

Hormone on the market

Small company teams up with Brazilian pharmaceutical industry to produce a medicine against dwarfism

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By the end of next year, Brazil will be joining a very select club: the makers of growth hormones using genetic engineering techniques. The entrance doors to this club will be opened by Hormogen Biotecnologia and by Genosys Biotecnologia, which have developed separately and on a pilot scale their first batches of hGH, the acronym for Human Growth Hormone. The medicine will get to the market thanks to two partnerships. Hormogen recently sold 75% of its shares to the Brazilian company Biolab-Sanus, one of the largest pharmaceutical companies in the country, which is going to invest US\$ 2 million from 2003 on to launch the product commercially. Genosys signed an agreement for production and distribution with another large pharmaceutical company, Braskap, which also has Brazilian capital (*see issue 65 of Pesquisa FAPESP*). At the moment, Brazil imports about one million doses of growth hormone a year, spending an estimated US\$ 15 million, but with these partnerships, it will start exporting the medicine.

Hormogen's original path was the same as followed by Genosys and other small companies that received funding under the FAPESP's Small Business Innovation Research program (PIPE)

and started their business activities at the Incubator Center for Technological Companies (Cietec), in São Paulo. Hormogen is going to carry on doing research as a sort of subsidiary of Biolab. These are new products and processes that have earned an important financial incentive for carrying on research inside the company.

There is no lack of other promising technological innovations. Komlux, a company from Campinas, has now put onto the market a blanket woven with optical fibers, called Blanket Lux, to treat jaundice in newborn children. Clorovale, from São José dos Campos, recently launched dentists' drills with synthetic diamond tips, far more resistant than the metal ones. The company is also getting ready to launch a version of this drill that is coupled to an ultrasound apparatus, which provides for a treatment without the awful noise of conventional drills and without any pain for the patients. In the telecommunications area, Asga, a company set up in Paulínea (SP), has developed a line of multiplexers and modems used in transmissions via optical fibers in telephone networks, the Internet and data processing. Their commercial success is already considerable. Asga sales leaped from R\$ 16 million in 1999 to R\$ 90 million in 2001, in the wake of

the expansion of telecommunications in the country.

The same successful path seems to be the destiny of companies using PIPE, which in five years has clocked up investments of R\$ 25.6 million and US\$ 3.9 million. The importance does not lie merely in the economic value that will come from it, but the social value as well, as in the case of the growth hormone, which may have prices up to 30% lower than the imported product.

Fifth country - Prescribed above all for children with short stature, or dwarfism, in medical jargon – a disease that today affects around 10,000 Brazilians –, hGH has been employed in an increasingly wide range of clinical treatments (*see table*). For the time being, it is produced in only four countries: in Sweden, by Pharmacia (recently acquired by Pfizer); in Denmark, by Novo Nordisk; in the United States, by Genentech and Eli Lilly; and in Italy, by Sero. "We have already filed our patent with the National Institute for Industrial Property (INPI)", explains Paolo Barto-

Bioreactor: bacteria secreting the hormone at Hormogen's factory



Biolab's factory: hormone compactor

lini, one of three partners in Hormogen. He is also head of the Molecular Biology Center of the Nuclear and Energy Research Institute (Ipen).

The experience of transferring knowledge developed in a research institute to the market is also part of Genosys's story. The technique for obtaining hGH was carried out at the Chemistry Institute of the University of São Paulo (USP) by Professor Hamza Fahmi Ali El Dorry, who invited biochemist Jaime Francisco Leyton to set up Genosys. It was the company's first product.

hGH, says Bartolini, was also the first product developed by Hormogen. At the moment, the company is getting ready to leave the incubator and to move to Itapicera da Serra, in the metropolitan region of São Paulo, where it will occupy part of the installations of one of the four Biolab-Sanus factories and will carry on with the already begun research into new medicines based on hormones. For Bartolini, the greatest appeal of the Biolab-Sanus deal – concluded in Fe-



PHOTOGRAPH BY VICENTE GRECOBIOLAB

bruary, after one year of negotiations – was the commitment taken on by the industrial concern to continue to invest funds in research.

For the shares that ensured its control of Hormogen, Biolab-Sanus paid US\$ 100,000, a symbolic amount, according to Cleiton Castro Marques, vice-president of the Castro Marques

group, which the company belongs to. “But, in compensation, we took on 100% of the new investments”, he explains. This year, the new parent company is setting aside R\$ 100,000 for Hormogen, besides ensuring the pay of the partner-researchers (all from Ipen), who kept a 25% stake, until hGH, their first-born product, starts to be marketed. “In the following years, we will invest whatever it takes for the company to become operational”, explains Castro Marques.

To arrive at its pilot production and to attract the interest of potential investors, Hormogen turned to FAPESP, which between 1998 and 2001, has released to the incubated company some R\$ 350,000, through the Small Business Innovation Research program (PIPE). The funds were spent mainly in reagents and equipment – on its own, the bioreactor, for example where the hGH secreting bacteria multiply, soaked up US\$ 113,000. With the pilot production assured, Hormogen has started to test the medicine, which has now been through the biological laboratory tests (using dwarf mice) and

Far beyond dwarfism

The most common indication for growth hormone (hGH) is dwarfism, a disease that affects some 10,000 Brazilian children, according to researcher Paolo Bartolini. But, he explains, it can also be transmitted by the genes and propagated through consanguineous marriages, as happens in the small town of Itabaianinha in Sergipe, 115 kilometers from Aracaju; it has in its records some 100 bearers of short stature, the largest concentration of these cases in the country.

Besides fighting dwarfism, hGH can be administered to adults with a hormone deficiency, patients who have undergone a kidney transplant, girls with Turner's syndrome – which causes short stature and infertility or Aids victims at an advanced stage (when there is a loss of muscular mass). But the range of applications of this medicine continues to grow. There is a movement of doctors in the United States that is proposing the assistance of this hormone in fighting osteoporosis and the reduction of muscular mass in the elderly, be-

sides contributing towards reducing localized fat. There are also several advanced studies, including in Brazil, according to Bartolini, that demonstrate the benefits of hGH for women in the menopause. But the use of the hormone by adepts of physical activities, in search of muscular development, is dangerous. It may, for example, result in diabetes and in other diseases deriving from hormones being out of balance”, says Bartolini.

Approved by the Food and Drugs Administration (FDA), the American agency that controls the quality of food

through the two modalities of the physicochemical and toxicological tests (with dogs), and immunological tests, to prove the hormone's potency and purity; it cannot contain more than ten parts a million of the protein of the original bacterium, which are the main contaminants of the future medicine.

The next stage is the clinical, or bioequivalence, tests, which should be concluded in six months at the most. In this stage, Hormogen's medicine and another similar imported product, available on the market, will be applied on 24 healthy persons. First, 12 volunteers will be given the product already available, and the others, the Hormogen product. Next, the procedure will be repeated, exchanging the medicine, in such a way

that the whole group receives the two products. "It is a complex procedure, which needs the hiring of a pharmacologist, and the volunteers have to be taken into hospital", Bartolini explains. "These tests should take about US\$ 200,000", Castro Marques estimates.

The company is hoping to get a high return from the investments carried out. According to Castro Marques, hGH is fifth in volume of sales amongst genetic engineered medicines. Hormogen's product, he believes, should win over 20% of the Brazilian market in one year, a period in which they may also start supplying some of the 17 countries in Latin America in which Biolab-Sanus has partnerships with distributors. This year, the first in which it is working in the foreign market, this executive says, the company exported the equivalent of US\$ 800,000 to these countries, an amount that in five years may reach US\$ 30 million, including sales of hGH.

Created only five years ago, to occupy more specialized niches in the market for drugs – the other laboratory of the group, União Química, basically makes generic and hospital products - Biolab-Sanus had a swift ascent. It is now the third company in prescriptions for cardiological medi-



PHOTOGRAPH BY EDUARDO CESAR

Batches from Hormogen: pilot scale

nes, a segment that accounts for 55% of its sales. These should add up to between R\$ 170 million and R\$ 180 million this year, a 50% increase over 2001. Together, the sales of Biolab and União Química should come to about R\$ 340 million in 2002, a performance that justifies its position, in 12th place, on the list of the largest pharmaceutical companies in the country, according to the Gazeta Mercantil newspaper, and also fifth place in the Exame magazine's

ranking of the most profitable in the sector. "These results are a reflection of our focus in 2002 on products that do not have, nor will have, similar generic products in the next few years", explains Castro Marques.

New culture - What Biolab-Sanus wants now is to add technology, making more and more exclusive products. Actually, this strategy started three years ago, with the launch of Lovelle, the only vaginal contraceptive marketed in Brazil. Besides Hormogen, they acquired another incubated company, Dalmatia, which makes cosmetics with a therapeutic action; it used to be housed in the Bio-Rio incubator, and it is currently associated with 18 projects from research institutions like the University of São Paulo (USP), Ipen and the Butantan Institute. With the purchase of Hormogen, Biolab-Sanus is planting its roots in the most prestigious and promising segment of medicines in the world, the genetic engineering segment. "We want to create in the company the culture of biotechnology, which is the future", says Castro Marques. A future that should start as soon as next year, with the beginning of production and the commercial launch of the growth hormone.

Oddly enough, the Biolab-Hormogen partnership is going to join a race with another partnership, Genosys-Braskap – which is building its industrial plant –, to see who will be first to put hGH onto the market, with the phrase "Made in Brazil" on its packaging.

THE PROJECT

Optimization of the Yield of Bacterial Expression, Fermentation and Purification of the Recombinant Human Growth Hormone

MODALITY

Small Business Innovation Research Program (PIPE)

COORDINATOR

PAOLO BARTOLINI – Hormogen-Ipen

INVESTMENT

R\$ 72,800.00 and US\$ 154,000.00

and medicines, in 1985, hGH is obtained using the recombinant DNA technique. With the use of this technique, scientists clone the genes that codify the molecule of the hormone produced by the pituitary gland, located at the base of the skull. This sequence of DNA is modified so that it adapts to the needs of its new maker, usually the *Escherichia coli* bacterium. Afterwards, the sequence is inserted into a molecule of the bacterial DNA, the plasmid, which is finally introduced into the bacterium, which there upon starts producing hGH. Next, the bacterium goes to the bioreactor for fermentation, in the course of which it multiplies

rapidly: in about ten hours, a single bacterium can generate billions of them, all producing the hormone.

The next step is the centrifugation of the bacteria, from which a raw protein extract is obtained. This is the start of a long stage of the purification of this extract, a sequence of chromatographies and precipitations that lead to the hormone being obtained and the contaminants (the proteins of the bacterium) being separated.

According to researcher Paolo Bartolini, the process used by Hormogen makes it possible to obtain a hormone that is "identical" to the one made naturally by the human organism.