorvastatin, a drug due to Pfizer that has kept 2 digit billionaire worldwide sales for over a decade, ending its monopoly period with sales, in 2011, of

around US\$ 13 billion, with probable total worldwide sales during its patent protection

period of US\$ 135 billion, between 1991 and 2011.

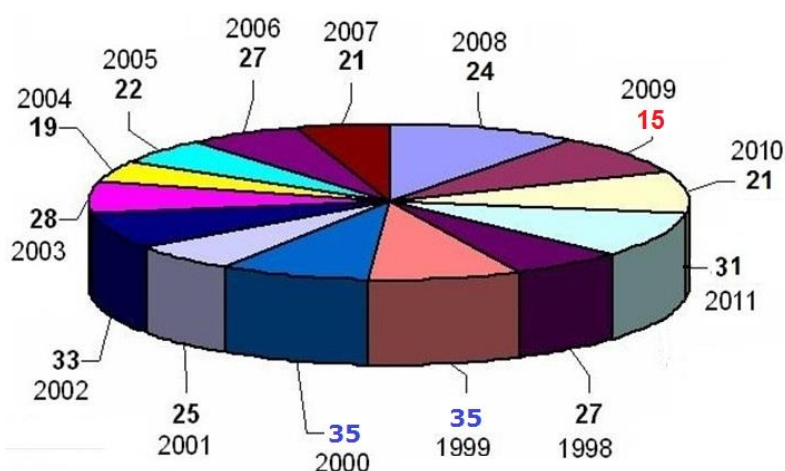


Figure 8. Number of pharmaceuticals released yearly from 1998 to 2011, according to FDA approval in the USA¹⁷

4. Contemporary innovative pharmaceuticals

Several specialists have pointed out that the current stage of reduced innovative capacity by the Big Pharmas,^{19,20,21} illustrated in Figure 8, may have several different diagnoses, made by distinct specialists, in many publications, all agreeing on one point: the loss of innovative capacity by the pharmaceutical industry has been significant in the last decade, considering the average of *ca.* 20 releases per period, with a slight increase in 2011.

Somehow, there is a certain coincidence between the different approaches used in these diagnoses, indicating that the model for managing pharmaceutical innovation used so far successfully by the industry, has now been made less useful by its complexity (Figure 9). The fusions and mergers that have recently taken place in several large pharmaceutical companies, which have made the management of their research centers

especially challenging, due their large geographical distribution as well as the flow of large volumes of scientific information generated by these activities.²² There has also been, as another factor, the frustration of the sector, which did not achieve the expected success in the adoption and implementation of new research techniques for new pharmaceutical candidates with the application of integrated combinatory chemistry to high-throughput screening (HTS), for example.²³ Combinatory chemistry, in which a random assembly of construction blocks or molecular fragments is constructed, was a great hope for the pharmaceutical industry, but did not yield the expected results. These factors, whether isolated or combined, have contributed for the lower innovative capacity of pharmaceutical industries. This reality has forced the adoption of new models of pharmaceutical innovation management in PIs, such as open innovation, which has allowed the chain of radical innovation to take on a new face, as illustrated in Figure 10.²⁴

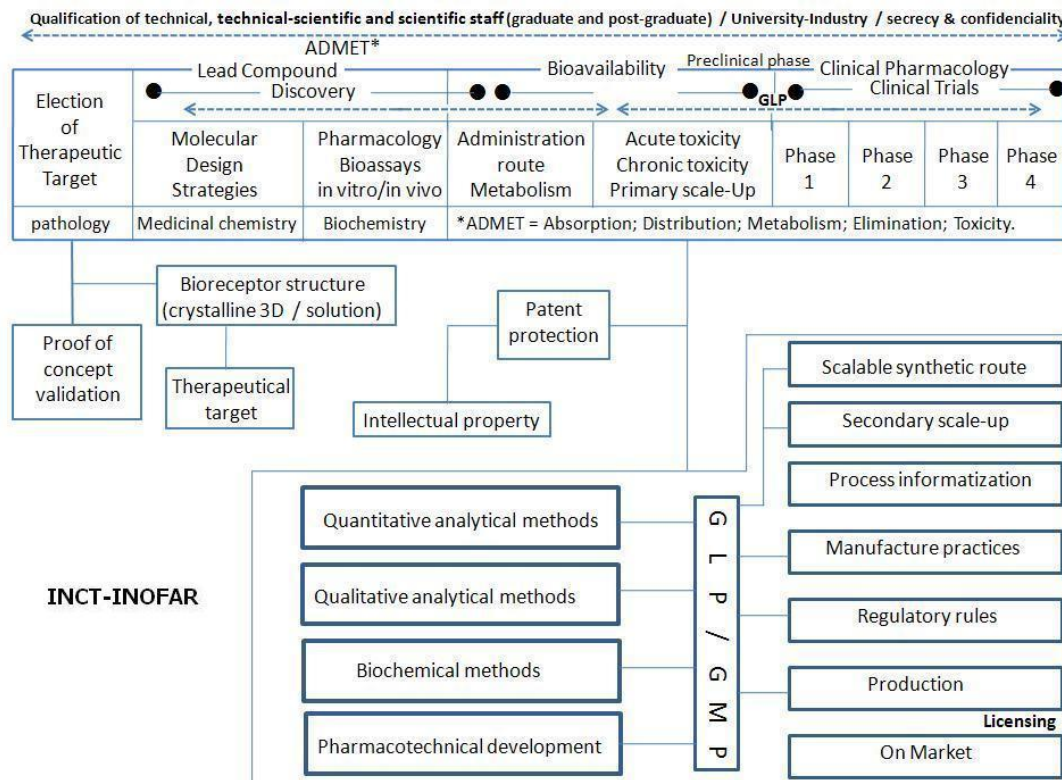


Figure 9. Schematic linear view of the chain of innovation in drugs and medicines including the research and the development stages, from the initial stage of election of therapeutica target, the design of new lead compounds by medicinal chemistry to the clinical trials

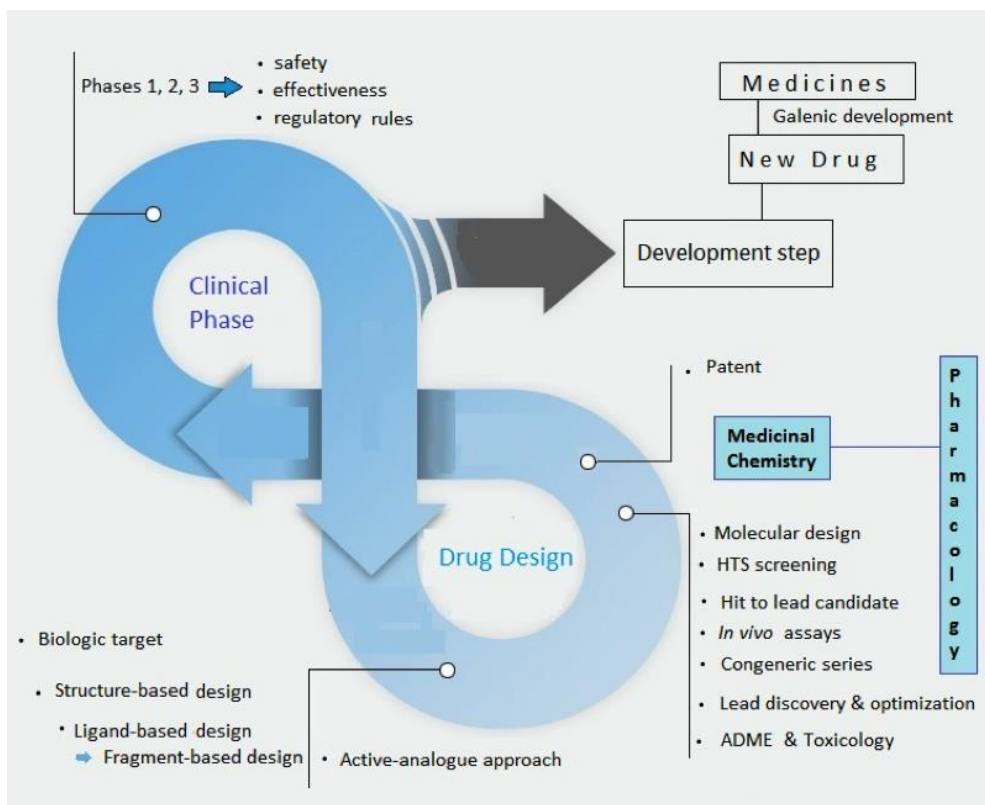


Figure 10. The new face of the chain of radical pharmaceutical innovation, demonstrating its most interactive and integrated aspect (adapted from the Ely Lilly Web site)²⁴

Table 1, chronologically illustrates the releases in the timeframe of 1997 to 2011 of some new drugs that represent significant therapeutic innovations, due to the originality of the pharmacological mechanism of action. Among these, montelukast (Figure 11), an antiasthmatic agent that acts as a selective antagonist for the cysteinyl leukotriene receptors, released in 1997, had achieved world sales of US\$ 4.6 billion in 2008. Sildenafil (Figure 11), celecoxib (Figure 6), and esomeprazole (Figure 11), released in 1998, 1999, and 2000, respectively, have also become world sales leaders, surpassing 2.5 billion a year. Among these, esomeprazole has been, since 2002, among the top five sellers worldwide, when it reached US\$ 2 billion a year, continuously surpassing this mark after that (2003 = US\$ 3.8; 2004 = US\$ 4.3; 2005 = 5.0; 2006 = US\$ 6.2; 2007 = US\$ 6.9; 2008 = US\$ 7.7; 2009 = US\$ 7.9; 2010 = US\$ 8.4 billion). Imatinib (Figure 6), released in 2001, by Novartis, is an effective and efficient therapeutic innovation, and was the first medication for effective control and treatment of several kinds of cancer acting

through through a novel pharmacological mechanism, the inhibition of tyrosine kinase (TK). Imatinib then inspired the creation of several *me-too* drugs, like sunitinib, released in 2004, among others, as shown in Figure 12. Ziprasidone (Figure 11), released in 2002, has reached expressive sales in just a few years. Rosuvastatin (Figure 11), a hydroxymethylglutaryl coenzyme-A reductase (HMGCo-AR) inhibitor, represents a recent statin released in 2003; it had sales, by 2012, of US\$ 8.1 billion, being highlighted in its class for having the best bioavailability. The other pharmaceuticals included in Table 1 are examples of expressive therapeutic innovations in different therapeutic classes, like chemotherapeutics of continuous use, up to the discovery of tofacitinib (Figure 11).²⁵ This is an immunomodulator released by Pfizer for the treatment of chronic-degenerative inflammatory illnesses like rheumatoid arthritis, which is the first inhibitor of Janus kinase 3 (JAK3) to be used therapeutically, approved in November 2012, by the FDA-USA.

Table 1. Therapeutic innovations released between 1997 and 2012

Year	Pharmaceutical	Therapeutic Use	Company
1997	Montelukast	Antiasthmatic	Merck
1998	Sildenafil	Erectile Dysfunction	Pfizer
1999	Celecoxib	Anti-inflammatory	Pfizer
2000	Esomeprazole	Peptic ulcer	Astra-Zeneca
2001	Imatinib	Cancer	Novartis
2002	Ziprasidone	Central Nervous System	Pfizer
2003	Rosuvastatin	Antilipemic	Astra-Zeneca
2004	Erlotinib	Cancer	Genentech
2005	Eszopiclon	CNS	Aventis
2006	Vorinostat	Cancer	Merck/Patheon
2007	Maraviroc	Antiviral	Pfizer
2008	Etravirine	Antiviral	Janssen
2009	Saxagliptin	Diabetes	BMS/Astra-Zeneca
2010	Dabigatrin	Anticoagulant	Boehringer-Ingelheim
2011	Rivaroxiban	Antithrombotic	Bayer
2012	Tofacitinib	Anti-inflammatory	Pfizer

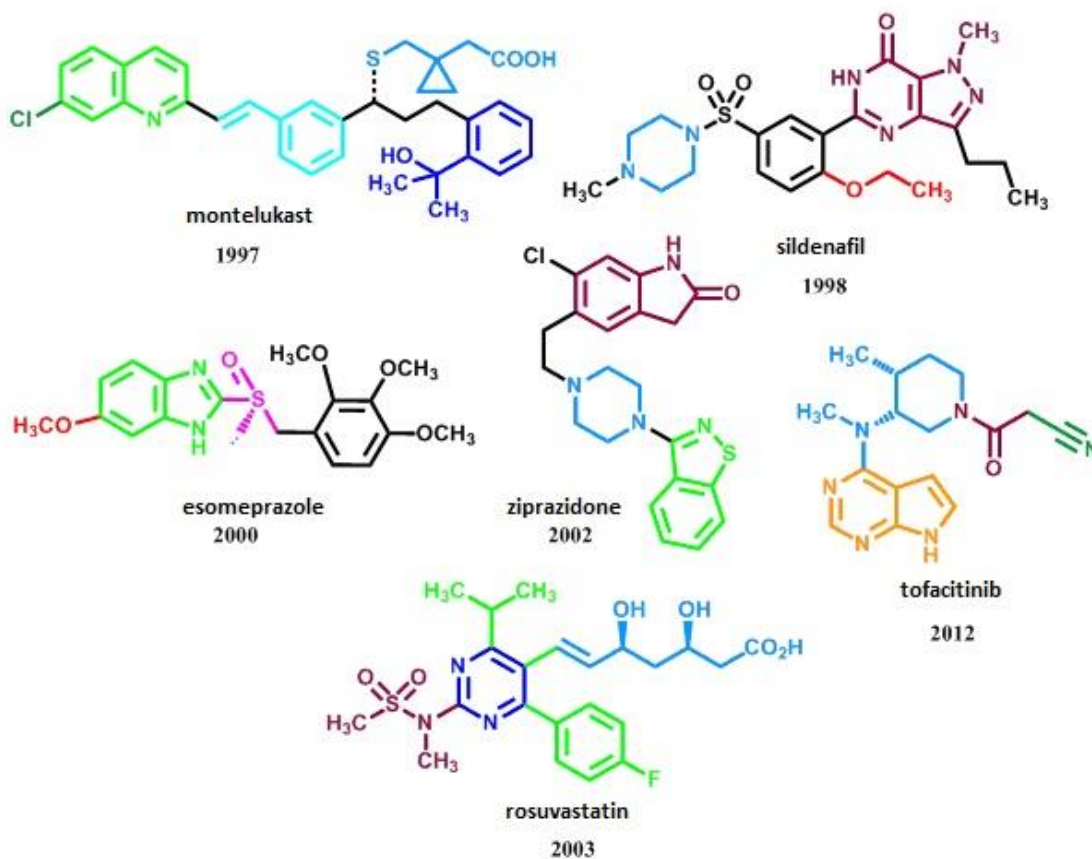


Figure 11. Chemical structure of some chemically innovative drugs released between 1997 and 2012, included in Table 1

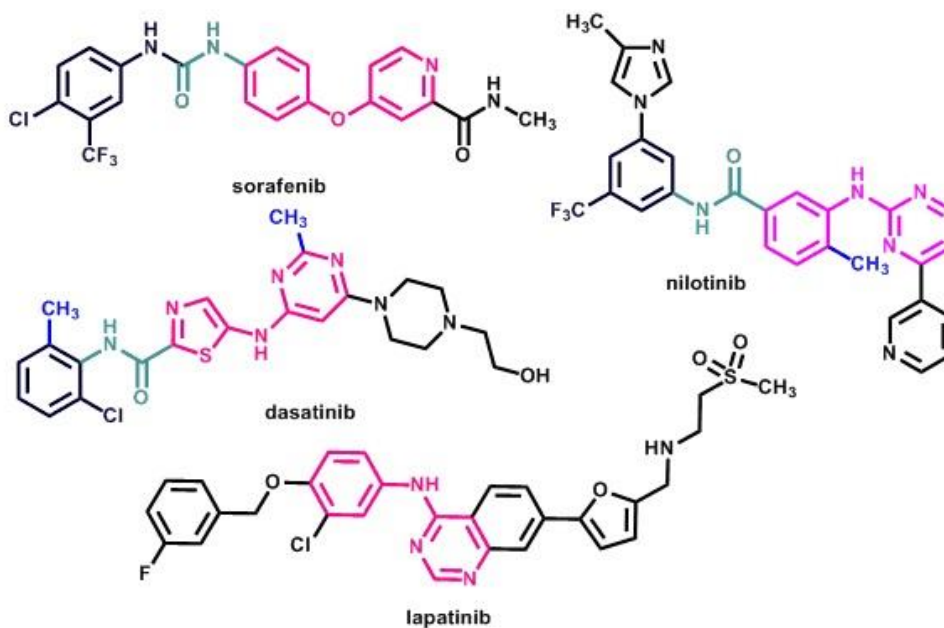


Figure 12. Tinibs released in the market after imatinib was launched

5. Contribution of the National Institute of Science and Technology in Drugs and Medicines (INCT-INO FAR)²⁶

The National Institute of Science and Technology of Drugs and Medicines (INCT-INO FAR; www.inct-inofar.ccs.ufrj.br) has the goal of contributing to radical and incremental innovation in drugs and medicines, the training and qualification of human resources, and the transfer of technology and knowledge. With a solid scientific structure, inspired by the chain of innovation in drugs and medicines, illustrated in Figures 9 and 10, distributed through several states in Brazil, INCT-INO FAR has been dedicating itself to the development of new pharmaceuticals as well as the synthesis of molecules that lead the world market sales. The best example of this competence is the synthesis of the active principle of the

best selling pharmaceutical in the world. A few months after its patent having expired in July 2010, atorvastatin (Figure 13) was synthesized by Professor Luis Carlos Dias of the Institute of Chemistry at UNICAMP with the post-doctoral student Adriano Siqueira Vieira, an INCT-INO FAR, scholar, in December 2010.^{27a} Recently, Professor Angelo da Cunha Pinto and post-doctoral student Barbara Vasconcelos da Silva, this time in the research laboratories of the Institute of Chemistry of the Federal University of Rio de Janeiro, and also INCT-INO FAR members, have concluded the synthesis of sunitinib (Figure 13),²⁸ an important pharmaceutical that is a tyrosine-kinase inhibitor with usage in the treatment of several types of cancer. Sunitinib, due to its high price, has an expressive impact on the Unified Health System (SUS) of Brazil. Another generic drug synthesized in the Institute of Chemistry at UNICAMP by Professor Dias, was fluoxetine,²⁹ a potent neuroactive agent, used in the treatment of anxiety (Figure 13).

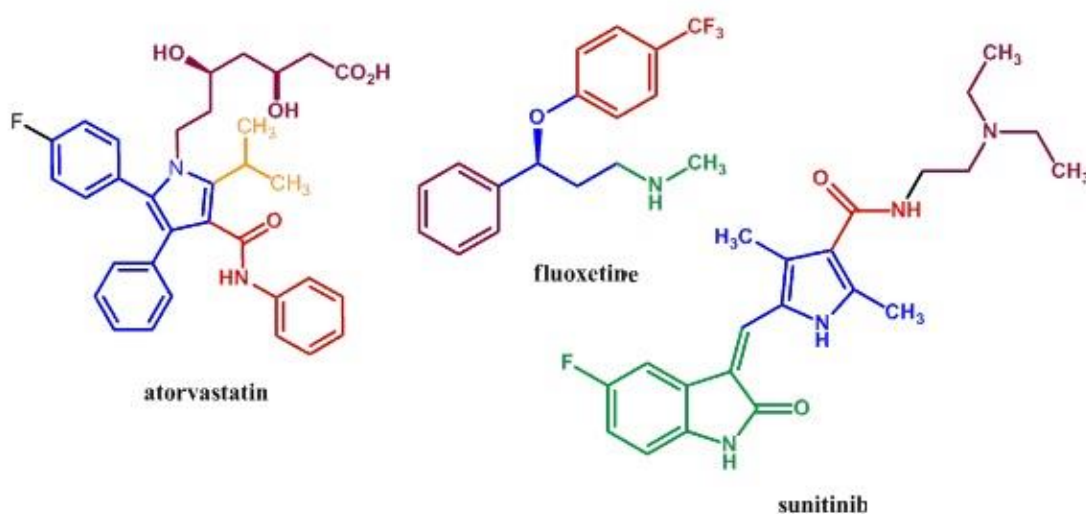
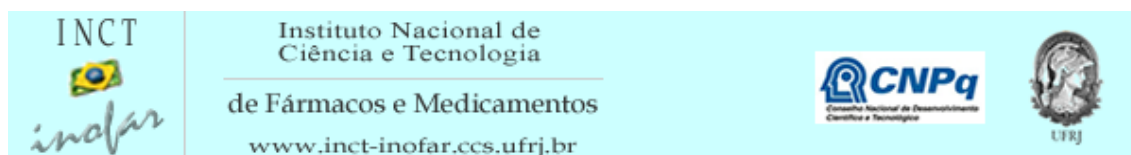


Figure 13. Chemical structures of atorvastatin, fluoxetin and sunitinib with total synthetic routes studied in INCT-INO FAR

The synthesis of the substances illustrated in Figure 13 represents a great milestone in Brazilian medicinal chemistry, the first of many that might follow, achieved by the efforts of **INCT-INOVAR**.

In radical innovation activities, **INCT-INOVAR** has identified several attractive substances that are authentic candidates to prototypes of new drugs in different therapeutic classes, all of which are documented in its yearly activity reports (Figure 14)^{27b,29} and in the special issue of the *Revista Virtual de Química* dedicated to **INCT-INOVAR** (Figure 15).³⁰ In its portfolio of research projects are included the molecular design, synthesis and evaluation of new analgesic compounds, especially focused on neuropathic pain. Also new anti-inflammatory

prototype that act through new dual pharmacological mechanisms, capable of being effective in the treatment of severe chronic conditions, as obstructive pulmonary disease (COPD) are included in the research projects portfolio. New neuroactives compounds that might allow the control of cognitive conditions, antiparasitic agents for the treatment of neglected diseases like leishmaniasis, antiproliferative drugs that may be used in the treatment of cancer, and substances of interest in the treatment of cardiovascular diseases, like inotropic agents and vasodilators.³⁰ Countless results have been achieved in several interdisciplinary research subprojects, which, due to confidentiality, may not be discussed here.



Figure 14. Cover pages of the *Annual Activity Reports* by **INCT-INOVAR** in 2009, 2010, and 2011, being available in its Web site²⁹



Figure 15. Cover of the special issue of the *Revista Virtual de Química* dedicated to **INCT-INOVAR**³⁰

6. Final Considerations

What about the future? The independence of a nation depends more and more on its ability to offer access to medication to its citizens. Brazil is now the 7th world economy, and maintaining its position or going higher in this rank demands a strong and innovative pharmaceutical industry that should not be limited to import active principles from China and India. To give up on the development of new innovative drugs is to give up on sovereignty, and to remain in the BRIC's when the goal for a nation as rich as Brazil is to be a part of the G-8.

In tune with the present President of the Republic of Brazil, Dilma Roussef, who in the General Assembly of the United Nations Organization, in New York, on September 19th of this year, said that "... the defense of access to medication and prevention should walk side by side", the **INCT-INOVAR** members believe that it is possible, in the next 10 years, for the creation of novel synthetic drugs and the acceleration of the development of new original routes for future generic drugs that will have their patents expired. For this to come true, the investment in consolidated research groups needs to continue, so that goals are not only the publishing of scientific papers, but also that these groups can establish solid partnerships with national entrepreneurs, always respecting the individuality of each partner. The discovery of new drugs will take place through these partnerships.

In its short existence, **INCT-INOVAR** has shown that it is possible to achieve a Brazilian drug, one that "speaks" our language, the Portuguese. Making feasible the creation of pharmaceuticals will depend on continuous funding and public-private partnerships. **INCT-INOVAR** is the best example that Brazil can become a player in the world pharmaceutical market. Maintaining this organization it is also a responsibility of the funding agencies. Gather a group of active and qualified researchers throughout the

country was not an easy task. However, separating them does not take a lot of energy, as is proven by the second law of thermodynamics and their sustainability is the next challenge. In the academy it is possible to find high scientific quality, what is needed is continued funding for Brazil to become, as example of developed countries, a country with strong pharmaceutical industry and qualified to the discovery and development of new innovative drugs to treat its population.

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