

Biotech's Comeback in France

by Emmanuelle M. Voisin

France has become the center of a blooming biotechnology sector and is home to about 300 small- to medium-sized enterprises (SMEs), after a long period of difficulties (1). French start-ups are generating highly innovative products, although this has been largely unnoticed by the pharmaceutical industry despite the growing research budgets. French policy is fostering the new biotechnology industry arising from research and development in small and innovative companies.

The Bigger Picture: In 2004, the volume of European biotechnology business was fairly low: €11.33 billion (US\$13.92 billion). In fact, Europe is the only region in the world where biotech revenues are not growing. The new millennium saw a significant slowdown in worldwide biotechnology until 2003. That recession was characterized by a slump of stock-exchange values, rarer introductions on the stock exchanges, and weak investments.

Now, however, on what can be called its 40th anniversary, the global biotech sector is doing better: Worldwide, it generated US\$46.6 billion in 2003 and \$54 billion in 2004 (that is a 17% rise). Although 2004 and 2005 showed signs of improvement in the United States (\$35.9 billion in 2003 and \$42.7 billion in 2004) and in Canada (\$1.7 billion in 2003 and \$2.1 billion in 2004), no recovery signs were visible



La Defense business center in Paris.

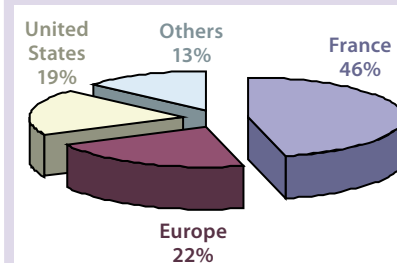
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in Europe during the same period. In 2004, global turnover for the European companies was €11.33 billion (\$13.92 billion), whereas it had been €11.27 billion (\$13.84 billion) in 2003. Taking into account that other countries such as Japan, Australia, India, and China are playing an increasingly important role in the biotech scene, Europe is the only part of the world where biotech business volume is not increasing.

NEW DYNAMISM IN FRANCE

French biotech industries are currently developing 195 molecules, ranging in progress from the preclinical stage to phase 3 clinical trials. Among them, 87 are currently in clinical

Figure 1A: Origins of French biotech companies' partners (FRANCE BIOTECH, WWW.FRANCE-BIOTECH.ORG)



development: 41 products in phase 1, 39 in phase 2, and 7 in phase 3. The evolution of this pipeline is characteristic of the sector's new dynamism. In 2006, the number of drugs under development increased by

13% over 2004 and by nearly 22% over 2003.

In 2005, two-thirds of all French biotechnology companies covered activities in which the country has traditionally been a European leader: human health care (52%), cosmetics (9%), and food (5%). A slight dominance of biotechnologies is evident among French companies focusing on human health applications: drug discovery, vaccines, immunology, proteomics, and protein engineering, each constituting about 10% of the market. Monoclonal antibodies, gene therapies, and tissue engineering represent just 3%, 3%, and 2%, respectively. The main therapeutic areas covered are oncology (17% of developed products), infectious diseases (11%), immunity (10%), and central nervous system disorders (10%). Nearly a third (30%) of the products developed are targeted for treating rare conditions or hereditary genetic deficiencies.

Intellectual Property: France is one of the 27 European Union member states that are party to the European Patent Convention, which allows a group of national patents to be obtained through a single application to the European Patent Office (www.european-patent-office.org).

Employment and R&D: Despite the country's generally poor economic environment, French employment in the biotechnology sector has been increasing since 2002. In 2004, research employment represented nearly two-thirds (60%) of the total biotech workforce. The average emerging French biotech company employed 17 persons (of which an average of 11 were researchers). Apart from the exceptional case of BioMérieux, French-based biotech companies have yet to expand worldwide.

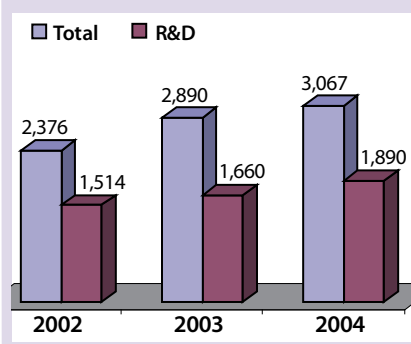
CEREP is the largest French biotech, with a team of 450 and annual sales of €51.3 million, whereas the principal investor in R&D is Flamel Technologies. French biotech companies declared about €1 million in sales revenue and allocated the same amount to R&D in 2005. On average, they spend between two and five times

Table 1: French biotechnology companies sorted by turnover (€ millions) FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)

Company	2004	2003	Rank
Cerep	51.30	34.10	1
Flamel Technologies	40.60	20.20	2
Genfit	12.20	11.80	3
Biogemme	10.80	8.80	4
OPI SA	7.10	4.50	8
Laboratoires Idenix Sarl	5.00	3.70	11
IDM SA	4.60	5.40	6
Cayla Invivogen	4.20	5.00	7
Argene	3.90	4.00	10
Ideal P4 Pharma	3.30	2.30	NM
TBF, Banque de Tissus	3.00	2.80	14
Hybrigenics	2.90	2.40	13
Transgene	2.50	2.50	16
Innate Pharma	2.10	0.24	NM
Trophos	2.10	1.50	NM

NM = new member in ranking

Figure 1b: Employment in French biotech companies (number of employees) FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)



less on R&D than their equivalents in the United Kingdom and the United States.

THE NEW FRENCH PARADOX

Despite a prevailing poor economic environment, progress in France's biotechnology sector has been made possible by the country's favorable regulatory environment, public incentives to small companies, R&D efforts, and public research partnerships.

Regulatory Environment: The regulatory framework for biotechnology in France is largely defined by EU regulations and the EMEA (the European Medicines Agency) guidelines. Most biotech products are evaluated by EMEA as products developed using biotech manufacturing processes as clearly

Table 2: French biotechnology companies sorted by size (number of employees) FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)

Company	2004	2003	Rank
Cerep	450	343	1
Flamel Technologies	222	177	4
Transgene	165	166	2
LFB*	160	0	NM
Biogemma	115	116	6
IDM SA	115	130	3
Genfit	105	97	7
BioMedical Diagnostics	78	125	5
Urogene	61	0	10
Nicox	56	62	8
Ideal P4 Pharma	48	48	12
Hybrigenics	47	49	11
Meristem Therapeutics	47	74	NM
Bioalliance Pharma	45	45	14
Genoway	45	40	NM

* department of biotechnology R&D only
NM = new member in ranking

Table 3: French biotechnology companies sorted by R&D expense FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)

Company	2004	2003	Rank
Flamel Technologies	25.9	16.1	2
LFB	25.0	0	NM
IDM SA	20.3	11.7	6
Transgene	19.9	20.2	1
Biogemma	16.9	17.3	3
Nicox	12.4	16.6	4
Genfit	12.3	10.5	8
Neuro3D	12.1	6.1	10
Cerep	11.9	11.8	5
Urogene	9.8	6.1	9
Innate Pharma	7.3	6.0	11
Diatos SA	6.0	3.7	15
Trophos	5.7	4.2	NM
Neurotech SA	4.7	5.3	13
Bioalliance Pharma	4.7	3.6	NM

NM = new member in ranking

identified in the mandatory scope of the EU's centralized procedure for marketing authorization application.

The French regulatory authority, AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé, <http://afssaps.sante.fr>), is recognized as a general reference in Europe for biotechnology products. In 2006, the agency considerably improved its external communication and increased its responsiveness. Now its website serves as a reference for information on healthcare products. By

A FLAGSHIP FRENCH BIOTECH COMPANY

Based in Marseilles, Innate Pharma was founded in 1999 to develop anticancer immunotherapy products based on the manipulation of nonconventional lymphocytes. The pioneering work of its scientific founders and research groups has generated three product platforms, each of which has been directly or indirectly validated in clinical oncology settings. Because of their mechanisms of action, Innate Pharma's drug candidates have strong development potential in fields outside oncology as well, particularly in the treatment of infectious disease and chronic inflammation. The company's most advanced molecule is in phase 2 clinical trials.

With a strong scientific positioning, a robust intellectual property portfolio, and real R&D know-how, Innate Pharma intends to become a leading player in the rapidly growing immunotherapy market. Before its IPO, the company had already raised some €50 million through three rounds of venture-capital financing (in 2000, 2002, and 2004), along with a reserved capital increase for its strategic partner, Novo Nordisk A/S, in 2006. In addition to Novo Nordisk A/S, investors in Innate Pharma have included benchmark biotechnology players: Sofinnova Partners (France), Alta Partners (USA), GIMV (Belgium), Axa Private Equity (France), Auriga Partners (France), INSERM Transfert (France), Gilde Healthcare (the Netherlands), Pechel Industries (France), Innoveris (France), NIF SMBC (Japan), and Quilvest Capital (France).

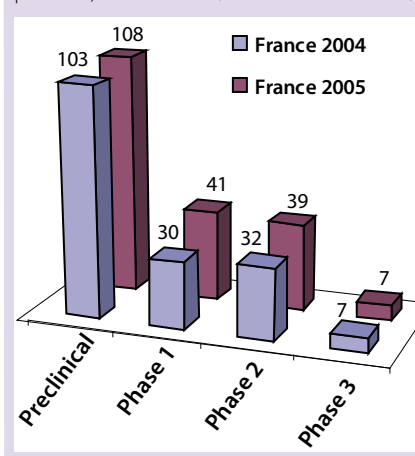
The company's R&D immunotherapy activities are ISO 9001:2000 certified. As of 31 August 2006, Innate Pharma had 66 employees, including 16 with doctorates in science, medicine, or pharmacy. For more information, go to www.innate-pharma.com.

2005, France had a strong position as Rapporteur and co-Rapporteur for centralized procedure applications, dealing with nine dossiers out of a European total of 57.

To fast-track the availability of certain innovative products, France authorizes restricted "pre-MAA" marketing for compassionate use in hospital environments. This procedure is known as authorization for temporary use (ATU). Although compassionate-use programs are also available in other European countries, the French program ranks alongside Italy's among the most advanced in terms of its regulation and authorizations. A key advantage of this system is that France allows

companies to receive payment for compassionate use of their products. Although acceptance into the ATU scheme involves a complex procedure, the AFSSAPS is transparent in its reasons for refusal. Currently, almost two-thirds (63%) of the products developed by biotechnology companies are first prescribed in hospital environments.

Use of embryonic stem cells in the European Union is regulated at a national level because ethical positions differ from one member state to another. France forbids the sale of or attribution of commercial value to human bodies or constituents thereof. Nonetheless, the French Ethics Committee (CCNE, [**Figure 1c:** Development pipeline \(number of products\) FRANCE BIOTECH \(\[WWW.FRANCE-BIOTECH.ORG\]\(http://WWW.FRANCE-BIOTECH.ORG\)\)](http://www.ccne-</p>
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ethique.fr) recently published its position on the commercialization of products derived from human cells and tissues and, more particularly, human stem cells. The CCNE believes it would be ethically acceptable to authorize therapeutic use of human tissues and cells as well as payment to companies for their engineering (processing of final products). That position could have an impact on future regulations.

A Constructive Funding Climate:

Although in 2005 total investments in Europe were 35% higher than in 2004, American biotech companies still receive 3.3 times more funding than their European counterparts. Venture capital investment represents more than half the funds invested in Europe. The percentage of risk capital in French company funding is much lower than that observed for its British, Swedish, Dutch, and Belgian neighbors. This essential role for

Table 4: Typical biotech companies in France (EUROPABIO, WWW.EUROPABIO.ORG)

Age (years)	0-2	3-5	6-10	11-15	16+
Employees	17	17	29	49	64
Revenue (€ million)	0.31	0.93	2.31	6.90	13.44
Research strength (personnel)	5	11	18	24	28
R&D budget (€)	0.57	1.08	2.70	5.90	2.87

Table 6: Typical biotech companies in the United Kingdom (EUROPABIO, WWW.EUROPABIO.ORG)

Age (years)	0-2	3-5	6-10	11-15	16+
Employees	16	16	26	54	70
Revenue (€ million)	0.31	0.62	1.52	10.60	16.51
Research strength (personnel)	7	11	16	15	26
R&D budget (€ million)	0.50	2.14	3.48	6.44	5.00

Table 5: Typical biotech companies in Germany (EUROPABIO, WWW.EUROPABIO.ORG)

Age (years)	0-2	3-5	6-10	11-15	16+
Employees	14	14	27	26	64
Revenue (€ million)	0.46	1.17	2.56	3.37	15.23
Research strength (personnel)	7	9	16	10	20
R&D budget (€ million)	0.75	1.36	3.50	1.81	4.67

Table 7: Typical biotech companies in the United States (EUROPABIO, WWW.EUROPABIO.ORG)

Age (years)	0-2	3-5	6-10	11-15	16+
Employees	15	28	49	77	109
Revenue (€ million)	0.53	1.51	4.67	7.63	20.92
Research strength (personnel)	9	18	27	47	41
R&D budget (€ million)	1.66	5.16	8.74	13.34	8.72

French biotech's success is mainly played by half a dozen firms: Sofinnova Partners, Apax Partners, Atlas Ventures, Banexi Ventures, Auriga Ventures, and Genavent. As financing sources, European stock markets do not play the same crucial role as the NASDAQ does for the biotechnology companies in the United States.

The number of French biotech companies is rising (225 in 2003, 233 in 2004, a 4% increase), although it is diminishing elsewhere in Europe:

- Germany (-6%)
- the United Kingdom (-6%)
- Sweden (-9%)
- Denmark (-3%)
- Norway (-6%)
- Switzerland (-3%).

Based on public incentives for small companies and R&D efforts, the funding climate for French biotech is one of the most favorable in Europe.

In 2004, the French government created a specific innovative start-up status for young, innovative

companies: Jeune Entreprise Innovante, JEI (2). This status exempts research-driven startups from paying social security contributions and local taxes. To qualify as JEIs, companies must be less than eight years old, allocate more than 15% of their total expenses to R&D, and have fewer than 250 employees. The French government has also used this new plan to encourage investors: All investments in biotech start-ups with JEI status benefit from a full and uncapped capital-gains tax exemption.

That has been a key driver in the creation of new biotechnology companies and in stimulating the growth of existing businesses in France. According to a survey by France Biotech (3), 74% of interviewed companies had chosen the young innovative company (JEI) status and made an average of 20.7% savings on social charges, about €52,000 each. That represents around €4 million of exemptions in the sampled companies alone. It was also found that those savings are largely

Table 8: French biotech companies sorted by total capital raised (€ millions) since their founding (FRANCE BIOTECH, WWW.FRANCE-BIOTECH.ORG)

Company	2004	2003	Rank
Transgene	242	242	1
Flamel Technologies	135	135	5
Nicox	127	101	2
IDM SA	99	89	3
Drugabuse Sciences	74	74	4
Meristem Technologies	65	65	6
Neuro3D	57	25	14
Hybrigenics	53	47	8
Neurotech SA	47	47	9
Exonhit Therapeutics	47	47	7
Innate Pharma	42	35	10
Novoxel	40	0	NM
Carex	38	19	16
Synt:em	34	34	11
Diatos	33	33	15

NM = new member in ranking

reinvested: 74% of companies hired R&D employees, 51% launched new R&D projects, and 49% bought new R&D equipment.

Along with its JEI measures, the French government has increased research tax credits in 2004. This system is significantly attractive. In most other countries, incentives are based only on year-to-year increases in reinvestment. With France's research tax credit (Le Crédit d'Impôt Recherche, <http://160.92.130.199/technologie/mesur/cir>) companies can now receive tax credits on a combination of their total R&D investment and year-to-year investment increase. Before 2004, this was previously limited to €8 million per company, but it was significantly extended to €10 million in 2006. The tax credit is used in France by more than 2,700 companies and represents €430 million savings.

Direct Public Funding: In recent years, France has significantly increased its direct investment in biotechnology (€140 million in 2003, €160 million in 2004), although this remains lower than biotech investments in Germany and the United Kingdom. It is clear that such state funding commitments will need to be reinforced in the future if France wishes to catch up with its neighbors.

Figure 1d: Biotech financing (2003–2005, US\$ millions) FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)

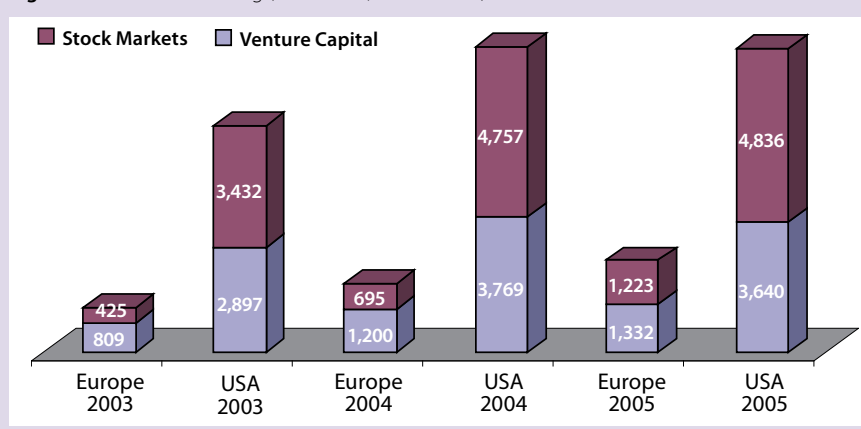
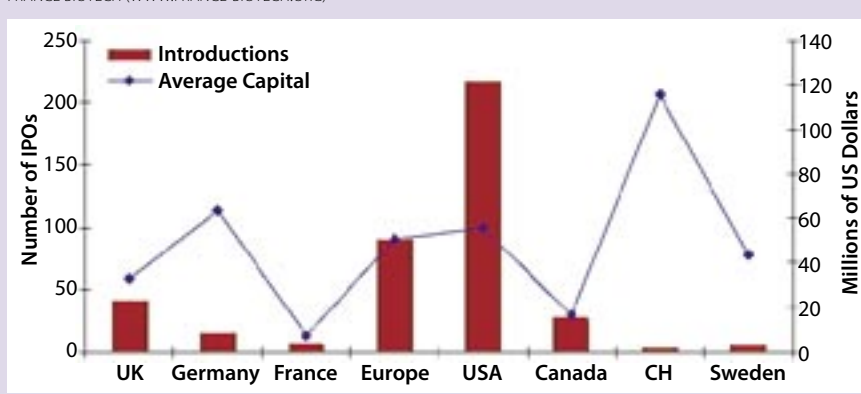


Figure 1e: Number of IPOs and average amount of capital raised 1996–2004

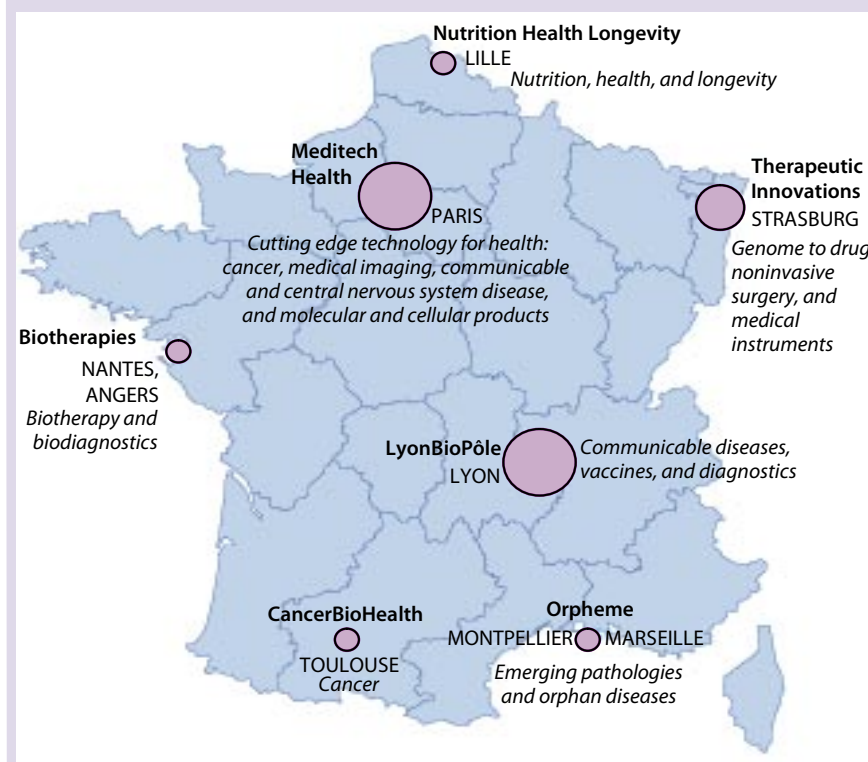
FRANCE BIOTECH (WWW.FRANCE-BIOTECH.ORG)





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Figure 2: Biotechnology regions in France (AFII, WWW.INVESTINFRANCE.ORG)



Until recently, the EU competition law imposed complex and uncertain limits for tightly controlling state aid (4). In 2006, a significant step cleared rules to entitle the national authorities to provide assistance for local research, development, and the introduction of new technologies. State aid of up to 100% can be provided for

- fundamental and industrial research and experimental development
- technical feasibility studies related to research, development, and investigation

• costs that smaller companies face in protecting their intellectual property.

Partnerships: One main characteristic of biotech companies is their partnerships both within and beyond their industry. In France, 38% of such partnerships involve public research centers with about 20 internationally renowned organizations such as

- the Pasteur Institute (www.pasteur.fr)
- Institut National de la Santé et de la Recherche Médicale (INSERM, www.inserm.fr)

- Centre National de la Recherche Scientifique (CNRS, www.cnrs.fr)
- L'Institut National de la Recherche Agronomique (INRA, www.inra.fr)
- Commissariat à l'Énergie Atomique (CEA, www.cea.fr), and the Curie Institute (www.curie.fr).

Those institutes lead a network that also includes numerous hospitals and university laboratories.

In the private sector, two-thirds of partnerships with biotech companies are European. For example, NovoNordisk has chosen France for a new production site to produce an insulin-pre-filled injection device (5). The French CEA in Grenoble has also recently been given the responsibility for coordinating Nano2Life, the first European Network of Excellence in nanobiotechnology. That grouping includes 23 specialized centers or regional “poles” from twelve European countries, with a group of 21 private companies also associated. French companies involved include BioMérieux, Thalès, and DGTec. American pharmaceutical companies are also present on the French landscape, representing 19% of all partnerships. They include Amgen, Baxter, Bio-Rad, Bristol-Meyers, Cephalon, Genzyme, Idenix, Johnson & Johnson, McKesson, Merck, Osteotech, Pfizer, and Wyeth. Another interesting trend is that 13% of French partnerships involve countries such as Israel and some Asian nations.

Biopoles: Networks and “bioclusters” have become the French industrial policy’s new tool for optimizing interactions between the different protagonists involved in technology transfer and helping companies grow by offering relevant infrastructure and assistance. The French government provides such centers of excellence with financing and tax incentives of up to €1.5 billion over three years. Seven of these centers specialize in healthcare as illustrated in Figure 2 (3).

The Institut National du Cancer (INCA) is a national plan against cancer initiated by President Chirac with the aim of reducing mortality

related to cancer by 20% between 2003 and 2008.

The "Canceropole" of Ile-de-France includes

- 100 hospital services
- 78 INSERM laboratories
- 40 CNRS laboratories
- 30 university research teams
- 10 CEA research teams.

BIOTECH ASSOCIATIONS AND GOVERNMENT ACTIVITY

French state policy is based on a strong consensus to focus on R&D and assist innovative small companies. This is led by a network of associations (see the box on this page) and government organizations. Their aim is to position France as a top-ranked European biotech locale by improving the economic, legal, and regulatory environment. At the broader European level, France Biotech and the LEEM are lobbying for tax incentives to encourage investors to invest in listed JEI companies, which should increase interest in such companies on European stock markets.

The current action is a plan for 2010 that aims at improving the country's attractiveness as a location for production of biologicals. This plan revolves around propositions centered on three main themes: improving the scientific and technical environment related to biological production, developing a stable and

attractive pharmaceutical policy for innovative products (and biologics more particularly), and adapting fiscal incentives available for R&D toward biologicals production.

EDUCATION

France offers high-quality, university-level courses in a number of biotech-related subject areas: health care, agro-food, environmental, and chemistry. The variety of training in France satisfies the employment needs of the local biotechnology industry for R&D and production. In new educational packages appear every year in response to the demands of a constantly evolving industry.

France offers some 600 university-level courses that provide students with an entry into the working world just two years after high school. Those wishing to continue on mainly do so at the universities and follow one of 300 masters-degree programs. Students also can choose between one of 30 engineering universities that specialize in biotechnology.

A LONG ROAD AHEAD

The French biotech industry's dynamism should drive investment in the near future. A continued and massive effort will be necessary to help France become a key player in the European biotechnology scene.

FRENCH BIOTECH ASSOCIATIONS

ADEBIOTECH: This committee came from the merger of the French branch of the European Federation of Biotechnology and the former ADEBIO organization. Adebiotech is a nonprofit association charged with providing information on the biotech industry in France. Each year it publishes a catalog of the French biotech industry. www.adebiotech.org

France Biotech is the French association of biotech enterprises and their partners. It brings together 150 members, which represent the majority of French biotechnology investments, pipeline activity, and employees. This association is working toward four key factors of success for a strong biotechnology industry: improving academic R&D dynamics and funding, ensuring a fluid chain of financing for young biotechnology companies (from seed funding to the stock market), working on the managerial environment, and improving the public's perception and understanding of life sciences. www.france-biotech.org

LEEM (Les Entreprises du Medicaments) is a professional organization representing the French pharmaceutical industry. That includes all enterprises devoted to research, development, and manufacturing of healthcare products in France, about 300 companies. LEEM represents 97.7% of pharmaceutical activity in the country. www.leem.org

RENOWNED UNIVERSITY PROGRAMS

INSA Lyon: The INSA network includes five of the top engineering schools in France. The Biosciences department at INSA in Lyon (southeast France) has trained 45 engineers specializing in biosciences each year since 1957. One of this school's strengths is to provide intensive knowledge in the life sciences (e.g., biochemistry, microbiology, and molecular biology) in combination with engineering. Students can also follow one of four masters programs: microbiology, mathematics and bioinformatics, ecology and biometry, and biochemistry. A PhD may be attained by completing a double-subject course.

ESC Grenoble: The Management School of Grenoble offers a masters degree in management of biotechnology companies. This course is unique in France and is naturally located in Grenoble, home to numerous biotechnology and nanotechnology companies: Protein Expert, Genome Express, Creacell, and Roche Diagnostics. With extensive local knowledge in life-science management supported by the Rhône Alpes region's industry, graduates are quickly placed with pharmaceutical and development support companies (e.g., consulting and venture capital).

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