The Unhappy Partners for Pain Relief Innovation

Antonio C. M. Camargo, PhD
Director
Center for Applied Toxinology Institute
Butantan
São Paulo, Brazil
&
Marcio Falci, PhD
Medical Director
Biolab and Unãio Química
São Paulo, Brazil

"Brazil contributed no pharmaceutical innovations during the 20th century. We have the biodiversity; we have the intellectual capacity. What Brazil lacks most is the will to innovate."

-Antonio C.M. Camargo

"We don't really want innovation here in Brazil, we just say we do."

-Marcio Falci

Dr. Antonio Camargo directs the Center for Applied Toxinology at Institute Butantan. Dr. Marcio Falci directs R&D at sister companies Biolab and União Química. Together they are "The Unhappy Partners for Pain Relief Innovation." They are "unhappy" because they are unsatisfied with their environment for innovation, but "partners" because of the potential that nevertheless exists for drug innovation in their country.

Dr. Camargo believes that the greatest potential source of competitive advantage for new drug development in Brazil lies with animal toxins. He recalls that in the 1950s Dr. Rocha e Silva, with whom he would later work at the University of São Paulo, discovered that certain snake venoms had cardiovascular medicinal potential and could greatly contribute to the understanding of the physiology of cardiovascular diseases. Then, a few years later, he and his student Sergio Ferreira identified a component of the snake venom with potential to treat human hypertension. But Dr. Silva's labs lacked the technical capacities to go further, so Ferreira went to the Royal College in London to collaborate with John Vane, the Nobel laureate, on the cardiovascular research.

Ferreira went to the Brookhaven National Laboratory in the United States, where the compound was isolated and characterized. "One of the most important anti-hypertensive drugs started with that research," explains Dr. Camargo. "Bristol Myers Squibb made billions on it, but Brazil gained nothing. That is the big motivation for what we are doing now. We are building the labs and learning how to do drug research. We are working with Brazilian companies, but they lack the know-how to innovate. We in Brazil have the potential for radical innovations, but we are all learning how to do it."

Reforming Intellectual Property; Building Innovative Capacity

Dr. Camargo says, "Everything began to change when the government accepted TRIPS." The TRIPS agreement regarding Trade-Related Intellectual Property Rights was agreed to by the member states of the World Trade Organization in 1994, as one of the Uruguay Round multilateral trade negotiations. In 1996, the Brazilian government in Brasilia passed a reform of intellectual property law. It had traditionally been the case that drug product patents were not recognized in Brazil; rather, innovative ways of manufacturing or processing drugs were patentable. The new patent law and its 2005 implementing regulation provides incentives to Brazilians to innovate and was thereby a revolution in the country's R&D system. Brazilian generic drug makers, including Aché, Biosintética, União Química, and Biolab, became interested in drug product innovation for the purpose of drug R&D.

"FAPESP was the pioneer," explains Dr. Camargo. FAPESP, the State of São Paulo Research Foundation, articulated a strategy for R&D in their state that set the introduction of innovations in the marketplace as the goal. FAPESP announced a plan to establish a number of research centers that would focus on applied R&D in partnership with the private sector. With advice from the National Science Foundation in the United States, FAPESP called on university and public research institutes to establish ten centers seeded with 11 years of funding of US$1 million per year. A group of scientists at the Institute Butantan and the São Paulo State Universities submitted a proposal to FAPESP that resulted in the creation of a center for research, innovation, and dissemination in toxinology in 2000, which became the Center for Applied Toxinology (CAT-CEPID). Among several research projects that resulted in new knowledge with patentable potential, the most interesting to the researchers was the analgesic properties of the rattlesnake venom. The research built on a hundred year old observation at Institute Butantan. Focused R&D effort would yield results with new medicines with great value both to health and to economy. The terms of FAPESP funding called for industry partnership, so COINFAR was established as a research consortium composed of Biolab, Biosintética, and União Química. Aché acquired Biosintética and, thus, took over the position in COINFAR.

Dr. Camargo had been a medical scientist on the faculty of the University of São Paulo but left to become director of CAT. He went to the United States to seek medical science advice at MIT and technology transfer advice at Cornell. In addition to going to academic conferences, he started going to industry conferences, for that was the world about which he needed to learn if he was going to be successful in his new role. What he learned was that he had to provide "proof of concept" to the private sector. Previous research at Institute Butantan indicated to Dr. Camargo that the venom of the rattlesnake (*Crotalus terrificus*) was a good target for pain relief drug development and the venom of the jararaca (*Bothrops jararaca*) was a good target for innovative cardiovascular drugs. He designed the laboratories at CAT to isolate, identify, and synthesize the active compounds in the venoms. It was a scientifically complex task that required new equipment, including a mass spectroscopy facility, and new organizational skills. With the help of a Japanese chemist who conducted research with the CAT team for three

years on a scholarship from FAPESP and COINFAR, the CAT research team identified a molecule in late 2004. Animal tests showed effects similar to morphine, but more potent and lasting, and apparently without the dependency side effects of morphine. Dr. Camargo had his first candidate for product development. They worked with the COINFAR team to draft the patent application, which they submitted to the patent offices in Brazil and the United States in 2005.

Re-Organizing to Innovate Drugs

Dr. Marcio Falci says that when he first talked to Dr. Camargo about his research efforts with snake toxins, he quickly appreciated their medicinal and market potentials. He also realized that Dr. Camargo's CAT provided a model for how Brazilians could tap the potential for drug development that lay unused in its biodiversity and basic sciences labs. Dr. Falci was then the medical director at Biosintética, a position that had brought him back to Brazil after many years in the United States and Europe. Educated as a surgeon at the University of São Paulo Medical School, he practiced surgery for a few years before developing an interest in the clinical research and business of pharmaceuticals. He says, "I caught the pharmaceutical development virus. You become addicted. It's really intellectually challenging; there are so many constraints. It's like a love story." He worked in the United States and Europe in clinical research and marketing positions at G.D. Searle, Hoechst, and Boehringer-Ingelheim and thus had learned about the business of innovative medicines. Biosintética was a maker and seller of generic pharmaceuticals, and Dr. Falci was recruited home to São Paulo to organize their compliance with the bio-equivalence demonstration demand of the Brazilian drug regulators, the National Sanitary Supervision Agency, ANVISA.

Dr. Falci identified a number of challenges faced by potential Brazilian innovators. First, they possessed no organizational capacity to innovate new drugs. Their labs were organized to reverse engineer the drugs that had been innovated in the United States and Europe and to demonstrate bio-equivalence with the original drugs. Their labs were not organized to test compounds for some useful medicinal property. Second, they were organized to sell drugs for which market demand was already known, not to estimate the market potential for a drug that did not yet exist but which, in the most optimistic scenario, was probably ten years from market launch. They were organized to know what their competitors were now selling, but not to guess what innovative drugs their competitors might be working on in their own labs for market release many years in the future. Dr. Falci knew better than most of his Brazilian colleagues that it was a wholly different matter to be a drug innovator.

Third, they lacked the organizational capacity to manage and analyze clinical trials in hospitals involving thousands of patients to demonstrate product efficacy and safety to drug regulators. He explains that innovative drug development starts in the laboratory. Then, promising drug candidates are tested on animals. Drug candidates that survive the animal tests then proceed to the human clinical trial phases. In Phase I, healthy volunteers are tested for dosage safety. In Phase II, a larger number of actual patients suffering from the malady are treated with the therapy, usually a family of

related therapies, to test for efficacy and safety. In Phase III, many thousands of patients involving many hospitals and clinics are evaluated to demonstrate efficacy and safety. Dr. Falci was concerned about the lack of experience not only in the drug companies but in the hospitals among the doctors and nurses to carry out the very exacting procedures of clinical trials according to international standards of best practice.

Dr. Falci wondered, too, whether his fellow Brazilians fully appreciated the challenges of doing innovative drug R&D. Drug industry managers and their investors were inexperienced with the very real, perhaps inevitable, risks of product development failure. Most drug candidates still fail the efficacy and safety human trials, even if laboratory and animal tests appear promising, and hence never reach market. Only about 1% of chemical compounds identified in the laboratory as having therapeutic potential emerge from the development and regulatory process, so R&D "losers" make the drug innovation process exceedingly risky and expensive. The clinical trials are the core of the drug development process and typically cost about $300 million in direct research costs in the United States and Europe. When the costs of capital and of failure are figured into the equation, the real cost of introducing a new drug in the United States and Europe is about $800 million. Dr. Falci likes to point out that his boss at Searle was Donald Rumsfeld, who would later become infamous as U.S. Secretary of Defense for explaining that the war in Iraq was handicapped not only by known unknowns but also by unknown unknowns. He is convinced that Rumsfeld discovered in the innovative pharmaceutical business the power of unknowns to disrupt plans.

Confronting Innovation-Unfriendly Drug Regulators

If the list of challenges within the companies seeking to become innovators was not sufficiently long and daunting, then Dr. Falci adds to the list the disincentives the Brazilian government imposes on potential private investment into drug innovation. Pharmaceutical prices, he explains, are controlled at the retail level by the Medicine Pricing Review Board. Drug prices had been frozen in 2000, but later allowed increases less than the level of inflation. Since 2003, a price cap system for pharmaceuticals has been implemented that sets prices at the lowest price in a basket of nine countries. In 2004 the Price Coefficient system was introduced that provides an additional linear 24.69% discounted price for government—federal, state, local—purchases. Dr. Falci says that he always suspected drug price controls would be a problem for their innovation strategy, but it was not until they took a Biolab innovative product to the Pricing Review Board that it became clear how real the problem would be for them.

He explains that many poor pregnant mothers get insufficient amounts of folic acid and vitamin A, which leads to childhood diseases such as spina bifida. The Health Ministry buys vitamin supplements at a cost of about 92 reais per dose for distribution to poor mothers, but the folic acid and vitamin A are sold separately and in dosages that exceed the World Health Organization recommended ideal. The Biolab project he led solved the problem by placing the folic acid and the vitamin A into a gel-capsule at the ideal dosage levels. Biolab proposed to the Pricing Review Board in 2007 that their innovative product be purchased by the government at about 33 reais per dosage, saving

the Health Ministry millions of reais each year in acquisition costs. The Pricing Review Board nevertheless determined that the price should be about 4 reais per dosage. Dr. Falci concludes bitterly, “We spent several years and a great deal of money innovating a new drug, but we are not going to sell it, at least not in Brazil, because the government insisted on a price for it that would not even pay for the packaging. We don’t really want innovation here in Brazil, we just say we do.”

Regarding the potential analgesic, Dr. Falci explains that the COINFAR managers and their investors decided that their lack of R&D capacity meant that this potential drug needed to go the United States for development. So they hired a clinical research organization to conduct additional laboratory and animal studies. They hired an American patent attorney to study their patent application from 2005. Their new attorney identified some mistakes and re-filed their application. After several years of laboratory and animal studies the plan to conduct human safety and efficacy clinical trials in the United States got interrupted. The public-private collaborators found themselves in dispute over ownership of the patent rights. The clinical research studies will not start until the patent dispute is settled, say Dr. Antonio Camargo and Dr. Marcio Falci.

They know that some years of product development lie ahead before their investment can earn anything back for them. Dr. Falci’s concerns that the companies were not ready to develop a drug proved right. Furthermore, he wonders whether drug price regulators will begin to reward innovative drug risk-taking. More optimistically, Dr. Camargo and Dr. Falci now know what capabilities they must build in the years to come if they are to become innovators. The medical potential in animal toxins is still there and waiting to be researched and developed.