Interview: Jaime Rabi â?? Director, MicrobiolÃ³gica, Brazil

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Jaime Rabi, director of MicrobiolÃ³gica, documents the unique development path of the company and its pioneering contribution to the production of antiretroviral medicines in Brazil, as well as its international partnerships with American success-stories like Pharmasset, which originally developed the breakthrough therapy sofosbuvir. He also provides insights into the remarkable collaborative approach favored by the company, be it regarding API or finished product development, as well as its longstanding commitment to enriching the Brazilian R&D ecosystem.

MicrobiolÃ³gica displays one of the most eye-catching histories in Brazilâ??s healthcare and life sciences industry. Could you walk us through the companyâ??s main milestones?

Four professors of the Institute of Microbiology â?? hence, the name of the company â?? and one professor from the Natural Products Research Centre (NPPN) of the Federal University of Rio de Janeiro set up MicrobiolÃ³gica in March 1981, at the beginning of the so-called â??lost decadeâ?• that hit the region. At that time, Latin American countries reached a point where their foreign debts exceeded their earning power and they were not able to repay it â?? in a wider context marked by the consequences of the second oil crisis. In such difficult times, governmental bodies started to question the concrete impact of academic research on the social environment of the country â?? be it regarding economic or healthcare outcomes. This critical situation prompted these five entrepreneurial-minded professors to found MicrobiolÃ³gica with the idea to apply scientific processes used in the academic setting to an industrial purpose.

In the mid-80s, the companyâ??s founders identified the development of Active Pharmaceutical Ingredients (APIs) for the domestic pharmaceutical industry as an attractive market opportunity for MicrobiolÃ³gica. This model was moreover actively promoted by Brazilâ??s Ministry of Health in an attempt to decrease the external dependency and the costs of pharmaceutical products purchased for countrywide public health programs. However, the companyâ??s founders lacked the necessary experience and knowledge to develop the program on their own. Knowing that I was doing consulting work for pharmaceutical and chemical companies alongside my academic responsibilities and considering my own formation as an organic chemist, they invited me to help them develop this API business opportunity as an external consultant.

I initially picked up five products within the Essential List of Medicines, whose development was within our technical reach. Thanks to the resources provided to us by the Ministry of Health, we set up a small research and manufacturing facility near the university and started the production of two APIs. At that time, my experience in the production of commercial-scale quantity of APIs was rather scarce. In addition, I had a very limited knowledge of the regulatory requirements framing industrial manufacture of products for human consumption. I followed a truly experimental process. However, three factors clearly ramped up our development: first, there was no patent exclusivity at that time â?? whether in terms of processes or products; second, ANVISA was only created in 1999, which means that the regulatory framework was almost inexistent in comparison to where it stands today; and third, most environmental laws did not exist either. Thus, the barrier we had to overcome was mostly limited to our own capacity to develop and establish the process technologies leading to the required APIs.

We ultimately managed to develop the required technologies while rapidly increasing our production capacity to meet the demand of the Ministry of Health. This API business was growing at a faster pace than the rest of the companyâ??s operations, and I became one of MicrobiolÃ³gicaâ??s partners at the end of 1985.

[Featured_in]

It is indeed quite exceptional to see such a reputed academic choosing to put its talents in the service of the industry â?? especially at that timeâ?¦

At first, my involvement outside the University was strongly rejected by most of my colleagues. However, time ultimately made them change their minds and eventually, in 1989, I was elected director of the Natural Products Research Center, becoming the first and only foreign professor to ever receive this honor. After completing my period as director of my institution at the university, I decided to take a sabbatical year devoted almost completely to my activities at MicrobiolÃ³gica.

As managing these operations was taking an ever-increasing share of my time, I eventually found myself at a crossroad, which implied having to choose between academia and industry. Conciliating the two was moreover extremely unusual â?? to say the least â?? especially given that I was a full professor at the Federal University of Rio de Janeiro and a 1A Research Fellow at the National Research Council. I then made the particularly difficult decision to pursue my career on the industry side exclusively. I resigned my permanent position at the University in 1994 before the end of my leave of absence.

Working in technology had quickly made me realize that my scientific vocation could find challenging objectives in industry too. In addition, when taking over the position of Director of MicrobiolÃ³gica, I immediately enjoyed the new and heightened flexibility I had to develop innovative projects and seize promising opportunities without the bureaucratic and financial constrains that I experienced at the university.

On the other hand, I realized that without the participation of academia, the life sciences industry could not progress in Brazil. The companyâ??s rising trajectory allowed me to participate in strategic committees at the Ministry of Science and Technology and at the National Research Council, where I could contribute ensuring that substantial resources were consistently allocated to research institutions. In a way, I offset my personal deviation from basic to applied chemistry.

MicrobiolÃ³gica has been a pioneer in tackling the HIV/AIDS epidemics in the 80s. Could you provide insights into the involvement of the company in this crucial matter and explain how it propelled the international development of MicrobiolÃ³gica?

In Brazil the AIDS epidemic climbed exponentially throughout the 1980s.

We held the technical and scientific capacities to produce azidothymidine (AZT), also known as, Zidovudine (ZDV) the first antiretroviral medication used to prevent and treat HIV/AIDS. As a reminder, this treatment marked a clear milestone in the history of the disease, as it emerged as the first hope we had to turn AIDS from a death sentence to a manageable chronic infection. In 1991, we started producing AZT (called at the time â??Brazilianâ?• AZT) to meet the demand of the Ministry of Health, the main purchaser of antiretroviral and viral medications in Brazil. During the â??90s MicrobiolÃ³gica produced tons of antiretroviral medicines annually. These included, in addition to AZT, stavudine (d4T) and lamivudine (3TC). It has been suggested that our activities contributed to the establishing of the National AIDS Program in Brazil. US scholars have also suggested that the results of our efforts contributed to the strong reaction of multinational pharmaceutical companies that eventually resulted in the new Brazilian Intellectual Property law (May 1997) to provide pharmaceutical patent protection.

AZT in particular and nucleoside-based products in general are relatively complex structures, which render their manufacturing particularly difficult. In this context, holding a domestic producer of these highly needed medications allowed the Brazilian government to make tremendous savings. In the meantime, the increasing sales of antiretroviral APIs enabled MicrobiolÃ³gica to build a particularly strong in-house research team. At that time more than 30 percent of our staff were Ph.D. holders or individuals with advanced education.

While still at the University in the early â??90s, I invited a professor from The University of Georgia to give a lecture at the NPPN. He and I shared a common academic background in that both of us had been post docs at the Sloan-Kettering Institute for Cancer Research in New York. He was part of a group of scientists that had become leaders in the discovery of antiviral drugs. I took advantage of his visit to show him MicrobiolÃ³gicaâ??s activities. He was particularly surprised to see that we had successfully developed the in-house capacity to produce large batches of complex nucleoside-based APIs. He mentioned to me his intention and the intention of his colleagues in the US to set up a new company in Atlanta, Georgia and that our essential competence in nucleic acid chemistry would nicely complement their expertise in medicinal chemistry.

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This is how you and MicrobiolÃ³gica became involved in the development of Pharmasset, which originally developed sofosbuvir and was acquired by Gilead Sciences for USD11 billion in 2011.

Our essential competence in nucleic acid chemistry at the industrial level gained by actively participating in the Brazilian effort to control the AIDS epidemic, had opened the doors to a new and exciting experience. We never expected to be involved in such a fantastic endeavor. We were lucky to be in the right place, at the right time with the right scientific and technical competence. MicrobiolÃ³gica did participate very actively in the development of Pharmassetâ??s pipeline. This

included products against HIV, hepatitis B and hepatitis C. I was part of the board of directors of the company from 1998 to 2003. When we realized the great potential that the hepatitis C segment held, we decided to concentrate our resources on this field. As a matter of fact, the lead structure that gave birth to sofosbuvir was discovered in 2003 and MicrobiolÃ³gica created part of the chemistry for this project in our laboratory in Rio de Janeiro.

Simultaneously with our involvement at Pharmasset, MicrobiolÃ³gica entered in a strategic alliance with Boston-based Idenix (originally called Novirio) which was developing nucleosides specific against hepatitis B. MicrobiolÃ³gica created all process chemistry necessary for the development of telbivudine, Indenixâ??s treatment for chronic hepatitis B. This technology was licensed to Novartis, which has been commercializing this drug under the name of Tyzeka since 2007. MicrobiolÃ³gica also produced for Idenix the initial chemistry related to their hepC technology. Idenix was acquired by Merck & Co. in a USD 3.85 billion deal in 2014.

While MicrobiolÃ³gica was forging prestigious partnerships in the US, how has the companyâ??s situation evolved on the domestic stage?

At the end of 90s, the Brazilian government decided to shift its tendering approach: until 1996, the Ministry was purchasing finished products, such as AZT capsules or syrup. However, the government set up the Brazilian National Program for AIDS, which notably implied that government would start manufacturing antiretroviral finished products by itself â?? therefore limiting our contribution to the manufacturing of the related APIs. This decision came as a big blow to us, as finished products are naturally of higher values than the corresponding APIs, while medicines manufacturers moreover benefit from greater market recognition and opportunities than API producers.

While the government took over the responsibility to manufacture finished products, they also looked at producing these medicines at the lowest cost possible and opened up the tendering process to international API manufacturers. The winner would be that offering the required API at the lowest price in a continuous bidding process! We successfully resisted to the market entry of Korean companies and did well against Indian companies too, but when Chinese producers ultimately entered the Brazilian market, we could not align ourselves with their prices. Part of our trained human resources had to be laid off and a large manufacturing facility shut down.

You were then left with no choice but to reinvent â?? again â?? the positioning of the company. What happened next?

As mentioned, we held great development opportunities in the United States, so we stopped developing and producing antiretroviral drugs in Brazil and essentially focused on our North American projects for a while.

We worked from Rio as a strategic ally of both Pharmasset and Idenix, which resulted in an exceptional experience for MicrobiolÃ³gica as a whole: our scientists were directly involved in the invention of new, groundbreaking medicines â?? something that was totally unprecedented in Brazil, while our quality group was being exposed to the regulatory requirements of the FDA for new drug developments. It was a unique learning opportunity that determined important transitions within MicrobiolÃ³gica: we moved from our focus in development to innovation and from quality control to quality assurance. This cultural transition has been essential to our continuous progress and ambition to create future growth.

Nevertheless, the pace of product development in the US â?? once a promising compound is identified â?? is absolutely mind-blowing, and we were not able to sustain the accelerated rhythm demanded by our American partners, which were engaged in bringing to the market some of the

most remarkable medicines discovered within the past decade. This showed to us in a very didactic manner that innovation and quality are of the essence but not sufficient if we are to participate as leaders of a paradigm shift; velocity is the additional factor that makes the difference that society recognizes.

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Where does the company stand in 2017? How have you been leveraging this unique expertise accumulated over the past three decades and by working with some of the most advanced pharmaceutical companies in the world?

Recognizing that technology development was not enough to sustain the company in Brazil, and simultaneously with our involvement in the US, we started to re-qualify some of our other technologies that had given origin to our fine chemicals operations in the â??80s. Working in close collaborations with European companies, we managed to prepare and register Drug Master Files for two APIs which we started to export early in the 2000â??s. Along the years we have continuously refined these technologies and kept exporting our actives principles to European pharmaceutical companies based in Germany, Switzerland, and the Netherlands â?? among others. Thus, once transformed into pharmaceutical drug products, our APIs reach several countries around the world. And, thanks to new indications, these relatively old products are finding new markets. Overall, by partnering with these European world-class companies in the joint-development and commercial-scale production of APIs, we have been able to maintain a high level of expertise and regulatory compliance, especially with regards to our GMP national and international certifications.

We also have customers in Brazil, which remains a very important market for us. The strengthening of the countryâ??s regulatory framework has bolstered the domestic demand for our products, which is extremely encouraging. In order to participate in the drug product business, we established a strategic alliance with an emerging Brazilian pharmaceutical company with which we are now jointly developing several products that should reach the market soon.

Finally, we have forged several promising partnerships with leading Brazilian Research Institutions for the development of new molecules targeting tropical diseases, such as Zika, chikungunya, dengue, and yellow fever. As a matter of fact, we have already found a number of active leads. We are well aware that we will not be able to fully develop these products by ourselves, which means that we will have to start looking for external partners to move these productsâ?? development forward.

As a final message to our international readers, how do you want them to perceive MicrobiolÃ³gica?

Over the past 36 years, MicrobiolÃ³gica has honed extremely strong essential competences in highly qualified organic synthesis at the industrial level with a special focus in the development and production of nucleoside based structures. Having partnered with Brazilian, American and European companies, MicrobiolÃ³gica holds experience in dealing with Anvisa, the US FDA and the EU EMA, which is rather unique in Brazil. Overall, I see MicrobiolÃ³gica as a knowledge hub with a bright future, which should be further propelled by our openness to leverage our technical expertise through local and international partnerships.

The challenge to transition scientific knowledge into innovative processes, and products, for the benefit of society was and continues to be the reason for the existence of MicrobiolÃ³gica. Along the

years, MicrobiolÃ³gica has had the opportunity to make a positive impact in the solution of many relevant problems and, in the process, promote meaningful professional evolution. As an academic and university professor, this aspect is absolutely crucial to me, and it is my first and foremost priority to preserve it moving forward.

We hope to be able to continue building on our record of excellence, achievements, and service to society. We feel confident that this is the basis of our sustainability and the key to our recognition in honoring our origin.

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