# Biopharmaceuticals and ethics in rheumatology

Valderílio Feijó Azevedo

**Abstract**

The purpose of this review is to set an analysis on Brazilian rheumatologists' ethical commitment in face of prescription of high cost drugs, chronic use and exceptional dispensation, the biologics. The author departs from a reflection about the factors that influence therapeutic decision making, the grounds for legal suits related to these drugs and their impact on public health policies.

**Key words:** Exceptional drugs. Biological factors. Ethics. Social responsibility. Rheumatology.

**Valderilio Feijo Azevedo** is a physician, expert in rheumatology, with a Master's degree in Medicine at the Federal University of Parana (UFPR). Professor of Rheumatology at UFPR, Coordinator of the Spondylarthritis Service at the Clinics Hospital (HC-UFPR), member of the Spondylarthritis Commission of the Brazilian Society of Rheumatology, Curitiba, Parana, Brazil

Medical sciences made astonishing evolution, especially in the past decades. Today, relief from suffering caused by an expressive number of illnesses that attack humans can be achieved or even the cure for some of them is achieved. However, there is not any doubt that such set of knowledge has further influenced diagnosis and therapy than disease prevention or health promotion.

Pharmacological science has specifically benefited from these tremendous advances, especially those arising from molecular biology, proteomics and immunogenetics, as well as for informatics applied to healthcare. Supporting this expressive evolution of Pharmacology is the pharmaceutical industry, which accounts for the development and production of new drugs, and it also contributes, so strongly around the world, to the cost of the clinical research. The generation of biopharmaceuticals, for example, requires a large amount of resources to be produced from expensive and time-consuming biotechnological processes, with rising

costs, estimated between US$ 500 million and US$ 1.24 billion to US$1.33 billion in studies lasting approximately five to seven years [1].

However, we cannot forget that the pharmaceutical industry is obviously composed of for-profit companies. In the capitalist and globalized world it is difficult to conceive an organization that does not seek the constant launching of new products and services through strategies aimed at consolidating its space on the market or to increase sales. As a result of these strategies, spending on drugs has grown at high rates over the past decades, mainly in developed countries [2], and health systems, public and private, have faced difficulties to cope with the new therapies. In the United States of America (USA), for example, the total spending with medication increased from US$ 279.6 billion in 2007 to US$ 284.7 billion in 2008, a growth of 1.8% [3]. In the last decade, the commercialization of new biomolecules for treating rheumatic diseases has contributed to the increase in public and private spending worldwide.

As an example of unquestionable success, the Brazilian pharmacological market is one of the ten largest in the world ranking and the figure reached in the sale of medicines in our country comes to be twice the Argentine market [4]. The expenditure of Brazilian families with medication has kept the pharmaceutical industry as a subject of intense social debate. Moreover, it appears that there is little more than ten years many users have filed legal demands against the Government in all its levels, with the goal to obtain expensive medicines and chronic use [5], an occurrence which has generated strong financial-economic impact on the health budget.

The considerable increase in life expectancy reached mainly in the twentieth century has been driven by social advances and by the technological development of medicine, which brought new forms of early diagnostic and more effective and efficient therapeutic methods for the treatment of diseases prevalent among the population. However, the growing number of older people and chronic-degenerative diseases has been correlated to the increase in spending on health financing both for citizens and their families as part of the Governments. This panorama shows the pressing need for broad ethical reflection regarding the practices of pharmaceutical industry social responsibility front, focusing on prescription drugs and especially of in biopharmaceutical manufacturing used in Brazilian Rheumatology.

## Brazilian policies for pharmaceutical assistance and the exceptional drugs

The Single Health System (SUS), when promoting universal and egalitarian access to all actions and services related to the promotion, protection and recovery of the

health of the population, among other related responsibilities, included the free provision of drugs[6]. Currently, the medical class and public managers devote special attention to cases of drugs called exceptional.

The acquisition and distribution of these drugs is the responsibility of member States of the Federation from resources funded by the federal Government, through the Ministry of Health. Over the last decade, the Exceptional Drugs program, specially created for the purchase and distribution of these medications, has undergone considerable expansion in both the number of available compounds and in the amount of patients benefited, as well as on financial resources allocated thereto[6].

Every year, several drugs classified as exceptional are launched by the pharmaceutical industry into the world and the Brazilian markets, a fact that has generated the need for more effective control on this distribution. Currently, we have in Brazil the following biomolecules considered exceptional drugs and approved by the National Health Surveillance Agency (Anvisa) for the treatment of rheumatic diseases: infliximab, etanercept, adalimumab, rituximab, abatacept and tocilizumab, and golimumab that still is in the process of authorization.

As a measure of control, clinical protocols and therapeutic guidelines have been established for each new medicine and disease. The manufacturing process of protocols allows them to be properly subject to public consultations, promoting broad discussion and enabling effective participation of the scientific-technical community, medical societies, health professionals, SUS, managers and users of pharmaceutical industry itself. However, even so, before State authorization procedures for purchase and distribution of these drugs are completed, and even before therapeutic guidelines and clinical protocols are developed, many patients have appealed to lawsuits against the Government, at the federal, state or municipal levels, to obtain those drugs[5].

## The role of the pharmaceutical industry on medical decision making

Highly professionalized actions by the industry related to publicity and advertising of drugs have been gradually expanded over the past few decades, causing the industry to increase spending in this area [1], without, however, causing in the middle class the full perception, ownership and critical analysis of the issue. Unfortunately, most doctors do not recognize that they can be influenced by the actions of industrial marketing, noticing the fact that their therapeutic decisions can receive influence. When questioned, probably many professionals will consider themselves immune to this process, although the evidence proves the contrary [7,8].

We can enumerate some effective strategies developed by industry to achieve this goal: direct visits from representatives to physicians in their working places, donation of gifts, sponsorship of events and social dinners, sponsorship of continuing medical education events and national or international Congress sponsorship to clinical research, assistance in propaganda to class entities and medical services involvement in financing the therapeutic protocols and guidelines. Additionally, many medical journals disseminate industrial propaganda and, in some, add-ins are fully sponsored. Several studies in modern medical literature show that after simply reading scientific material sponsored or delivered by industry, there is greater encouragement of physicians to prescribe these drugs [9].

The danger that the pharmaceutical industry's involvement in the research clinic can lead to distortions of medical-scientific evidences, still does not seem to be priority issue for the everyday practice of Brazilian rheumatologists. In the country, like several other emerging nations, the pharmaceutical industry has invested considerable resources in training lecturers from the most respected universities [10]. These speakers are generally renowned teachers, with good concept among their peers and holders of high training and academic degrees. Some of them have research centers almost entirely sponsored by the pharmaceutical industry[11].

Many clinical studies in biopharmaceutical products are developed in partnership with these centers. Moreover, as reproducers of industrial information, good opinion formers, estimated by their academic and social positions, speakers can influence the requirements of the medical class [2,7]. Although many declare conflicts of interest during their exhibitions and participations in symposia, roundtables, conferences, workshops or special events, this completely ethical attitude seems to cause little impact on future therapeutic decision of audience of physicians.

The set of knowledge, criteria and concepts disseminated by clinical epidemiology and by what we recognize as evidence-based medicine has shown to be a powerful and useful tool for the critical reading of medical literature, being a precious assistance to the exempt scientific development attitudes, more and less subject to influences of industrial marketing. However, the evidence-based medicine, as an isolated tool, does not have achieved success in counterbalancing this effect in medical prescriptions, exactly because the industry also appropriated it to develop its strategies and research. The majority of clinical trials of new medications, for example, is impeccably developed within strict scientific rigor utilizing contours of increasingly complex research, controlled and tabulated by an appropriate statistical analysis [12].

However, it is notorious that the industry only sponsors the publication of studies

demonstrating positive effects of their drugs and, generally, sponsored studies are published in internationally recognized journals with a strong editorial sieve, a strategy that increases the credibility of the research. Diagnostic studies have also increased (focused primarily on early diagnosis) under industrial sponsorship, which, although they can take the best approach and prognosis of patients [13], they can induce early use of pharmacological therapy.

As an example, we may cite the case of patients with spondiloartrite, currently benefitted from the best indexes of functional assessment and activity of their diseases than two decades ago [13]. It is notorious that evaluation criteria be used appropriately by the pharmaceutical industry for the manufacture of therapeutic protocols and for its acting with government entities to ensure a stronger lobby for the acceptance and purchase its drugs. However, in the modern world, neither the medical clinic and the industry, or the academic medicine and industry, can survive independently one of the other. The recognition of interdependence is essential for any discussion related to the role that each of these actors plays, in order to ensure advances in health policies and also to establish ethical codes of conduct among them [9,14].

**Pharmaceutical industry and the associations of patients with rheumatic diseases in Brazil**

In Brazil, most entities representing groups of patients have few resources and do not have financial independence. In partnership, they are benefited with funds provided by the industry, with the goal of keeping their projects and services to the associates. So, they can grow at faster pace than would be possible only with funds from its associates, and can also benefit from additional sources of information or, even, produce information, through its own newspapers and magazines [15]. However, it is not hard to imagine that these entities' agendas can be modified by other priorities of the sponsors.

The pharmaceutical industry, in parallel, takes advantage of this relationship with the expansion of its market, since part of its clients that can potentially use their products are linked to these entities, especially when the product produced is directed to the processing of a specific illness. In addition, with this approximation, the industry provides a legitimate response to the aspirations of society, making visible its social responsibility and its roles in health care of disease bearers. At the same time, this joint action also ensures greater legitimacy in the actions aimed at interference in restrictions imposed by the public health policies and regulations related to the purchase and distribution of drugs.

The contracting of external services by industry, hired to monitor the quality and safety of patient care, has been increasingly frequent and those

intermediary organizations promote and manage programs to support users of drugs. The possibility that the increase of Brazilian State funds for projects and the survival of nongovernmental organizations can fix partially the bias induced by those entities' relations with industry should be seriously considered. These measures are necessary for the Government, given that many legal demands are originated with the support of entities representing patients, in order to obtain greater legitimacy and transparency, even if these actions are not of a collective nature.

**The influence of medical education in the prescription of biological products and the issue of equity and integrality of assistance by SUS**

Another Brazilian problem related to the increased use of biopharmaceutical products, which certainly interfere in the therapeutic decision-making tree, regardless of the specificity of disease and indicated therapy, is the relative lack of knowledge of SUS operations' rationale by part of the Brazilian medical class. Although many rheumatologists are exercising their functions in private services, they still maintain some connection with the public service, both in municipal, state or federal level [16].

The SUS organic law establishes that the system must be the originator of the human resources training policy in health and, therefore, a natural unfolding to would be the medical internships in rheumatology to play a more important role in integrating young specialists to the public health policies in Brazil.

Legal suits to obtain expensive medicines have originated both in private clinics and outpatient public health services, particularly those of secondary and tertiary level. In accordance with the principle of fairness of SUS, it is legally guaranteed to patients from private health plans or private clinics the same priority in obtaining exceptional medicines that have patients whose health care depends solely and exclusively on public system. This seems to be a socially unfair situation when we compare the difficulties faced by exclusive patients of SUS with those faced by patients from the private system, to access secondary and tertiary services until the moment they receive the indication of a medicinal product which will be acquired through legal suit.

The real understanding of the imbalance that such demand causes to SUS implies that the medical profession realizes correctly that, in addition to the increase of action in health, fragilities imposed by the Union budget intended to generate a serious shortfall in health actions of a system that, because of its principles and fundamentals, is in constant process of collective construction. In Brazil, we have reached a situation in which the budget allocated to social welfare goes far beyond fourfold of that targeted to health.

This partially explains why SUS is in such difficulty, since it has in its clientele 30 million retirees and pensioners whom it should assist, without receiving a penny collected from the welfare budget of R$160 billion.

Representatives of Brazilian medical entities also recognize that the increase in resources devoted to health can have some impact on the budget of other important areas of development and national sovereignty. In these two decades, for example, our Government has faced social pressures for legitimate expansion in several other areas that historically suffer restrained demand, such as education, transport, the national industry, imports and exports, agriculture, among others.

The social impact of legal suits for the acquisition of exceptional drugs, particularly the biological, has concerned entities that recognize the need for a more in-depth bioethical discussion on the aspects of financial resources allocation for the purchase of new drugs, involving the entire class. Economic and financial data available at state agencies must be continuously disseminated and may contribute to physician's awareness about the relevance of the theme.

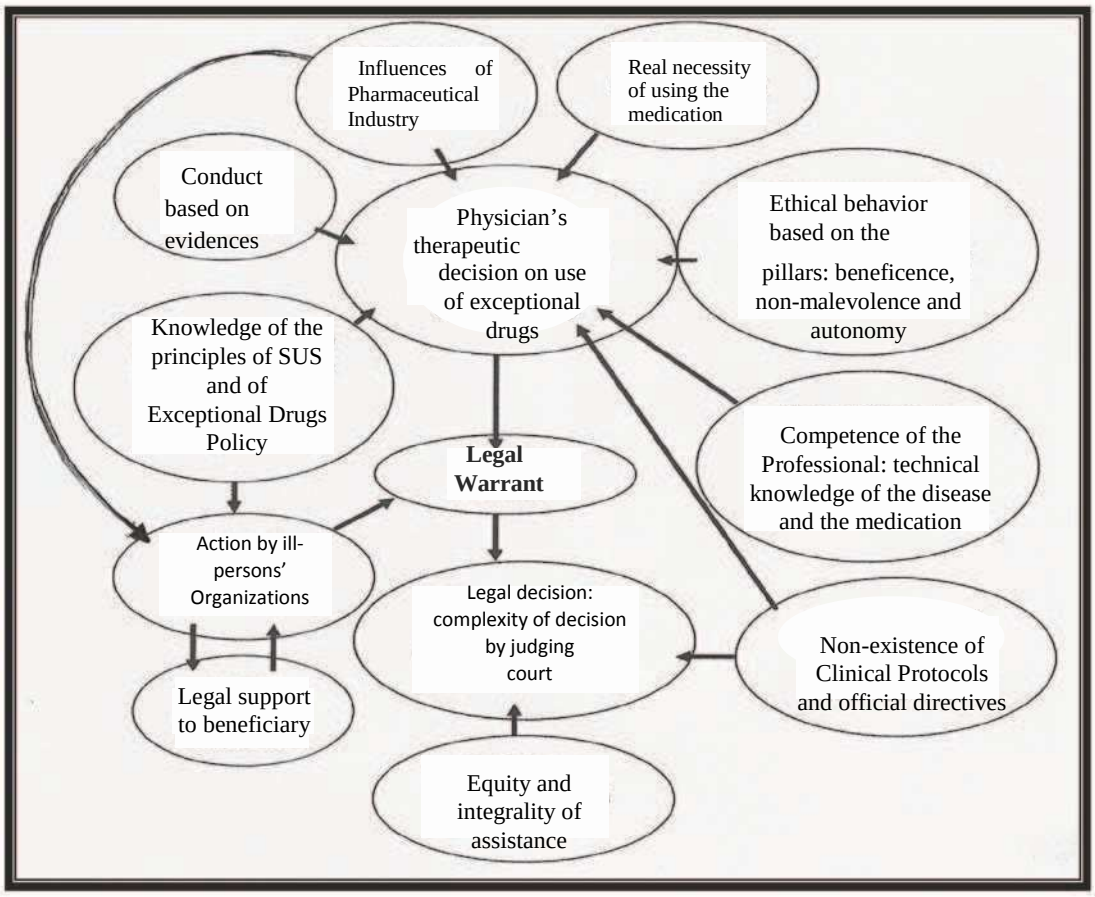
The challenge is set, mostly, for the resolution of cases in which the claimed drugs do not have any registry at Anvisa and the State is required to provide them by legal means. However, there are records of a legal suit in which the claimed drug is not insured by legislation for the treatment of the requested illness, although its use has already been approved for a similar illness and, in both, the therapeutic benefits are at the same level of evidence.

An example was what motivated proceedings in which were involved antiTNF alpha agents, released through a ministerial ordinance for the rheumatoid arthritis treatment [17]. These medicines were only released for people with ankylosing spondylitis and psoriasis arthritis at the beginning of this year, even if proven benefits related to the improvement of functional capacity and clinic activity in these ill persons [18-20]. Such evidences were shown, including in therapeutic protocols supported in developed countries and approved by their regulatory agencies. In this case, the authorization, which involved public consultation and required bureaucratic procedures, was very slow and, acting as catalysts, both rheumatologists and patients candidates to their use, knowing that the evidences and benefits were easily demonstrable, preferred to anticipate the acquisition through legal proceedings.

Rheumatologists' therapeutic decision clearly is not based only on pharmacodynamic, pharmaco-kinetics, pharmaco-economic or pharmaco-technique principles or even in

the understanding of the proper functioning of the SUS. It also depends on ethical centenarians principles that are true cornerstones of medicine: *primo non nocere*. The first concept that guides the medical practice is to do no harm, to not cause harm to the patient: the principle of non-maleficence; the second is the principle of beneficence: take best benefit possible with the treatment; the third is based on the principle of autonomy, i.e., accept the patient's consent, because if he doesn't want to make use of the medication, provided that he has been properly oriented, does not prescribe. Respecting patient autonomy is fundamental, especially in areas such as rheumatology, in which it is known, in recent history, over use cases of drugs and results of post-marketing studies were removed from the market due to serious clinical complications induced by the extended use [21].

The figure below shows some variables involved in the doctor's therapeutical decision and on the legal mandates regarding the biological products and other exceptional drugs:



## Final considerations

The challenge is for society as a whole and, in particular, to the Brazilian rheumatologists' class: understanding and intervening in this growing phenomenon which is the demand for more expensive and chronic use drugs. We must continually ask ourselves to what extent the therapeutic and medical needs of patients are *unnecessarily* created [22] and the extent to which society should finance the exceptional use of medicinal products to the detriment of investment in health promotion and disease prevention. We live a dilemma that divides us across paths nearly unlimited that science can provide and the ethical control, absolutely indispensable to route them, about financial, human and physical resources. So, we should not divide the understanding of what is by nature antagonistic, nor compartmentalize it because it prevents us from learning *what is woven together* [23].

The problem of non-ethical prescription exceeds the limits of medicine and of the individual to reach the limits of social sciences, of the collective and of the own species. It is known that the radical separation of what is public and what is private is not necessary for achieving the purposes of social awareness of the problem. Rheumatologists, encouraged by their representative bodies, should participate in continued reflexive actions on their performances in the control of exceptional drugs, by weighting the factors that interfere with their conducts, including resetting, when necessary, their relationships with the pharmaceutical industry.

Due to its great social responsibility, the rheumatologist also needs to dedicate a few hours of study to know and update on laws and regulations in force related to social security, to professional practice and health. Finally, it is still essential for the specialists, who take care of rheumatic diseases, the application of balanced therapeutic measures between their patients' real individual needs and the pressing needs of collectivity.

**Resumo** O objetivo desta revisão é estabelecer uma análise do compromisso ético dos reumatologistas brasileiros perante a prescrição de medicamentos de alto custo, uso crônico e de dispensação excepcional, os biológicos. O autor parte de reflexão acerca dos fatores que influenciam a tomada de decisão terapêutica, as causas de demanda judicial relacionada a essas medicações e seu impacto para as políticas públicas de saúde.

**Palavras-chave:** Medicamentos excepcionais. Fatores biológicos. Ética. Responsabilidade social. Reumatologia.

## Resumen

**Biofármacos y ética en la reumatologla**

El propósito de esta revisión es establecer un análisis del compromiso ético de los reumatólogos brasileños frente a la prescripción de medicamentos caros, de uso crónico y dispensación excepcional, los biológicos. El autor parte de la reflexión sobre los factores que influyen en la toma de decisiones terapéuticas, las causas de una demanda judicial relacionada con estos medicamentos y su impacto en las políticas de salud pública

**Palabras-clave:** Drogas excepcionais. Fatores biológicos. Etica. La responsabilidad social. Reumatología.

## References

1. Grabowski H. Follow-on biologics: data exclusivityand the balance between innovation and competition. Nat Rev Drug Discov. 2008 jun;7(6):479-88.
2. Fiúza EPS, Lisboa MB. Bens credenciais e poder de mercado: um estudo econométrico da indústria farmacêutica brasileira. Rio de Janeiro: Ipea; 2001. p.1-73. (Texto para discussão; 846).
3. Hoffman JM, Doloresco F, Vermeulen LC, Shah ND, Matusiak L, Hunkler RJ et al. Projecting future drug expenditures 2010. Am J Health Syst Pharm. 2010;67(11):919-28.
4. Carvalho KM, Teixeira RM. A influência de estratégias promocionais na adoção de novos produtos: o caso da indústria farmacêutica. Cad Pesq Adm. 2002;9(1):61-74.

5. Messeder AM, 0sório-de-Castro CGS, Luiza VL. Mandados judiciais como ferramenta para garantia do acesso a medicamentos no setor público: a experiência do Estado do Rio de Janeiro, Brasil. Cad Saúde Pública. 2005;21(2):525-34.
6. Negri B. Política federal de assistência farmacêutica 1990-2002. Brasília: Ministério da Saúde; 2002. (Série B. Textos Básicos de Saúde).
7. Granja M. Ligações perigosas, os médicos e os delegados de informação médica. Acta Med Port. 2005;18:61-8.
8. Roughead EE, Harvey KJ, Gilbert AL. Commercial detailing techniques used by pharmaceutical representatives to influence prescribing. Aust N Z J Med. 1998;28(3):306-10.
9. Wazana A. Physicians and the pharmaceutical industry. Is a gift ever just a gift? Jama. 2000;283(3):373-80.
10. Coyle SL. Physician-industry relation. Part I: Individual physicians. Ann Intern Med. 2002;136(5):396-402.
11. Baird P. Getting it right: industry sponsorship and medical research. CMAJ. 2003;168(10):1267-9.
12. Melander H, Ahlqvist-Rastad J, Meiger G, Beermann B. Evidence b(i)ased medicine- selecting reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ. 2003;326:1171-3.
13. Rudwaleit M, van der Heijde D, Khan M A, Braun J, Sieper J. How to diagnosis axial Spondylarthritis early. Ann Rheum Dis. 2004;63(5):535-43.
14. Jibson MD. Medical education and the pharmaceutical industry: managing an uneasy alliance. Acad Psychiatry. 2006;30(1):36-9.
15. Herxheimer A. Relationships between the pharmaceutical industry and patientrs organizations. BMJ. 2003;326:1.208-10.
16. Machado MH. 0s médicos no Brasil: um retrato da realidade. Rio de Janeiro: Editora Fiocruz; 1999.
17. Brasil. Ministério da Saúde. Portaria n° 2.577, de 27 de outubro de 2006. Aprova o Componente de Medicamentos de Dispensação Excepcional. Disponível: http:ttdtr2001. saude.gov.brtsastP0RTARIAStPort2006tGMtGM-2577.htm. [acesso 11 set 2010].
18. Braun J, Baraliakos X, Brandt J, Listing J, Zink A, Alten R. et al. Persistent clinical response to the anti-TNF-a antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology. 2005;44:670-6.
19. Davis JC, Van der Heijde D, Braun J, Dougados M, Cush J, Clegg D et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005; volume 64:1.557-62.
20. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J et al. Efficacyand safety of adalimumab in patients with ankylosing spondylitis. Arthritis Rheum. 2006;54:2.136-46.
21. Bijlsma JW. Patient benefit-risk in arthritis-a rheumatologist's perspective. Rheumatology (0xford). 2010 May;49 Suppl 2:11-7.
22. Shankar PR, Subish P. Disease Mongering. Singapore Med J. 2007;48(4):275.

23. Morin E. Os sete saberes necessários a educação do futuro. 9a ed. São Paulo: Cortez; 2004.

Received: 12.2.10 Approved: 8.21.11 Final approval: 10.1.11

**Contact**

Valderílio Feijó Azevedo – *valderilio@hotmail.com*

Rua Lamenha Lins, 1.110 - aptº 11A, Rebouças CEP 80250-020. Curitiba/PR, Brazil.

The author states that he has not received any financial incentive to write this article. He further states that he was a member of Advisory Board of Golimumab and Infliximab in Brazil. In 2010, he received financial incentives for research from BMS laboratories and for lecture from Roche, Pfizer, MSD and Abbot laboratories..