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## Roadmap to commercialization: Costa Rica



### GENERAL INFORMATION

- ◆ **Implementing institution:**  
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- ◆ **Head:** Dr. Alfio Piva Mesén (deputy director)
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- ◆ **Implementation period:** 2000-2004
- ◆ **Costs:**  
The total cost of the project is approximately US\$405,000 shared among the Multilateral Investment Fund of the Inter-American Development Bank (50 per cent), Laboratorios Lisan S.A. (30 per cent) and the Instituto Nacional de Biodiversidad (20 per cent).

## SUMMARY

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As a small developing country covering just 50,000 square kilometres — slightly larger than Denmark — Costa Rica has few natural resources. However, located in the tropics, it is renowned for its abundant biodiversity and, dating back to 1969, its pioneering efforts to conserve it. A joint programme between the Instituto Nacional de Biodiversidad (INBio) and the Inter-American Development Bank (IDB) through its Multilateral Investment Fund (MIF) was developed to promote the sustainable use of this biodiversity for commercialization by local small enterprises.

Under the programme, INBio and Laboratorios Lisan S.A., a Costa Rican pharmaceutical company, agreed on a collaborative research strategy aimed at developing pre-commercial-stage pharmaceuticals from selected medicinal plants.

Six phytopharmaceutical products were successfully developed during the programme and these have now been registered for use in Costa Rica. Among the other major areas of impact of the project were:

- validation that research and development programmes can be led by institutions in developing countries;
- benefits to the company through the development of standardized phytopharmaceuticals as alternative medicines;
- the generation of new training and employment opportunities through the introduction of non-traditional

products that adhere to the high-quality standards required by developed countries; and

- the sustainable use of biodiversity.

## BACKGROUND AND JUSTIFICATION

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The majority of pharmaceutical products sold worldwide have been developed from natural products. Over the past several years, therefore, INBio has developed research expertise in plant extraction techniques and chemistry. Much of this experience was gained collaborating with international pharmaceutical companies. However, these efforts did not result in any tangible products that could be developed for the market in either the short or medium term. As such, INBio's expertise was not being fully exploited. For these reasons, INBio began searching for partners among local pharmaceutical companies.

Costa Rica's biotechnology and pharmaceutical sector is composed mostly of companies that use pre-existing techniques, produce generic drugs or are subsidiaries of international firms. Needless to say, small and medium-sized enterprises (SMEs) that invest in research and development are few and far between, and national funding sources are scarce. Venture capital funds for Costa Rican SMEs, for example, are more frequently channelled towards the growing software industry.

As with other local pharmaceutical companies, the business plan of

Laboratorios Lisan S.A. was to produce and sell synthetic generic drugs. Prior to this programme, the company had ventured into natural product formulation but had encountered many difficulties. Instead, as a result of collaborating with INBio, Laboratorios Lisan has now successfully launched a range of natural products as part of its Lisanatura initiative. The resulting Lisanatura products are novel and provide the company with a comparative advantage over other local companies that produce only generic drugs or natural products lacking adequate quality control.

## DESCRIPTION

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INBio, founded in 1989, is a non-profit, public-interest, private institution dedicated to the conservation of biodiversity through research and by facilitating its non-destructive, sustainable economic use. Its mission is to promote a new awareness of the value of biodiversity and thereby achieve its conservation while improving the quality of life of people in Costa Rica and elsewhere. The institution operates under the assumption that a developing tropical society will conserve a major portion of its biodiversity only if it can generate enough scientific knowledge to have value as intellectual property that can be used to generate income. INBio is convinced that biodiversity can be used in a sustainable way to generate commercial outputs that can, in turn, promote economic development and rainforest conservation.

With this in mind, a team of INBio staff and Inter-American Development Bank (IDB) partners developed the INBio/IDB-MIF Programme — a programme that catalysed the interest of Laboratorios Lisan.

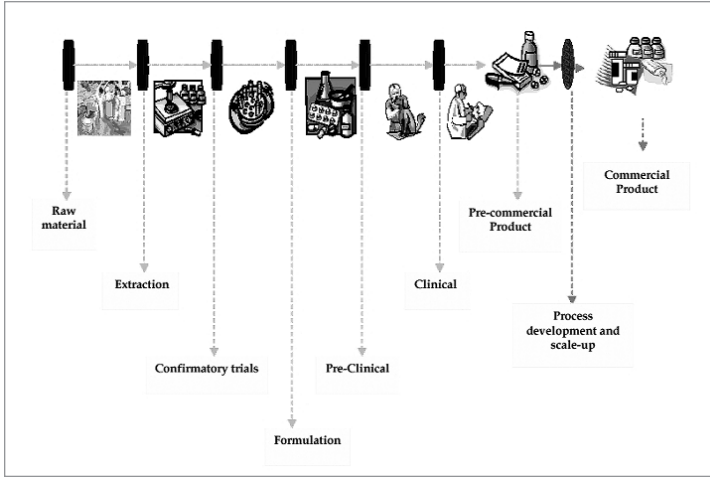
Founded in 1980, Laboratorios Lisan aims to offer excellent quality and competitively priced products to the pharmaceutical market for both human health and veterinary use. Its products are supported by a quality control department equipped with the latest laboratory equipment. In the context of the INBio/IDB-MIF Programme, Laboratorios Lisan aimed to position products with natural components on the market as an alternative to generic drugs and in the context of the sustainable use of biodiversity.

Getting started was difficult. IDB guidelines require that an action plan be presented for consideration by the INBio/IDB-MIF Programme executing agency and its consultative committee. Both INBio and Laboratorios Lisan recognized that INBio's botanical and chemistry expertise complemented Laboratorios Lisan's strength in formulation and quality control. Hence, both parties signed a confidentiality agreement to explore the possibilities of establishing a joint research programme. Eventually, INBio presented a comprehensive proposal to carry out the main research activities with Laboratorios Lisan and a collaborative agreement was signed.

The programme covered four main phases (administrative, research, knowledge transfer and pre-commercial) divided as follows and outlined in fig. 1:

- signing of the confidentiality agreement between INBio and Laboratorios Lisan;
- generation of a comprehensive list of medicinal plants from published references and selection of a limited number on which to focus. It is important to emphasize that the plants should be grown locally and, preferably, should be endemic species;
- elaboration of the comprehensive research proposal presented to Laboratorios Lisan by INBio, including detailed technical data on the plants and a plan of action;
- review and approval of the proposal;
- identification and location of potential suppliers;
- laboratory evaluation of the plant material in terms of taxonomy and chemistry, including qualitative and quantitative analyses. Depending on the chemical profile of the plant material, a reference or marker compound was selected;
- development of efficient extraction protocols to ensure the highest yield of the reference compound. If the reference compound was not commercially available, the marker compound had to be isolated and purified in-house;
- production of a standardized extract — the “raw material” used to begin product formulation;
- transfer of the extraction and purification protocols to Laboratorios Lisan so that the company could perform activity and stability tests on the formulated product. Quality control analyses, using thin layer chromatography and high performance liquid chromatography techniques, for example, were also performed by Laboratorios Lisan. In some instances, INBio also provided detailed botanical descriptions to aid accurate identification of the plant sources;
- formulae were tested for stability by Laboratorios Lisan using accelerated stability chamber testing;
- depending on the product and plant, lethal dose (LD50) toxicity tests were carried out by the Laboratory of Biological Assays of the University of Costa Rica (UCR-LEBI);
- registration with the Ministry of Health;
- activity tests were performed with volunteers. Laboratorios Lisan arranged for studies to be performed locally and in Cuba; and
- advancement to full-scale production — under the control of Laboratorios Lisan.

The plants selected for further investigation in the initial stages of the project were: *Quassia amara* (amargo or bitter ash, family Simaroubaceae), *Plantago major* (common plantain, family Plantaginaceae), *Aloe vera* (aloe, family Asphodelaceae) and *Justicia pectoralis* (fresh cut, family Acanthaceae) (figs. 2-5).



**Figure 1 |** Outline of procedure for developing pharmaceutical products from plant material.



**Figure 2 |** *Quassia amara*, used to develop Q-assia tablets (see table 1).



**Figure 3 |** *Plantago major*, used to develop Encigel gel and CS and Alivion creams (see table 1).

**Figure 4 |**  
*Aloe vera*, used to develop Lisaloe cream (see table 1).



**Figure 5 |**  
*Justicia pectoralis*, used to develop Estilo tablets (see table 1).



Results obtained to date include:

- comprehensive laboratory procedure manuals, including protocols for extraction and for standardization;
- generation of preclinical and clinical data;
- a healthy business and research relationship between an academic institute and an SME;
- suppliers that comply with good agricultural practice (GAP) identified and agreements drawn up;
- five phytopharmaceutical products launched early in 2004, with a sixth to be launched later in the year (see below). (An illustrative prototype of *Q. amara* tablets is shown in fig. 6.);
- Laboratorios Lisan received an award for innovation in 2003; and
- positive media coverage.



**Figure 6 |**  
Illustrative prototype  
of commercial *Quassia*  
*amara* tablets.

## PATENTING AND COMMERCIALIZATION

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To date, extracts from the three plant species have been translated into six phytopharmaceutical products. A cream, a gel and a soluble powder have been generated from *P. major*. In addition, tablets of *Q. amara* and a cream containing *A. vera* have been produced. Indeed, in the case of *Q. amara*, instead of the liquid extracts recommended by INBio, Laboratorios Lisan technologists developed stable powder extracts as raw materials for further formulations.

## PARTNERSHIPS

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The whole successful initiative was based on the two partners, INBio and Laboratorios Lisan, working closely together on a pre-agreed product development project.

Laboratorios Lisan approached the Universidad Nacional of Costa Rica for botanical certification and the University

of Costa Rica (UCR-LEBI) for biological testing, and collaborated with the Hospital Clínico Quirúrgico Docente Joaquín Albarrán in Cuba, where clinical trials on volunteers were carried out.

Approved raw material suppliers included Ark Herb Farm, Bougainvillea S.A. and Hypericum Pharma S.A. Future suppliers could be organized as cooperatives.

## REPLICABILITY

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This experience is relevant to other companies in the country, in the region and in the world. Together, INBio and Laboratorios Lisan have demonstrated that SMEs are capable of developing projects whose end points are commercial products. Furthermore, such projects add value to a country's biological resources and set in motion economic development.

In order for this particular successful initiative to be replicated more widely,

## Description of each product, its presentation and therapeutic uses.

PLANT	PRODUCT	PRESENTATION	USE
Aloe ( <i>Aloe vera</i> )	Lisaloe® cream	15g tube	To alleviate skin redness and inflammation. Used to treat skin wounds and ulcers, burns, solar erythema (sunburn), sensitive skin and nipple fissures.
Amargo ( <i>Quassia amara</i> )	Q-assia® tablets	Blister pack of 10 tablets	Digestive aid in case of dyspepsia (uncomfortable sense of fullness after meals), to reduce stomach acidity and promote bile secretion.
Plantain ( <i>Plantago major</i> )	Encigel® gel	15g tube	Used topically as an anti-inflammatory and to treat mouth mucosal disorders (gingivitis, irritations, minor wounds, canker sores).
	CS® cream 1	15g tube	Used topically as an astringent and anti-inflammatory, and to treat mild and moderate acne.
	Alivion® cream 2	15g tube	Used topically as an anti-inflammatory and antipruritus (against insect bites, itching, rashes).
	Soluble powder	3g packet	Digestive aid.
Fresh cut ( <i>Justicia pectoralis</i> )	Estilo® tablets	Blister pack of 10 tablets	Central nervous system sedative.

other countries need to assess their current situations — both with regard to the knowledge of the biodiversity and the ability of their SMEs to transform this knowledge into commercial products. SMEs, therefore, must develop an awareness of the need for investment in research and development. Laboratorios Lisan branched out from the common pool of SMEs and invested in research and development to create an innovative line of products that, it is hoped, will open a new market for the company and that will position it as a leader in a rapidly growing field. Countries interested in promoting economic growth based on biodiversity and research should establish practical funding programmes and guidelines to create incentives for other like-minded SMEs.

Countries must also put in place the necessary legal and health frameworks for this type of product in order for them to comply with international quality standards — essential for satisfying global market demands.

## **POLICY IMPLICATIONS**

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The project has resulted in strengthened legislation regarding the conservation of plant species and environmentally friendly practices of cultivation and harvesting.

## **LESSONS LEARNED**

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The principal lessons learned are that technical and administrative difficulties can be overcome and success can be

achieved. To do so requires funding, a highly skilled multidisciplinary team, a solid knowledge base of biological resources, good organization and good communication between partners, and an entrepreneurial drive to carry out the project.

Funding programmes often entail administrative procedures that must be followed when beginning a project. Some of these guidelines seem to complicate matters in the short term but do ensure the smooth implementation of the project in the long run. By itself, establishing a business and research relationship is not easy and coming together to deliver a final product is a challenge.

The supply of good-quality, botanically certified medicinal plants was highlighted as a key issue that had to be addressed. Also, real-time and good communication between the parties needed to be addressed and improved. It has been a learning experience for all parties.

In this particular project, a major issue was the fact that an evaluation was necessary. As the INBio/IDB-MIF Programme was a pilot project, funding was withheld for about a year while IDB conducted its review. This caused a delay in the research and prompted Laboratorios Lisan to use its own sources of funding for a period. Research projects do tend to suffer delays; however, although the initial commercial launch and projections had to be modified, the company continues to be on the right track for success.

Another significant challenge faced became apparent during the transfer and

implementation of protocols from INBio to Laboratorios Lisan. In particular, there are important differences between generic drugs and phytopharmaceuticals. For example, in the analysis phase, generics deal with limited quantities of materials while working with plants calls for larger quantities. In the formulation stage, this project required the isolation and characterization of reference compounds from the selected plants that were more difficult to obtain and work with than known, commercially available compounds.

On a national scale, the previous experience of the Ministry of Health has been related to materials that have been extensively studied by other organizations, as is the case with generic drugs. For this reason, the phytopharmaceuticals INBio developed with Laboratorios Lisan were considered novel and, for the time being, have been registered on the basis of such criteria as botanical certification, scientific references and methods of analysis. In the future, the Ministry of Health might be interested in investing in capabilities to validate such phytopharmaceutical products.

Finally, one major weakness of the project that needs to be addressed is that existing suppliers must be able to provide the required quantities of high-quality plant material within an acceptable time frame. In the worst-case scenario, new farmers must be brought online as suppliers to meet both market demands and agricultural quality specifications.

## IMPACT

The impact of the programme has included the following:

- Benefits have accrued along the whole production line, from farmers to lab technicians. In particular, the number of certified suppliers of the raw materials has increased. New jobs could be created because of the demand for cultivation, harvesting, processing and quality-control tests.
- Technologies and expertise found within Costa Rica are now being exploited and put to good use. There have also been improvements in scientific infrastructure and an increase in technical training opportunities.
- Under the agreement for non-refundable technical cooperation, the INBio/IDB-MIF Programme requires that reimbursements from any profits generated from the commercialization of products arising from the project be made to the executing agency. This maintains a rotating fund that is used to support further initiatives.
- The programme has promoted the economic development of the country.
- Laboratorios Lisan can offer phytopharmaceuticals of high quality, produced entirely in Costa Rica.

In addition, from the environmental point of view:

- Under the agreement with Laboratorios Lisan, INBio will receive royalties obtained from the sale of any commercial products. These royalties will be shared equally between INBio and the Ministry of Environment and Energy, which has earmarked the funds to promote the sustainable use of biodiversity and to consolidate the national system of conservation areas.
- The project was designed to avoid "extractivism" (i.e., taking resources in an uncontrolled and unsustainable way); thus the raw materials are acquired only through lawful suppliers.
- Suppliers of the medicinal plants are encouraged to cultivate the resources in sustainable ways. Producers have also been required to comply with good agricultural practices.

Indicators of success include:

- The products generated at a pre-commercial level comply with good manufacturing and good laboratory practices.
- Results and know-how have been transferred from INBio to Laboratorios Lisan (i.e., manuals on analytical and extraction methods).
- There is a possibility of acquiring patents for certain procedures and therapeutical applications.
- Once the commercialization phase of the project begins, a clear indicator of success will be the position of the products in the marketplace.

Articles in major national newspapers have prompted good responses from the general public towards the products and there is a growing trend for consumers to prefer natural remedies. However, most medical professionals in the country are reluctant to recommend the use of phytopharmaceutical products.

The commercialization phase for the innovative experience is only now being launched, but Laboratorios Lisan plans to sell the products on both the national and international markets. Educational and marketing campaigns to cultivate social acceptability and commercial success are being recommended.

## FUTURE PLANS

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INBio has approached Laboratorios Lisan to facilitate contact with an international company that is interested in learning more about the company's products. It is hoped that a joint venture or some other type of collaboration will materialize. Furthermore, the door is open for further interactions between INBio and Laboratorios Lisan.

This case study is a clear example of the interest of both parties in sharing their innovative experiences. Additionally, it is a statement of commitment by organizations such as TWAS, TWNSO, UNDP and the World Health Organization (WHO) to promote the popularization of plants as sources of alternative medicines. INBio is confident that this study will be a reference point for other organizations embarking on this type of research.

## PUBLICATIONS

### ARTICLES IN COSTA RICAN NEWSPAPERS:

Cordero, C. *Reinventar como tradición* (Re-inventing as tradition). *El Financiero*, 15-21 December 2003. Special report, pp. 10-11.

———. *Lisan lanzará fármacos naturales* (Lisan will launch natural pharmaceuticals). *El Financiero*, 10-16 November 2003, Technology section, p. 26.

———. *Impulsan innovación para productos naturales* (Promoting innovation for natural products). *El Financiero*, 4-10 August 2003, Technology section, p. 30.

Ugalde, P. *Seis empresas costarricenses desarrollan nuevos productos a partir de las riquezas naturales de Costa Rica* (Six Costa Rican companies develop new products from natural riches in Costa Rica). *La Nación*, 1 November 2002, Viva section, pp. 1 and 6.

### OTHERS:

Hamilton, R. From our forest to your medicine cabinet. *IDBAmérica* (Magazine of the Inter-American Development Bank), March 2004, Focus section. See [www.iadb.org/idbamerica/index.cfm?thisid=2653](http://www.iadb.org/idbamerica/index.cfm?thisid=2653).

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*Giselle Tamayo*, scientific and technical coordinator, INBio: Project director, coordination and follow-up of INBio research activities, administrative liaison with Laboratorios Lisan.

*Ana Lorena Guevara*, director, INBio/IDB-MIF Programme: Negotiated the terms of and compliance with the Programme's requirements.

*Andrés Cordero*, systems and promotion specialist in INBio/IDB-MIF Programme: Ensured compliance with IDB guidelines.

*Poett Ryan*, director, Laboratorios Lisan: Current director of the project at Lisan. Worked closely with INBio to ensure that the company's needs were being met and that the projected return on the investment was on the right track. Supervised the operative progress of the project at Lisan, analysed the clinical data and handled the product registrations at the Ministry of Health.

*Rodolfo Carboni*, president, Laboratorios Lisan: Helped to establish the project, including Laboratorios Lisan's investment in research and development.

*Carlos Carboni*, founder and CEO, Laboratorios Lisan: Formulation expertise and product development.

*Armando Calvo*, consultant, Laboratorios Lisan: Organic synthesis and formulation development.

*Betsy Murray*, MIF Officer, IDB: Follow-up activities.

*Julio Sánchez*, former consultant, Laboratorios Lisan: Original director of the project at Lisan, including coordination of the clinical data and trials.