
FUTURAGENE
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# THE DEVELOPMENT OF FORESTRY HIGH PERFORMANCE GENETICALLY MODIFIED EUCALYPTUS: THE SUCCESS OF A PARTNERSHIP THAT GENERATED NEW COMPETENCIES TO A GREAT CELLULOSE COMPANY




Biotechnology is one of most promising scientific areas – and it has been like that since the scientists deciphered (in 1953) the DNA. Since then, this science has been promising to contribute for the human being in facing challenges such as cancer, improvement of quality and yielding of animals and plants, production of substances relevant for health, food consumption, sanitizing or removal of environmental pollution.

As this is a field of the scientific knowledge where the discovery is so directly linked to possible industrial applications, a large number of promising ideas were born in universities, research institutes and, many times, in startup companies, with founders coming from those environments. However, all that potential has not yet been effectively unfolded into products and processes streamlined with the expectations. There are frequent disappointments of investors seduced by business plans associated to discoveries in this area. The path between the discovery and the commercial results is long and filled with obstacles.

FuturaGene's pathway, from the university seat up to the current stage of development, has very relevant and useful lessons about Brazil's possibilities in the field of biotechnology, so fertile and so promising in global terms. To follow close, when not leading, the frontier of scientific knowledge represents an extraordinary opportunity to idealize products or services that might be very competitive. However, the quick and safe following of that path does not depend only on the entrepreneur scientists or on the created startup companies; there are conditions of the economic and institutional environment which are determinant for the success of the business.

Institutions capable of understanding the risks of the enterprise and accepting them as an integral part of the innovation process are essential for the high technology sectors to succeed and comply with what is expected from them: the generation of highly competitive new products and processes.

## 1. THE COMPANY AND ITS SECTOR

FuturaGene nowadays is a Brazilian company, but its first seed was born in the high performance scientific environment of Israel, more than 20 years ago. The company was then named CBD Technologies and its

team of researchers, led by Professor Oded Shoseyov – with notorious experience in plants genetics, protein engineering and nanobiotechnology – was dedicated to proteins engineering.

In parallel to that Israeli origin, FuturaGene was born in the USA, as a spin-off from Purdue University. After the listing in the London Stock Exchange (2004), the company was merged with CBD Technologies. Suzano Papel e Celulose made the first investment in CBD Technologies in 2001 and, in 2010, acquired FuturaGene, which now has as its main focus, but not the only objective, the enhancement of forestry assets of Suzano.

The scientific knowledge about modification of plants growth is of special interest to the forestry sector. And forests are, in Brazil, an important subject for several companies. That is the case of Suzano, which has worked for decades with eucalyptus classical breeding. Other companies were doing the same; and the actual Brazilian forestry sector, collectively, defined a set of actions to guarantee advancement of the agenda of researches on their interest. Even thus, the collective actions may be insufficient to guarantee progressing of process at the speed adequate for the company's purposes.

Hence, Suzano, determined to enter into a new path, invested in a solution that was already under development and could make a shortcut towards the relevant results for the company.

Suzano's acquisition allowed FuturaGene to access genetic material of high quality eucalyptus, thanks to the large number of clones available in its germplasm bank and to a captive market of its technologies. In that sense, the reunion of the companies offers the opportunity for negotiating assets and competencies of two phases of the research and development process: Suzano's forestry matrix, which represents the platform on which the company can, actually, develop its innovative concepts; and the forestry basis, considered to be the laboratory where it will be possible to know what the technology will be able to add.

FuturaGene has thus become a Brazilian company, with internationally rooted technologies and competencies. And its strategy, since then, was increasingly directed to the technological challenges of the Brazilian subtropical agricultural world. The biotechnology company's bet is to face the challenges of the different agricultural crops and regions, with technologies that more and more incorporate the best of science.

The adopted business model is based on the discovery and acquisition of technologies, prototyping in commercial plants and transfer of know-how, as well as creation of partnerships with the main companies of the forestry sector to expand

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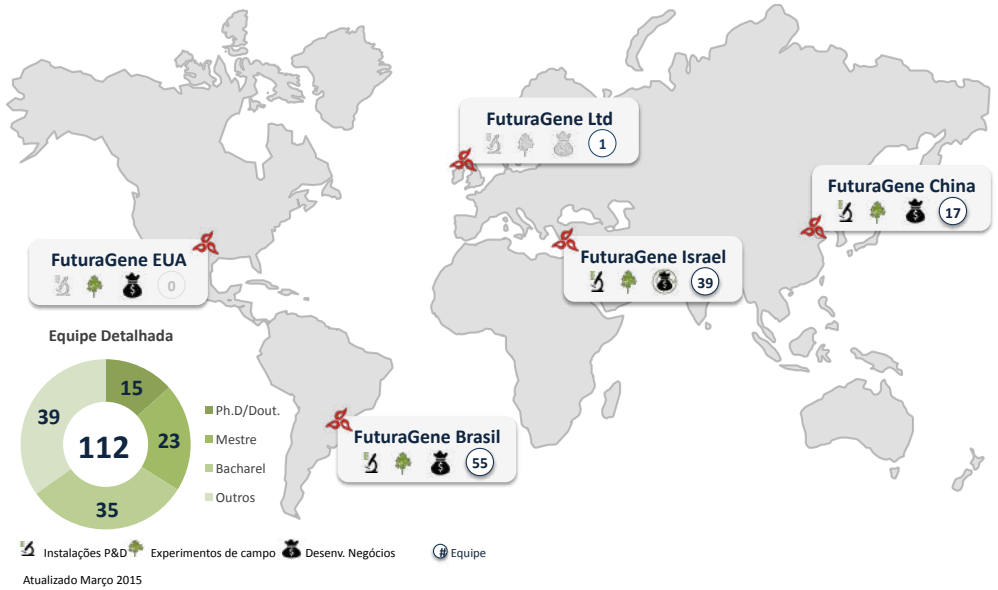
coverage of its products. The company also cooperates with institutions from sectors that are not within its core activities, by licensing technologies to those segments.

*FuturaGene's business model enables engaging partners in all the stages of the biotechnology value chain.*

Besides in-house development of technologies, the company purchases licenses to develop and trade technologies with universities and corporate partners after initial feasibility studies. Today, it has institutional and academic partnerships in several countries, such as the United States, Canada, Australia, Israel, China and Brazil. Those Brazilian institutions include Embrapa, São Paulo University (USP), and São Paulo State University (UNESP) and Viçosa Federal University (UFV). FuturaGene holds agreements with international leaders on silviculture and agriculture, such as China Academy of Forestry (CAF), AA Alliance, BioCentury Transgene, and other forestry basis companies, under confidentiality agreement.

The company's activities are distributed into corporate and R&D structures in Brazil (São Paulo and Itapetininga, both in the State of São Paulo); China (Shanghai) and Israel (Rehovot). The field trials are performed at several sites inside the three counties and in the United States. The most advanced technologies of the Group are to improve productivity of the forestry plantations in a sustainable manner. The company counts more than 110 direct employees distributed across its advanced research centers, most of them in Brazil. From that total, about 40% hold Master and Doctor degrees.

**Figure 1 - FuturaGene's global presence**




Source: FuturaGene's Institutional Presentation (2015)

## 2. THE STRATEGY – THE PROJECT ALIGNMENT WITH THE BUSINESS

Brazil holds the largest world productivity in culture of eucalyptus, resulting from the climatic conditions and technologies developed by companies and research institutions in the country. The classical breeding, by

selection and propagation of the best individuals, offered an important contribution for the productivity gains; however, exceeding of those events is increasingly harder. Therefore, it is essential to create new research lines and development of technologies so that the country shall maintain its competitiveness in the forestry sector. In that sense, biotechnology has been presenting promising results, indicated as an important tool to maintain the country ahead in the market of wood and of its byproducts.

FuturaGene holds prominent position in the area of genetic research and development of plants for the global markets of the forestry, bioenergy and biofuel sectors. The company develops solutions to meet the growing demand for raw-material producing cultures for those three purposes, within a scenario of progressive reduction in the availability of new land and incremental unavailability of water resources. The developed technology is focused on two main platforms: i) increased productivity during the plant's growth and/or increment of the processing capacity, after the harvest; and ii) protection of the crop as a response to climatic changes and reduction of natural resources[1].

The purchase by Suzano, Brazilian paper and cellulose company, leveraged the mission of becoming world leader in the genetic research and development of plants in a sustainable manner.

To accomplish that target, the company counts on the skill in the use of its technologies for selecting elite events in superior genetic material and establishing channels with the market by its broad operation in Brazil and in partnerships in the South of Africa, Southeast of Asia and South of China. The scientific and technologic assets of the two companies form a combination of extraordinary potential to add values to the businesses of that platform, while both partners reduce their risks.

The company developed know-how on genetic transformation of plants and has been able to establish different uses for its technologies in strategic cultures, including the culture of eucalyptus, which is the largest sustainable plantation of forestry species for the paper and cellulose industry and the culture of poplars, a tree increasingly used for production of bioenergy or biofuels. The developed techniques apply also to corn, which is broadly used in the animal nutrition and biofuels markets[2].

## 3. THE PROJECT

The Brazilian forestry basis industry is weakened towards its main competitors, losing the status of lower world cost.

1 Available at: <http://www.futuragene.com/pt/>. Access on: September 24th, 2014.

2 Available at: <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aPV5VK3RZ3fU#share>. Access on: September 9th, 2014.

Even though, figures from 2013 disclosed by Brazilian Trees Industry (IBÁ) reinforce the irrefutable economic and social-environmental relevance of the sector. More than 4.4 million direct and indirect jobs were generated. The sectorial gross domestic product reached the milestone of BRL 56 billion and taxes collection exceeded BRL 8.8 billion.

The eucalyptus is the forestry culture occupying the largest planted area in Brazil. According to the IBÁ, between 2006 and 2013, the crop presented average growth of 2.8% per year, totaling about 5.5 million hectares of planted forests, in 2013.

The planted forests are responsible for supplying almost half of the Brazilian wood market and, in the paper and cellulose sector, they are the single raw-material[3] source. It is over that broad forestry basis that the company defined its technological priority.

FuturaGene developed the first genetically modified eucalyptus with increased productivity, which performed tests evidenced about 20% gain in wood production when compared to the conventional eucalyptus.



3 ABRAF – ASSOCIAÇÃO BRASILEIRA DOS PRODUTORES DE FLORESTAS PLANTADAS. Anuário estatístico ABRAF 2013: ano base 2012. Brasília: ABRAF, 2013.

## CHART 1. FUTURAGENE'S SCIENTIFIC DEVELOPMENT AND ITS APPLICATION TO THE EUCALYPTUS

*The genetically modified eucalyptus was developed through expression of a plant enzyme (1,4-β-endoglucanase) which operates in the cellular elongation process during the plant development.*

*The genetic modification performed in eucalyptus, by the company, was directed to the cell wall (or cell membrane) aiming at increasing yielding of the varieties. The cell wall is responsible for the cell structure and its semi-rigid character impedes morphological changes of the organisms, providing structural strength to the plant and creating an important physical barrier against diseases and plagues – which is the reason why they developed natural resistance to destruction, a fact that creates a major obstacle for the industrial processing of their fibers or for availability of the simple sugars that form them. The difficulty derived from the very nature and evolution results into adverse economic effects.*

*In terms of chemical composition, the plant cell membrane is formed by cellulose, hemi-cellulose and lignin[4]. This complex composition is responsible for stiffness of the plant cells, which is relaxed only during the plant's growth and development. Formation of the wall in the plants cells starts with deposition of primary cellulose coverage, allowing the plant growth during that stage. After this phase, the membrane receives new layers of cellulose and other substances (suberin and lignin), granting more resistance to it.*

*FuturaGene's technology involves the capacity of producing modified plants that activate relaxation and reconstitution of cell walls during growth. The company developed a new approach to attain plants with that profile. Through Genetic Engineering, it included the gene of a plant, Arabidopsis thaliana, which codifies one of the specific enzymes that participate in chemical composition of the cellulose, the endoglucanase. The insertion of the exogenous[5] gene and the expression of the enzyme result into early growth and higher production volume (in case of species such as the eucalyptus). The genetically modified eucalyptus makes it possible to obtain the same amount of timber than conventional eucalyptus using smaller area.*

4 CARVALHO, W. et al., 2009.

5 It belongs to another species and it is inserted into the receiving organism to lead it to express a new protein.

» **CHARACTERIZATION OF THE BIOTECHNOLOGICAL EVENT**

*FuturaGene obtained, in 2003, the H421 event genetically modified eucalyptus, developed to increase biomass accumulation. The technology enabled greater productivity of wood per planted area, at shorter time when compared to its conventional parent lineage. The higher growth characteristic is due to the expression of Cel1 gene of Arabidopsis thaliana, which codifies the 4-β-endoglucanase enzyme that acts in the cell elongation process during the plant development[6]. The expression of this protein results into the larger cell growth and into consequent increased productivity in wood volume per production area.*

*The genetically modified eucalyptus (H421 event) has been assessed in containment since 2001 and in the field since 2006, demonstrating excellent plant profile for intensive cultivation and wood production. Tests performed by the company confirmed that the event does not have potential to become a weed and its cultivation does not present any adverse environmental impact when compared to the conventional eucalyptus cultivation. The composition analysis confirmed that the tissues of the modified eucalyptus are equivalent, in composition, to the tissues of the conventional eucalyptus.*

*The H421 eucalyptus was produced by the method of transformation mediated by agrobacterium tumefaciens, using the pBI121 plasmid and invariability of the integrated DNA confirmed by the PCR technique (Polymerase Chain Reaction)[7]. The constructions included into the eucalyptus DNA, as well as their insertion regions were maintained in the tested progenies obtained in controlled crossings with different species and conventional commercial varieties. The stability was confirmed by molecular analyses, demonstrating that the genetic heritage follows the Mendelian[8] segregation principle, as expected.*

6 SUKNO, S. *et al*. Expression and Regulation of the Arabidopsis thaliana Cel1 Endo 1,4 *β Glucanase Gene During Compatible Plant-Nematode Interactions*. The journal of nematology, v. 38, n. 3, set. 2006.

7 DNA amplification method (creation of multiple copies) without use of living organism.

8 Law of recombination or independent segregation, by which, in a crossing involving two or more characters, the factors determining each one of them are independently separated during formation of the gametes and recombined at random, to form all the possible recombinations.

“The genetically modified eucalyptus developed by FuturaGene is responsible for approximately 20% increase in the forestry productivity for the cellulose, energy and biofuel markets.”

The benefits of the modified eucalyptus variety drive the interest of the paper and cellulose industry, considering that the cellulose extracted from the plant wall is the raw-material for the industrial fiber used to manufacture paper. In addition, it generates material for several other agricultural products, including sugars that might be used to produce second generation ethanol or yet to produce chemical compounds obtained by biotechnological routes.[9]

*The genetically modified eucalyptus developed by FuturaGene is responsible for approximately 20% increase in the forestry productivity for the cellulose, energy and biofuel markets.*

This is a worldwide innovative initiative. It is the first genetically modified forestry species submitted to commercial release in the country, besides being the first private Brazilian company to submit a genetically modified plant to commercial approval.

The developed eucalyptus has been assessed in the field since 2006. After executing the performance and biosafety tests – which resulted into a dossier - the company initiated the regulatory process with the CTNBio (Brazilian Technical Biosafety Commission) in January, 2014. The event was

approved after evaluation by the Commission, in April, 2015 for planting for commercial purposes becoming the first genetically modified eucalyptus in the world approved for commercial use[10]. It is important to highlight that this process and all the other activities involving Genetically Modified Organisms (GMOs) in Brazil are regulated by the Law on Biosafety, which defines the parameters for performance of the studies. The Brazilian regulatory system is considered to be one of the most complete and strict in the world.

Chart 2 presents a brief summary of the adopted model and the Brazilian regulatory process.

9 Evanildo da Silveira. Mais celulose por centímetro quadrado. Revista Pesquisa FAPESP. ED. 204 – FEVEREIRO 2013. http://www.ctnbio.gov.br/upd_blob/0001/1947.000202-201471%20part%201.pdf

10 Available at: : <http://www.futuragene.com/CTNBio-aprova-eucalipto-GM-da-FuturaGene.pdf>. Acess on: April 10th, 2015:

## CHART 2. REGULATION OF THE GENETICALLY MODIFIED ORGANISMS IN BRAZIL

*Brazil signs the Cartagena*[11] *Protocol and it incorporates the approach of precaution in its laws regulating the transgenic products. The adopted precaution model sets forth procedures for GMOs risk assessment for activities in containment or with planned release to the environment. The matter of biosafety is governed by Law no. 11.105, dated March 24, 2005 (BRAZIL, 2005). Among other questions, the law sets forth the safety rules and mechanisms for inspection of activities involving genetically modified mechanisms and their by-products. That law is responsible for creation of the Brazilian Biosafety Council - CNBS and the Brazilian Technical Biosafety Commission - CTNBio, besides considering the Brazilian Biosafety Policy - PNB (BRAZIL, 2005).*

*The CTNBio is responsible for assessing and analyzing the risks of any and every activity related to GMOs and to issue previous conclusive technical opinion about any release in the environment – the principle of precaution is applied by CTNBio in its assessment and monitoring, case by case, of any and every genetically modified organism's safety. Brazil holds one of the most complete regulatory processes in the world. The Law on Biosafety sets forth several control mechanisms ranging from product development up to its monitoring in the market. They include the requirement for any research institution to have an Internal Biosafety Commission (CIBio), responsible for guaranteeing safe handling of the GMO; the need to attain prior approval and registration of installations and qualified personnel to perform the research activities, through the character of the Certificate of Quality on Biosafety (CQB) issued by the CTNBio.*[12]



11 The Cartagena Protocol on Biosafety is a treaty on biosafety signed during the Convention on Biologic Diversity (CDB) held in Cartagena, Colombia. Approved on January 29, 2000 and valid since September, 2003, the text regulates matters involving the study, handling and transportation of genetically modified organisms (OGM) between the countries signors of the agreement.

12 Available at: <http://www.ctnbio.gov.br>. Access on: September 1st , 2014.

## 4. INTERNATIONAL SCENARIO

Expansion of the genetically modified cultures was extraordinarily significant in the last two decades. Between 1996 and 2013, the total land surface with transgenic crops increased from 1.7 million hectares to 175 million hectares. Its growth rate was close to 10% per year in the last eighteen years[13]. Approximately 60% of the world population lives in the 27 countries that implemented biotechnological crops in their agriculture, during this period.

Brazil holds the 2nd place in the rank of the largest producers of genetically modified crops (behind the USA only) and it is being positioned as a strong world leader in the market. In 2013, the total area planted with genetically modified crops reached 37.1 million hectares, representing 14% increase, compared to the former year, which, on its turn, had already recorded more than 21% growth compared to the 2010/2011 harvest.

The paper and cellulose industry uses plantations composed, mainly, by exotic species – usually hybrids and clones of eucalyptus and pines. Those species have been, in time, selected by the forestry improvement programs to obtain more productive trees, with characteristics adapted to the several regions and resistant to plagues, diseases and adverse weather conditions. In Brazil, the wood from species of Eucalyptus genus is highlighted as one of the main sources of raw material for the forestry basis industry, due to its high capacity of adaptation to different environments.

The main difficulties of the forestry species breeding programs are due to the long life cycle of the species, the size of the trees and high complexity for analysis of the descendants, after the crossing and back crossing – and consequently the high costs of that activity.

Since the end of the 1980's, when the first transgenic plants were released for commercial cultivation, it is estimated that more than 800 field trials have been performed across the world with genetically modified trees, in about 40 species.[14]

In Brazil, eucalyptus and pines planted forests are the primary source of fiber and our forestry biotechnology researchers are focused mainly on those crops. Nowadays, the country has several forestry product companies engaged in the development of researches related to forestry biotechnology;



13 International Service for the Acquisition of Agri-biotech Applications (ISAAA). Global Status of Commercialized Biotech/GM Crops: 2013. Available at: <http://www.isaaa.org/resources/publications/briefs/46/executivesummary/>. Access on: September 25th, 2014.

14 Evanildo da Silveira. Mais http://revistapesquisa.fapesp.br/2013/02/11/mais celulose por centímetro -centimetro-quadrado. Revista Pesquisa FAPESP. ED. 204 — FEVEREIRO, 2013.

however, there are not yet genetically modified species of trees traded.

China is prominent in the trade and plantation of genetically modified trees. The first transgenic tree released for commercial plantation was the Poplar, in 1989 (with introduction of the Bt event, known for driving resistance against insects deemed to be key plagues and intensely used in crops such as corn, cotton and soy). China then launched 1.4 million of genetically modified poplars in an area counting from 300 to 500 hectares.

Historically, the United States has always been ahead in biotechnology. In terms of forestry biotechnology, the country is simultaneously working in several fronts. There are already profitable biotechnologies available for commercial plantation – papaya trees resistant to the mosaic virus are available since 1997. In the field of forestry biotechnology, selection of events that provide increased productivity and important changes to the plants composition has been (for decades) an ongoing research line. Governmental agencies, private companies and universities are studying biotechnological trees with those characteristics – there is already genetically modified eucalyptus in the stage of regulatory process[15, 16]

15 Available at: <http://www.forestbiotech.org/>. Access on: September 9th, 2014.

16 Available at: <http://www.centerforfoodsafety.org/files/ge-tress-one-page-spread-final_67649.pdf>. Access on: September 9th, 2014.



## 5. RESULTS FOR THE COMPANY

The developed technology puts the company into a leadership positioning in the forestry biotechnology area, making it the first in the world to trade a genetically modified eucalyptus species with increased productivity.

From the economic perspective, the product increases competition of the Brazilian eucalyptus forestry sector and of the national industry as a whole – as the technology may be diffused to other non-competitor forestry basis companies. Considering the increased productivity and costs saving enabled by the solution, Brazil may resume the position of wood producer at lower cost in the global cellulose industry.

The product also brings important social and environmental gains, as the technology enables producing of more wood, using less area, which represents reduction in the use of chemical supplies and water for irrigation, resulting from the lesser use of land; reduction in carbon emission during transportation of wood, due to reduction of the average radius up to the plants; and the potential for higher sequestration of carbon dioxide due to the fast growth of the forestry. By requiring smaller areas for plantation, it will also be possible to provide land for other uses, such as for production of food or preservation.

## 6. OUTCOMES OF THE PROJECT

The company intends to develop new clones, using conventional breeding methods. The purpose is to perform crossing of the modified eucalyptus (and which presents high yielding) with others that are better adapted to different soils and climatic conditions (using Suzano's rich germplasm base), adding social and economic interest characteristics, such as increased productivity, resistance to diseases and plagues and tolerance to stress conditions. Suzano's comprehensive germplasm base enables searching plants with different characteristics and enhances the project's chances of success.

The company is working on the development of new events, i.e., in the identification of new genes responsible for important characteristics for forestry cultivation, fostering increased competitiveness in the sector. Breeding of new varieties with high yielding and resistance to insecticides is in the phase of research.

## 7. PERSPECTIVES

FuturaGene's expertise is used to seek technologies that may be applied to improve quality of wood aimed for manufacture of cellulose and paper, besides the specific changes of the

biomass characteristics, in order to attain gains in bioenergy production, mainly the second generation ethanol and other wood by-products. The lingo-cellulosic biomass is a source of renewable carbon, potentially convertible into biofuels or bioproducts, such as chemicals, polymers and other material.

The company uses its biotechnology know-how and the experience attained during the creation process of the H421 eucalyptus – such as implementation of experiments in the field to identify elite events, elaboration of studies and tests to assess biosafety of the product and establishment of partnerships - to develop other agricultural crops, such as the poplar and the sugar-cane – considered to be strategic for Brazil's growth and economic development.

The main lesson from this project connects the high competitiveness of the Brazilian forestry sector to a shortcut to attain more advanced results that allow reinforcing that competitive level. For that matching, two others have joined forces: a high technology and next generation scientific basis company and a knowingly competitive cellulose company. One of the parties obtains access to research funds and high potential plant varieties base while the other is able to, by controlling of advanced biotechnology techniques, accelerate its transition to a higher level of development.

Would that be a role model path for the Brazilian industry? Apparently, it represents a healthy alternative, as it allows, in several cases, the companies to strongly leverage their competencies in new areas, with modest investments for their economic dimensions, where Brazil, for different reasons, is still crawling (such as in startups acceleration) or yet is lost into institutional difficulties (such as, for instance, the intellectual property; or the relations between science and technology institutions, on one side, and companies, on the other).

The FuturaGene model and its association with Suzano seems so innovative in the Brazilian business models matrix that possibly it would be the first of the kind in the large institutions for funding of scientific, technological development and in the development banks. And here we should make a suggestion for those agencies to carefully assess evolution of that partnership that might represent a valuable alternative for the public policies on industrial development promotion.