

biotech focus

Spanish biotechnology: anyone for PYMEs?

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Spain, with 42 million inhabitants, has the ninth largest economy in the world and the fifth largest in Europe. It has a good education system and a successful, even if relatively small, local pharmaceutical industry, which has been divided traditionally into two sectors: the indigenous industry, which does everything from bench to bed-side, and a sizeable presence of major international pharmaceuticals, concerned mainly with sales and marketing but also with some important manufacturing capabilities. A third potential industry that is growing up independently of these two is the Spanish biotech industry. *Pequeñas y medianas empresas* (PYMEs), which means small and medium enterprises, is an acronym constantly encountered when dealing with this sector in Spain.

Educational infrastructure

Spain enjoys high education standards at many of its top universities, a fact that is evidenced by the high number of young scientists that find employment as postdoctoral researchers in other European countries and North America. The Spanish Government has recently taken steps about this loss of talent and has set up a repatriation scheme, to hold 300 positions in academic institutions for scientists who have done postdoctoral work abroad to return to Spain.

In a country with historically high levels of unemployment across all sectors and only limited opportunities for career development in academic research, this has meant that those not wishing to emigrate have provided a ready supply of highly qualified people at relatively low cost.

The indigenous pharmaceutical sector

Spanish pharma is concentrated mainly in and around Barcelona, where four of the five biggest companies with an R&D division have their main laboratory and production facilities (Table 1). The Catalan big four (Almirall-Prodesfarma, Esteve, Uriach and Ferrer) are all private family-owned companies that derive a significant proportion of their income from in-licensed products. However, they all have their own R&D divisions with pipelines based on in-house projects and significant experience in drug development. The fifth largest Spanish company, Faes, based in Leioa, in the Basque Country near Bilbao, is quoted on the Madrid Stock Market.

Biotechnology in Spain

Genoma España, the Government-backed institute for the development of genomic research, estimates that in Spain there are up to 300 companies engaged in some form of biotechnology activity. These companies have been classified in three groups: those entirely dedicated to biotechnology R&D (71), others that have some biotech R&D component (79)

and the rest that are user companies (49). The Spanish Association of Biotechnology Enterprises (ASEBIO) has provided a classification by sector indicating that 49% of the companies are focused on healthcare, whereas 37% deal with agriculture and animal food stuffs.

Science parks and incubators

Spain has a rich network of science parks set up to foster innovation. The Spanish Association of Technology Parks (APTE) currently counts 20 full members and approximately other 30 associated members. The majority of these parks is clustered around Madrid, Bilbao and Barcelona, but, as the APTE map shows (Figure 1), most Spanish provinces (autonomous regions) are represented. The Network of Science and Technology Parks, XPCAT, in Catalonia alone has ten parks, hosting 46 institutes and research centres, 115 research groups, 173 companies with 34 academic spin-off companies and employing a total of 4490 people. This represents an investment of €332 million.

There are three parks in Barcelona alone, and another, The Barcelona Biomedical Research Park, will be housed in a new building by the end of 2005 (Figure 2). Because of space limitations, we cannot look in detail at such a wide range, but, if we take the Parc Científic de Barcelona (PCB) at the University of Barcelona as an example, we see a rich mixture of companies and ventures (Box 1).

Case study: Zeltia

The Zeltia Group's Pharmamar is the undoubted star of the Spanish biopharmaceutical sector. The focus of the company is the extraction of natural products from marine environments.

biotech focus

TABLE 1

Data from the five major Spanish pharmaceutical companies

Pharmaceutical company	Sales 2003 (€ million)	Sales 2004 (€ million)	R&D spend 2005 ^a (€ million)	Total employees	Employees R&D	Products	Pipeline
Almirall-Prodesfarma	886.1	956.31	78	3321	500	Almotriptan, Ebastine, Almagate, Clebopride, Aceclofenac	COX-2, Phosphodiesterase inhibitors, Anti-muscarinics
Esteve	884	818	38	2391	254	Aciclovir, Captopril, Omeprazol	Cizolirtine, Substance-P modulator, 5-HT6, 5-HT7
Ferrer	250	270	19.5	1200	150	Sertaconazole, Ebrotindine	na
Uriach	174.2	145	17	717	150	Triflusal, Fosfosal, Flutrimazole, Rupatadine	Albaconazol, Cimicoxib immunomodulator
Faes	173.3	163	19.5	808	93	Diosminil	COX-2, SNRI bilastine, Flufenoxine

^aData from company literature and Lavanguardia 7 March 2005. Abbreviation: na, data not available.

Pharmamar filed an application for marketing authorization to the European Medicines Evaluation Agency (EMA) for Yondelis®, developed in collaboration with Johnson and

Johnson, for the treatment of soft tissue sarcoma. However, the EMA assessors voted against approval of the product. The company took the unusual approach of not

withdrawing the file, a fact that led to a strong public rejection by EMA and a subsequent appeal by the company – which was also rejected. Pharmamar has surely learned a great deal from this experience, which will certainly help the company with other compounds in the portfolio.

Case study: Advancell

Advancell was founded in 1999 by two researchers from the department of Cell Biology at the University of Barcelona and the University of Valencia and is located in the PCB. Originally set up to provide a range of molecular biology services to the pharmaceutical and cosmetic industries, it has steadily expanded its services to incorporate *in vitro* absorption, distribution, metabolism and excretion toxicity (ADMET) assay development and other support services. In 2004, the company moved into drug development, acquiring preclinical stage projects from the University of Barcelona and drug delivery technologies from the University of Santiago de Compostela. With six therapeutic programs in its pipeline, it expects to enter two products in proof of concept clinical trials this year. It will be interesting to see how Advancell and similar companies will be able to survive and even grow in the medium term. An important



FIGURE 1

Location of the 20 members (socios) of the Spanish Association of Technology Parks (APTE).

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TABLE 2

Service and products for a selection of Spanish biotechnology companies

Biotech company	Foundation	Location	Specialty	Investment	Product services	Pipeline compounds
AdvanCell	2001	Barcelona Science Park	Screening services, drug delivery, oncology	Talde, BCN Emprèn, Unirisco	CacoReady	ADV-P1, ADV-P5, ADV-P2, ADV-P3, ADV-P4
Crystax	2000	Barcelona Science Park	X-ray crystallography, drug discovery	Najeti, BCN Emprèn, Invertec	High throughput crystallization, protein expression, 3D structural determination	
Diverdrug	1999	Gava, Catalonia	Medicinal chemistry	na	Compound libraries	
Enantia	2003	Barcelona Science Park	Enantiomeric synthesis	Barcelona University	Chiral syntheses	
Era Plantech	2003	Barcelona Science Park	Plant derived therapeutic proteins	BCN Emprèn	Plant proteins	
Oryzon	2001	Barcelona Science Park	Diagnostics, bioinformatics	Najeti	Oncology, diagnostic kits	
Sistemas Genomicos	1998	Valencia	Genomic diagnostics, personalised medicine	na	Diagnostic kits	
Genetrix	2001	Madrid	Medicinal chemistry	National Biotechnology Centre (CSIC) Spin Out	Anti-inflammatory, anti-Alzheimer's	Gx305, Gx307
Digna	2003	Navarra	Drug discovery	Private		
Pharmamar	1986	Madrid	Drug discovery, marine products	Zeltia, Pescanova	Oncology	Yondelis, Aplidin, Kahalalide, ES-285, Zalypsis
Neuropharma	2003	Madrid	Drug discovery, marine products, neurosciences	Zeltia, Pescanova	Anti-Alzheimer's	Cholinesterase inhibitors, GSK-3β
Progenika (formerly Medplant Genetics)	2000	Derio, Bilbao	Microarrays, <i>in vitro</i> diagnostics	Cromoduro Holding, Iberdrola Gas, SPRI SGCRPV Venture Fund	Lipochip, IBD chip, rat genome, 5K microarray	

Abbreviation: na, data not available.

factor in this will be their access to capital, to fund their growth.

Investment

Invertec is part of CIDEM, the regional Catalan government's development agency. It specializes in seed financing, filling the gap for early stage financing of biotech companies. It can give up to €300,000 to a single company from a fund of €3.5 million. It was one of the backers of CrystaX, along with Najeti and BCN Emprèn.

Barcelona Emprèn SCR, a pioneer in venture capital for biotech in Spain, was set up by the City Council of Barcelona in 1999, to foster investment in innovative technologies and to offer strategic advice to start-up companies in the metropolitan region. It provides seed capital and start-up capital to new

technological and innovative companies (€150,000–€500,000). BCN Emprèn has also helped to fund Advancell, who recently succeeded in attracting a further €1.8 million round of funding from Talde, Unirisco Galicia and The National Innovation Company (ENISA). This indicates a growing sophistication both in the PYMEs themselves and in the funds available in the investment sector.

Barcelona Emprèn has financed three other biotech companies, Era Plantech, Crystax and Xcellsyz (this latest company is currently based in Newcastle, UK). At present, Barcelona Emprèn is raising a new fund of €10–15 million, which it will invest exclusively in biotech.

The Spanish public has shown an appetite for investing in Biotech. Pharmamar, 76%-owned by the Zeltia S.A group, has been very successful in raising finance on the Spanish

equity market. Its stock values have survived setbacks with the registration of Yondelis® (see above). This might be due to confidence in the product's eventual success, but also to the pipeline behind this leading compound (Table 2).



FIGURE 2
The Barcelona Biomedical Research Park

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BOX 1

Links to websites of interest

Science parks and biotechnology associations

Association of Spanish Science Parks www.apte.org	DiverDrugs www.diverdrugs.com
Association of Spanish Biotechnology www.asebio.com	Enantia www.pcb.ub.es/enantia
Zamudia Technology Park, Derio (Bilbao Region) www.parque-tecnologico.net	Era Plantech www.eraplantech.com
Network of Catalan Science Parks Xpcat www.xpcat.net	Genetrix www.genetrix.es
University of Barcelona (UB) Science Park www.pcb.ub.es	Instituto Biomar www.institutobiomar.com
Traditional Pharmaceutical Almirall Prodesfarma www.almirall.es	Neuropharma www.neuropharma.es
Esteve www.esteve.es	Pharmakine www.pharmakine.com
Faes www.faes.es	Pharmamar www.pharmamar.com
Ferrer www.ferrer-int-grupo.es	Pevesa www.pevesa.es
Uriach www.uriach.com	Progenika www.progenika.com
Biopharmaceutical (incl. natural products) Advancell www.advancell.net	Zeltia www.zeltia.es
ASAC www.asac.net	Bioinformatics Alma Bioinformatics www.almabioinfo.com
CrystaX crystax.com	Noray Bioinformatics www.noraybio.com
	Diagnostics Biokit www.biokit.com
	Oryzon oryzon.com
	Owl Genomics www.owlgenomics.com
	Pharmakine www.pharmakine.com
	Teknovas www.teknovas.com

Whereas much of UK and German biotech benefited from experienced people moving out of big pharma to share expertise and lead efforts, a much smaller talent pool is available in Spain. This is not an unbridgeable gap, as companies have sought to hire Europe-wide or seek consultancy and out-sourcing assistance for particular issues.

We have still to see biotechs spinning out of indigenous pharma. As these companies face more difficulties in funding the later-stage development of key compounds, they might be tempted to spin out smaller companies to raise funds and to develop these molecules. More innovation in the financial arrangements used to fund R&D

might also help the industry to move forward.

The future success of Spanish biotech might partly depend on how well it works with the traditional industry in the country. Spanish pharma can only benefit from the innovative potential of its nascent biotech industry. The biotech industry will also benefit from partnering with the considerable drug development experience of local pharma.

Local investors need to study their companies and learn more about the science involved, or seek help in learning. They also need to start developing more-flexible investment strategies that will accommodate the long term commitments required to see biopharmaceutical products coming to the market. With these strategies in place, Spanish biotech has the opportunity to become a major authority on the European scene in the medium to long-term.

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