GenIbet

A Biopharmaceutical Contract Manufacturing Start-Up

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A Healthcare Strategy Case Study

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Abstract

Title: Genibet – A bioharmaceutical Contract Manufacturing Start-Up

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The thesis that is by this means present under the form of a case study intends to emphasize the challenges faced by a Portuguese start-up, Genibet, upon its initial years of operations and the need to grow internationally. The case study may also be used as a learning tool, once it enables instructors and students to apply strategic knowledge and frameworks on a real life situation of a company.

Genibet is a biopharmaceutical contract manufacturing organization that provides cell, bacterial and viral production services to biopharmaceutical companies and clinical research institutes. Genibet's services comprise the production of cell banks, virus banks, plasmid DNA, polysaccharides, vaccines and virus with therapeutic activity, recombinant proteins, cells for cell therapy and virus like particles.

After analyzing the environment of the bio-CMOs industry, we were able to make some important keynotes:

- The biopharmaceutical CMO market amounted to over $ 3 billion in 2013 compared to approximately $ 2 billion in 2011. Regarding the two production segments within the whole market, the most relevant one is the animal cells segment (mammalian) since it is expected to have a CAGR of 14,2% (2011-2018) against a CAGR in between 10%-15% of the whole market.
- To address start-ups and clinical/research groups needs, the more adequate providers are the small contract manufacturing organizations since they have just the right size and capacity.
- The regions in the world with emergent countries are where the industry will experience greater growth, meaning that the larger CMOs will tend to move to those places. For the small-medium CMOs will be left to cover the mature regions where the growth will not be as fast – Europe and US.

The aim of the case study was to scrutinize Genibet's current situation and strategy in order to find some possible improvement solutions for the coming years. Together with

a mission to offer customers excellency and flexibility of services that will provide evolution of biological investigation, the company's values rely on "Safety, Commitment, Excellence, Flexibility and Groupwork".
Thus, three segments were analyzed: Client segments, Production Segments and Geographic Segments.

The hereby displayed case is based on a small company's real life situation and its efforts to stay on the market through competitive advantage generated by its different Business Model structure.

Resumo

Título: Genibet – A bipharmaceuticak Contract Manufacturing Start-Up

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A tese que é por este meio apresentada sob a forma de Case de Estudo, tem como objective enfatizar os desafios enfrentados por um start-up Portuguesa, Genibet, durante os seus primeiros anos de operações e a necessidade da mesma de crescer a nível intrenacional. O Caso de Estudo pode para além do mais ser usado como ferramenta de aprendizagem, uma vez que permite ao professor e aos alunos aplicar conhecimento estratégico e quadros de aprendizafem na situação real de uma empresa.

A Genibet é uma empresa que fabrica produtos biofarmacêuticos ara terceiros (Contract Manufacturing Organization – CMO) que oferece serviços de cultura de células e bactérias, bem como o desenvolvimento do processo viral. Os seus serviços incluem especificamente a produção de bancos de células, virus, DNA plasmídeo, polissacarídeos, vacinas e vírus com actividade terapêutica, proteínas recombinantes, células para terapia e vírus como partículas.

Após uma análise do ambiente da indústria de CMOs biofarmacêuticas, for possível reter algumas ideias-chave:

- O mercado CMO biofarmacêutico foi avaliado em $ 3 biliões em 2013, em comparação com apenas $ 2 biliões em 2011. No que diz respeito aos

segementos de produção existentes no mercado em geral, o mais relevante é o segmento de células animas (mammalian) uma vezt que este tem uma CAGR esperada de 14,2% entre 2011 e 2018,
contra uma CAGR de 10%-15% do mercado em geral.

- Para responder às necessidades de start-ups e grupos clínicos e de investigação, os fornecedores mais adequados são as pequenas empresas de produção sub-contratada, já que estas apresentam a dimensão e capacidade certas.
- As regiões a nível mundias que incluem países em desenvolvimentos são aquelas que expericiarão maior crescimento. Isto significa que as empresas maiores terão tendência em mudar-se para estes sítios. Para as CMOs de pequena e média dimensão, ficarão disponíveis as regiões que já atingiram maturidade e que, como tal, não apresentam um crescimento tão acelerado.

O propósito do Caso de Estudo for aprofundar a situação actual da Genibet bem como a sua estratégia por forma a descobrir potenciais melhoramentos para os próximos anos. A par com uma missão de oeferecer aos clientes excelência e flexibilidade de serviços que providenciarão evolução biológica, os valores da empresa assentam em "Segurança, Compromisso, Excelência, Flexibilidade e Trabalho de Equipa".

Desta forma, três segmenstos foram analisados: Segmentos ao nível de clientel, Segmentos de Produção e Segmentos Geográficos.

O caso aqui proposto é então baseado na situação real de uma empresa e os seus esforços para se manter no mercado através de vantagem competitiva pela diferente estrutura que o seu Modelo de Negócio apresenta.

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Contents

List of Exhibits

List of Acronyms

FDA – Food and Drug Administration

EMEA – European Medicines Evaluation Agency

(SdAbs) - Recombinant Single Domain Antibody

R&D – Research and Development

cGMPs – Current Good Manufacturing Practices

CMO – Contract Manufacturing Organization

ATMPs – Advanced-Therapy Medicinal Products

API – Active Pharmaceutical Ingredients

NDA – New Drug Application

I. LITERATURE REVIEW

1. Introduction

Biotechnology (biotech) describes any technological process that harnesses cellular and bio-molecular processes to develop technologies and products that help improve our lives and the health of our planet (Xin Song, 2014).

As a consequence of the discovery of DNA during the 50's and its recognition as the genetic material of all known living organisms, there have been enormous advances in the field of biotechnology. It has a broad range of applications, namely food modifications, genetic evolution and cloning, the environment, pharmaceuticals, human and animal health treatments.

Furthermore, Biotechnology has been progressively identified as a decisive aspect for the economic growth of all countries, apart from their stage of development.

The major intent of this chapter is to scrutinize relevant knowledge regarding the biopharmaceutical environment and its recent developments with the purpose of clarifying essential marks about how essential a strong business model is.

Therefore the Literature Review will be divided into by three sub-sections: Background of Biotechnology; Innovation and Socioeconomic Development; Contract Manufacturing Landscape, wherein the last one includes a) Main advantages of CMOs and b) Concerns of CMOs.

2. Background of Biotechnology

Biotechnology exists, in a way or another, for many years now. People have been shaping living organisms to deal with complicated questions and better their quality of life for millennia.

Biotechnology as we know it today consists of three historical types of coexisting biotechnological undertakings (Nef, 1998). The first one dates 7000 BC to 1940's and

can be identified by experimentation and very little input of science and engineering. It consisted of typical yeasts and fermentation for the manufacturing of food, drinks and energy.

The next generation (1940s to 1980s) was considerable more advanced and allowed the production of pharmaceuticals, chemicals and fuels by the usage of fermentation, bio-conversion and bio-catalysis. Here it is already evident the great input given by science and engineering.

The third phase (from the 1980s on) or modern biotechnology is based on molecular biology and the employment of genetic engineering procedures, such as recombinant DNA. Nowadays, the functions of the modern biotechnology are attached to all biological techniques, resulting in new processes and goods.

Recently, healthcare biotechnology has been pointed as a crucial driver of economic growth. But, in this particular area of biotechnology, value is added by a long and expensive R&D process – numerous clinical trials both in animals and humans, regulatory approvals and lastly product commercialization. The success depends on valuable inputs provided by multiple parties, including universities, venture capitalists, pharmaceutical firms, governments and emerging firms (Ebers and Powell, 2007).

In the years before the economic downturn, biotechnology industry was booming. Gary Pisano (2006) considers that given the lack of profitability of the industry as whole, this boom should not have happened. In fact, the industry of biopharmaceutical drugs depends upon the managerial assimilation of diverse competencies in a cumulative learning course, that on average lasts 10-20 years to yield a marketable product with extremely unpredictability about its success. After 30 years biotech still looks like an emerging sector (Pisano, 2006).

It is possible to nominate some successful companies such as the AstraZeneca Company, the Roche and Boehringer Ingelheim groups. However, despite the huge increase in revenues for the industry in general, most biotechnology companies do not make profit. Based on earlier estimations, Adams and Brantner (2006) state that, the cost of developing a new molecular entity varies between $500 million and $2 billion in 2000 dollars. A year later, DiMasi and Grabowski (2003) estimate the average cost (in 2005 dollars) of developing biologics is $1.24 billion and pharmaceuticals is $1.32 billion. Regarding the considerable funding needed in general on the industry, Hess and Evangelista (2003) admitted that in the first ten years of its existence, 10% of Biopharmaceutical firm's funding comes from venture capital, 50% from R&D

alliances with established pharmaceutical companies and 40% from public equity markets.

3. Innovation and Socioeconomic Development

There are several distinct definitions on innovation. For instance, for Everett Rogers (1983) innovation is "an idea, practice, or object that is perceived as new by an individual or other unit of adoption". To the author, innovation is simply an invention that is newly adopted; he does not find a connection between innovation, technology and management. Nevertheless, others have argued that these are not separated processes – and that innovation is essentially the first step in the diffusion processes (Agarwal, 1987). In this more elaborated line of thought, innovations are ideas or technologies that are continuously adapted as they are adopted, picturing consecutive socio-cultural change.

Conventional literature maintains that innovations are widely the result of individual inventors that hold great intellects, insight and ambition to take risks. Kash (1989) thinks that "These innovators make the market economy function as they are also entrepreneurs and have a drive for profit". This entrepreneurial mindset linked with technological progress is relevant to the case study because of the innovative way in which GenIbet manages its business model and is open to discuss the possibility of any unfamiliar new project.

Previously to Kash, Freeman (1974) had already described technological innovation as "an essential condition of economic progress and a critical element in the competitive struggle of enterprises and of nation-states".

Since early times, economists of diverse schools have stated that changes in technology can have a considerable impact on economy. When studying technological change and its economic effects, Schumpeter (1966), made the distinction between invention, innovation and diffusion. Technology is firstly built on the invention of ideas that are formulated. Besides invention, these ideas will be also called innovation since they are later used to produce and sell new or improved goods, processes and services. The author highlighted the performance of the entrepreneur that embraces the new acquisition of knowledge derived from the invention and converts it into trading output.

Furthermore, Schumpeter underlined the importance of the properly formulated search for new commercially explorable knowledge incorporated in the research and development (R&D) exercise of the companies. Cœteris Paribus, the more extensively diffused innovation, the greater its effects.

The links between innovation, productivity, health and wealth are widely recognized and the need to encourage innovation is also apparent: "Innovation is far too important to be left to scientists and technologists. It is also far too important to be left to economists or social scientists (Freeman, 1974)."

Focusing on the present case of study, Shwen Gwee (2013), believes that smaller biotechs have the upper hand with innovations because they can differentiate, scale capabilities, and reimagine and adapt old business models with risk.

4. Contract Manufacturing Landscape

Nowadays, enterprises progressively outsource parts of their supply chains to contract manufacturers. Within a broad frame of literature many advantages, problems and theories on outsourcing have been advanced, debated and evaluated.
Contract manufacturing can be characterized as a supply chain arrangement that allows a manufacturing company to outsource some of its internal manufacturing processes, e.g., assembly operations, to contract manufacturers (Kim, 2003).
While outsourcing assigns to any activity that a company used to perform itself but is now performed by another company, contract manufacturing (being a form of outsourcing) focuses only on manufacturing activities.

Numerous reasons led to the growth of the contract manufacturing industry. An increased pace of technological change coupled with a reluctance to invest in manufacturing equipment (Mason et al. Yan 2002), a booming economy, and increased global competition (Frohlich and Dixon 2001) drove OEMs to look to CMs as more than capacity relief valves, but also as important supply chain partners (Carbone 2000b).

While contract manufacturing was initially a top-gap arrangement that firms employed to meet demand when internal manufacturing capacity was insufficient (Carbone 2000b;

Kador 2001; Harrington 2000; Gregory 1995), it is now seen as shedding activities once considered strategic to focus their efforts and resources on core competencies in pursuit of sustainable competitive advantage (Kroes and Ghosh 2010).

Nevertheless, the company that outsources the manufacturing service, is still the owner of the product branding rights and is the one who sells the final good to consumers.

Finally it is relevant to emphasize that, although contract manufacturing services practices is recent nearly recent, Lurquin (1996) recorded some years ago that supply chain optimization is one of the strategic issues that the pharmaceutical and biopharmaceutical industry will face in the coming years.

a) Main Advantages of CMOs

The majority of articles concerning outsourcing refer to it o a strategic level.

Therefore, there are six main advantages enterprises can take by using outsourcing, according to Iloranta and Pajunen-Muhonen (2008):

- Cost savings
- Freed capital resources
- Technological advantages
- Concentration on core competencies
- Flexibility

In general, cost savings are achieved from technological/scale benefits that the producer can reach from large quantities. As a consequence, the in-house operations get less expensive since the units are produced at lower costs. Moreover, the company pays less for the final products and for fixed capital, as the company concentrates in offering few services in a more efficient way (Lonsdale, 1999).

Regarding freed capital resources, contract manufacturers benefit in the area of manufacturing costs by enjoying economies of scope and high capacity utilization by manufacturing similar products for similar industries (Plambert and Taylor 2005; McClintock 2002) and, at the same time, by outsourcing activities suppliers are able to free up some of its capital to other greater value added activities (Iloranta and Pajunen-Muhonen, 2008).

The idea of focusing on core competencies has been recognized in the strategy literature as a critical success factor in the long-term survival of a company (Prahalad and Hamel, 1990; Brandes et al.,1997). The outsourcer is allowed to focus on its core competencies since some of the functions, that are not part of the core competencies, are sourced out and resources are freed to more productive activities (Zhu et al., 2001).

Technological benefits arise when the company does not own specific technologies or would incur in high investments to acquire it. This brings benefits to outsourcers as cooperation with suppliers may give them new insights into new products or processes which could not possibly hope to generate itself (Mclvor et al., 1997). The suppliers have benefits too since as it concentrates on a manufacturing activity provided for several outsourcers, the investment on technology is rapidly recovered – scale advantage (Iloranta and Pajunen-Muhonen, 2008).

Finally, flexibility increases with outsourcing activities once the outsourcer is faster in answering consumers' needs – time-to-market – specially when demand suffers of unpredictability (Blanchette, 2004) or there are seasonal peaks (Iloranta and Pajunen-Muhonen, 2008).

b) Concerns of CMOs

There is an optimal degree of outsourcing, according to Kotabe et al., (2007). The outsourcing syccess relationship gets an inverted-U shape, meaning that as enterprises move more away from their optimal level of outsourcing, by sourcing-out or sourcing-in in excess, their performance will be affected disproportionately.
Likewise the advantages of contract manufacturing, Fan (2000) and Heikkilä & Cordon (2002) collected the most usual threats faced when outsourcing:

- Transfer of critical know-how
- Confidentiality and security
- Quality
- Changes in the balance of power

When the outsourcer focuses only on the stipulated core activities, he might lose crucial technical skills and knowledge once owned (Jennings, 2002). Moreover, the supplier is provided with producing process' information which can eventually lead to the opportunity of becoming one of the outsourcer's competitors (Blanchette, 2004). Outsourcing may result in the loss of control of that resource and enable other firms to enter the market or compete more efficiently (Venkatasen 1992) or may enable access to a resource through the CM that was not previously available.

Not less relevant is the difficulty found in controlling that the final products are delivered with the expectable quality and on schedule.

For the above mentioned reasons, developing partnership-like relationships is critical to linking purchasing strategy to corporate strategy (Watts, Kim and Hahn, 1992).

II. CASE STUDY

1. Genibet's Overview

Genibet Biopharmaceuticals, S.A operates as a biopharmaceutical Contract Manufacturing Organization (CMO) company in Portugal. It was founded in May 2006 and it is involved in providing bacterial cell culture and viral production services to clinical research groups, biotech and pharma companies. The company's core activities include the production of cell banks, virus banks, plasmid DNA, polysaccharides, recombinant proteins, vaccines and virus with therapeutic activity.

In 2009 Genibet was granted a GMP (Good Manufacturing Practices) certification for biopharmaceutical API production. Its facilities are located in the same building as the IBET – Instituto de Biologia Experimental e Tecnológica - Pilot Plant facility, being IBET a partner and the company's main shareholder.

As it will be explained in more detail ahead, biotech and pharrma companies have a similar set of stages to get through until product commercialization: Discovery; Pre-Clinical Development; IND/CTA; Phase I; Phase II; Phase III. Genibet's core activity is the manufacture and supply of goods for being used mainly in the stages of Phase I to Phase III clinical trials.

It was the first company in Portugal with clean rooms (cGMP) for biopharmaceutical production and also the first one to produce for clinical trials – innovative products not listed in pharmacopoeias.

2. Scientific Introduction

The aim of this section is to give the reader some highlights regarding the biomolecular scientific domain that is implicit in the Case Study. To better understand the next topics it is crucial to bear in mind some concepts and explanations.

Biopharmaceutical products are pharmaceutical products (for example proteins, nucleic acids such as DNA, RNA and antisense oligonucleotides, etc.) that are produced using biotechnology techniques. This means that the pharmaceutical products are

manufactured by living organisms (bacteria, yeasts, animal cells) and they can be genetically modified. Biotechnology is relatively recent; the first product sale was in 1982 with human insulin. Its emergence introduced remarkable progress in the pharmaceutical industry since it allowed the production of innovative drugs, a large scale production of the existing drugs and a more specific targeting of diseases and groups of patients. This targeting is achievable because the diagnosis is done from the particular DNA or biology of the disease and the new products are therefore based on genes, cells and tissue engineering whereas in the past, the same diagnosis only allowed to define the disease by its dimension and localization.

Particular therapies that can be done through biotechnology are Cell and Gene Therapy:

Cell Therapy – it is based on the introduction of new cells in the tissues of an individual to treat a disease.

Gene Therapy – it is based on the insertion of therapeutic genes on an individual's cells or tissues to treat a disease.

Biopharmaceuticals present many unusual production and regulatory challenges since they show a much higher level of complexity and heterogeneity than the common drugs. The first ones are large and complex molecules compared with the second (See Exhibit 1 and 2).

3. Biopharmaceuticals Pipeline – Genibet's role

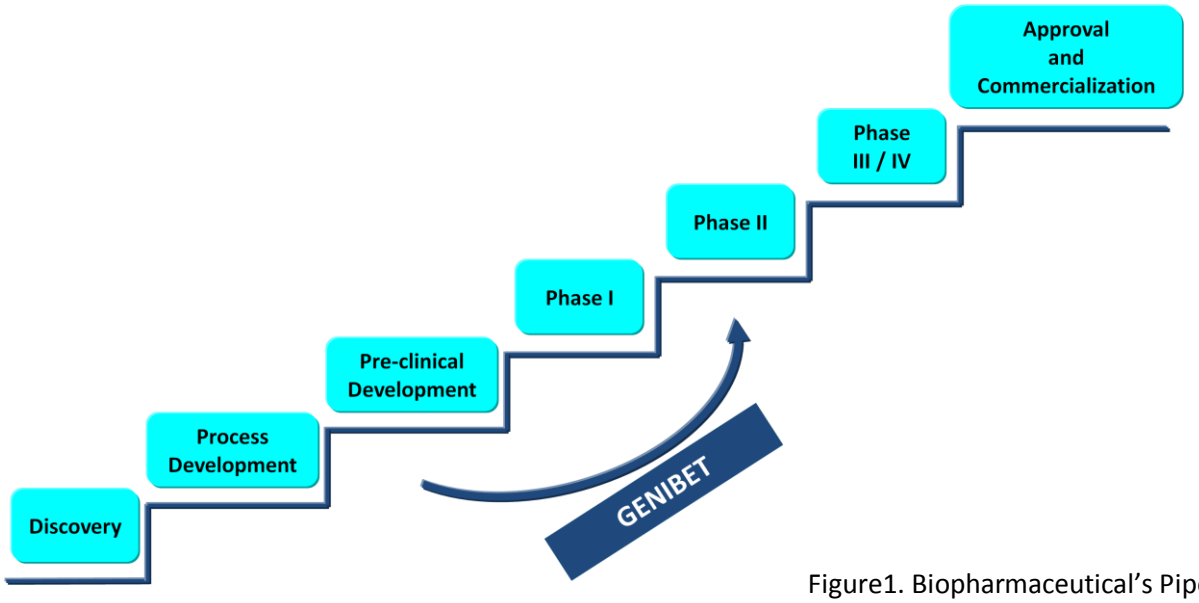


Figure1. Biopharmaceutical's Pipeline

Source: Author from in-depth Interviews

Biopharmaceutical's value chain structure usually follows the same stages of a drug's development from its early beginnings until the product is actually commercialized and all the process typically requires 10-15 years.

There are seven major stages in the biopharmaceutical pipeline (see Figure 1): Discovery, Process Development, Pre-clinical Development, Clinical Trials which include Phase I, Phase II and Phase III, and finally Approval and Commercialization.

Phase	State of Play
Discovery and Process Development	Target-molecules are identified and where a literature and patent evaluation are done. Also, at this stage, the potential lead compounds are identified.
Pre-clinical Development	Drug is tested *in-vivo* (on animals) or *in-vitro* to figure out if it is safe enough to test it on humans
Phase I (Clinical Trials)	Safety test: The drug is administered to healthy volunteers to access possible side effects such as

	toxicity, metabolism, absorption and distribution.
Phase II (Clinical Trials)	Reached only if the drug went successfully through Phase I trials and provides an efficacy test. The product is given to a bigger number of patients but, in this case, patients that have de disease for which the medicine was developed.
Phase III (Clinical Trials)	Tests are performed on a larger patient population in order to prove safety and efficacy in long-term use as well as find out the optimum dosage regimens of the drug. Generally, comparative studies against the best performers to treat the disease are done on this stage. There is also a formulation development – NDA - to be submitted to FDA or to EMEA.
Approval and Commercialization	If one of the two above mentioned entities approves the drug for safety and efficacy, it can be put in the market. There may be some further studies to evaluate additional side effects on more people.

Figure2. Phase's Table

Source: Author from Industry Reports in-depth Interviews

Genibet has a strategic valuable combination of partnerships and internal competencies that enable it to provide integrated services to biopharmaceutical start-ups and research groups. Biopharmaceutical start-ups and research groups often do not have the appropriate capacity for their manufacturing needs due to financial issues and also they often lack the knowledge of regulatory concerns. The needs usually emerge in Phase I-II of clinical trials. Besides handing over the GMP Production for Phase I-II for these

small companies, the partnership with IBET allows Genibet to arrange also the process development, analytical development of Animal Cells and Viruses (together with Clean Cells) and fill-and-finish.

4. Regulatory agencies – FDA and INFARMED

The biopharmaceutical industry is highly dependent upon regulatory entities that, besides being responsible for verifying if biopharmaceuticals are manufactured accordingly to the current Good Manufacturing Practices, ensure product quality, safety and effectiveness.

The risks that preoccupy companies the most are related to the contamination of drugs and facilities as well as the risks proceeding from the use of animal-derived materials. Contamination has serious consequences at a reputational and economic level, while the animal-derived materials present a constant challenge.

UD Food and Drug Administration is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. This department is in charge for ensuring the safety, effectiveness, and quality of pharmaceuticals, biologicals, and medical devices intended for human use as well as it is responsible for the surveillance of food, tobacco, dietary supplements, recipes and property of medications, among many other products, services and health devices.

The regulation programs vary extensively according to the type of product and its potential risks. The Center for Drug Evaluation and Research uses different prerequisites for the three main drug product categories: new drugs, generic drugs and over-the–counter drugs. New drugs, especially new molecular entities receive considerable inspection before FDA approval. These products require extensive toxicity testing on animals before a new drug is deemed “safe” for marketing.

Following this large period of animal testing, medicaments usually pass through three phases of clinical trials before they are considered for current human use. FDA reported that 92 out of every 100 drugs that successfully pass animal trials and go into human clinical testing fail during the human clinical trial phase.

This entity represents an obstacle for Genibet's clients since, only after FDA's approval the production of the products can be started for Phase I and II.

INFARMED is the National Authority for Medicines and Health Products. The goal of the agency is to monitor and regulate all activities relating to human medicines and health products for the protection of Public Health. Genibet has been subject to several audits by INFARMED and it has also been honored many licenses to produce new biopharmaceutical products. The company is well known for its regulatory expertise since the staff has regular training on regulatory concerns.

5. Production Services, Facilities and Human Resources

Genibet is a biopharmaceutical CMO that offers highly specialized microbial, cell culture and viral process development – Cell and Gene Therapy. The company's core activities amount to the production of cell banks, virus banks, plasmid DNA, recombinant proteins, vaccines using systems or animal cells as expression vectors, virus with therapeutic activity, virus like particles and cells for cell therapy. Hence, the specific services the company is able to provide are:

- Biopharmaceutical Process Development (in association with IBET)
- cGMP Bulk Biopharmaceutical Production
- cGMP Master and Working Cell Bank Production (bacterial and animal cells)
- cGMP Master and Working Viral Seed Stock
- cGMP Cell and Gene Theraphy Production
- Quality Control/Quality Assurance Services
- Fill and Finish
- Support Dossier Filing with different Regulatory Authorities

Genibet has a well equipped facility, comprising 1000 square meters of GMP upstream and downstream manufacturing facilities. These facilities were built with the most up-to-date technologies, being completely flexible in what concerns reconversion of the units with few monetary expenses.

It includes three distinct biological platforms with four different production units:

- Bacterial Unit – The bacterial unit consists in two divergent areas, a Biosafety Level 2 fermentation room with a 50L steel fermenter and a downstream production area. It is on these rooms that the production of biopharmaceuticals for clinical trials from phase I-II (sometimes also for phase III-IV) occur.

  The unit is equipped for all the appropriated actions for a bacterial facility: fermentation, harvest, clarification, solubilisation, culture media, supplements and inoculums preparation, buffer exchange, contaminants removal and filtration, etc.

  The products resulting from this unit are fragments, antibody proteins, vaccines, plasmid DNA and RNA.

- Viral Unit – The Viral Unit comprises two production areas, a Biosafety Level 2 bioreaction room and a downstream production area. Presently, the capacity used amounts to 50L but there is space to increase it over 200L bioreaction media. This unit

  produces drugs for phases I and II of clinical trials such as vaccines and viral vectors. Besides, the purification of the viruses produced is also performed in this unit as well as filling and finishing clinical batched may be performed in a class A isolator.

  Other relevant equipment present on the Viral Unit is a centrifuge, CO2 Incubators, a microscope, an autoclave and a refrigerator.

- Animal Cell Culture Unit – The Cell Culture Unit is devoted to the production and expansion of animal cell banks to be used in cell therapy. It has the capacity of 50L scale processes for cells in suspension and 100.000 cm^2 to adherent cells. Although the unit has a class A laminar flow cabinet, it is classified as a class B room.

- Fill and Finish Unit – The Fill and Finish Unit enables the semi-automatic filing of small vial series (1500 vials/hour-vials holding volumes of 0,1mL to 100mL). This unit works as a complement of the Animal Cell Culture and Bacterial Unit, it is for the filling these products manufactured in-house and also by other CMOs.

The company's human resources is composed by few people but extremely experienced, most of which have a PhD in engineering and scientific areas (see Exhibit 3).

There is not a formal Human Resources Management but it is possible to state that the staff receives broad qualified training "on the job". This vast training is done not only on core activities but also on regulatory affairs and that is the reason why Genibet recently was able to have a new business field – Regulatory Support Services – that is highly appreciated by the clients that do not have the possibilities to promote the expertise internally.

Genibet has an Administrative Council composed by five elements that are nominated in a shareholder's General-meeting. Part of this Administrative Council is a Executive Director that coordinates the different activity areas (See Exhibit 3). And regarding Genibet's accounting system, it does not formally exist too since it is included on IBET's accounting department.

Finally in what concerns Procurement, the acquisition of raw-materials, disposable equipment (largely used by Genibet), stock reception and conditions are done based on each project's requirements and needs (See Exhibit 4). The orders are usually performed be the Quality and Production Control systems and it is all recorded on a data base.

6. Clients and Valuable Partnerships

The majority of Genibet's customers are biopharmaceutical research groups and start-ups. These clients appear from their production needs mainly on the clinical trials in phases I-II.

Nevertheless, the company has also provided services to big companies such as Laboratórios Leti and Novartis Institute for Global Health, among many other biopharmaceutical groups in diverse countries.

Genibet has been exposed to clients in worldwide: Europe, North and South America and Asia. This expanding internationalization allows the company to see substantial growth in revenues each year.

Regarding Genibet's partnerships, the oldest and more important is the one with IBET – Instituto de Biologia Experimental e Tecnológica. It is a non lucrative top research institute headquartered in Portugal, whose main target is the biotechnology ground. By maintaining this strong link with IBET since the beginning, Genibet was capable of develop a steady reputation and extensive network in the marketplace. Besides, the relationship also allowed the company to have access to forefront technologies.

In addition, Genibet enlarged the set of activities offered through the establishment of alternative partnerships with companies that provide interdependent services that comprise the R&D stage and go until the GMP production. These partnerships include the analytical development of Animal Cells and Viruses that Genibet does together with the French company Clean Cells.

Genibet provides regulatory backing services along with Eurotrials which is a Portuguese company specialized in clinical research and scientific consultancy operating in many Latin American countries. Another relevant relationship Genibet maintains is the one with the Dutch company Cevec.

All these partners have also other partnerships and for this reason, Genibet not only benefits from a way of international expansion but is also able to offer its clients an integrated group of services and being a "one-stop-shop".

On top of that, the company has participated in many National and European Projects such as:

- Oncovir (QREN) – The Spanish company, IBET and Genibet have been working in a common project for a new medicine based on oncolylic adenovirus.
- Brain CAV – Along with an European Consortium formed of other eleven partners, Genibet is part of a research on new instruments to investigate brain maladies.
- SADEL – Genibet integrates an European Consortium that is working towards a new scaffold technology which allows therapeutics against Inflammatory Bowel Disease to be delivered orally.
- New Therapies, Novas Terapias (QREN SI Inovaçao) – The company was financed in 2011 through a loan to fund the facilities' construction.

7. The Business Model

So as to be competitive in the market, Genibet presents a solid Business Model in its core activities. The functioning of the Business Model can firstly be separated in two: the Support Activities (circles) and the Development and Production Activities (rectangles).

Starting by the outer circles, the first step is to evaluate clients' needs by clearly understand what they intend to have produced. For this reason, it is crucial to check in what phase (which square) they are already. The Documentation preparation refers to the reports required to be done during all the process to be delivered to the authorities. These documentation shall be carefully prepared and must include the description of what was produced, the materials used, among all the remaining details. Pre-sale and post-sale technical support comprises the services provided before and after the sales and can go from bureaucratic help with regulatory agencies or simply a consultancy project. Finally surveys are done in the end of each service offered by Genibet to assess clients' satisfaction.

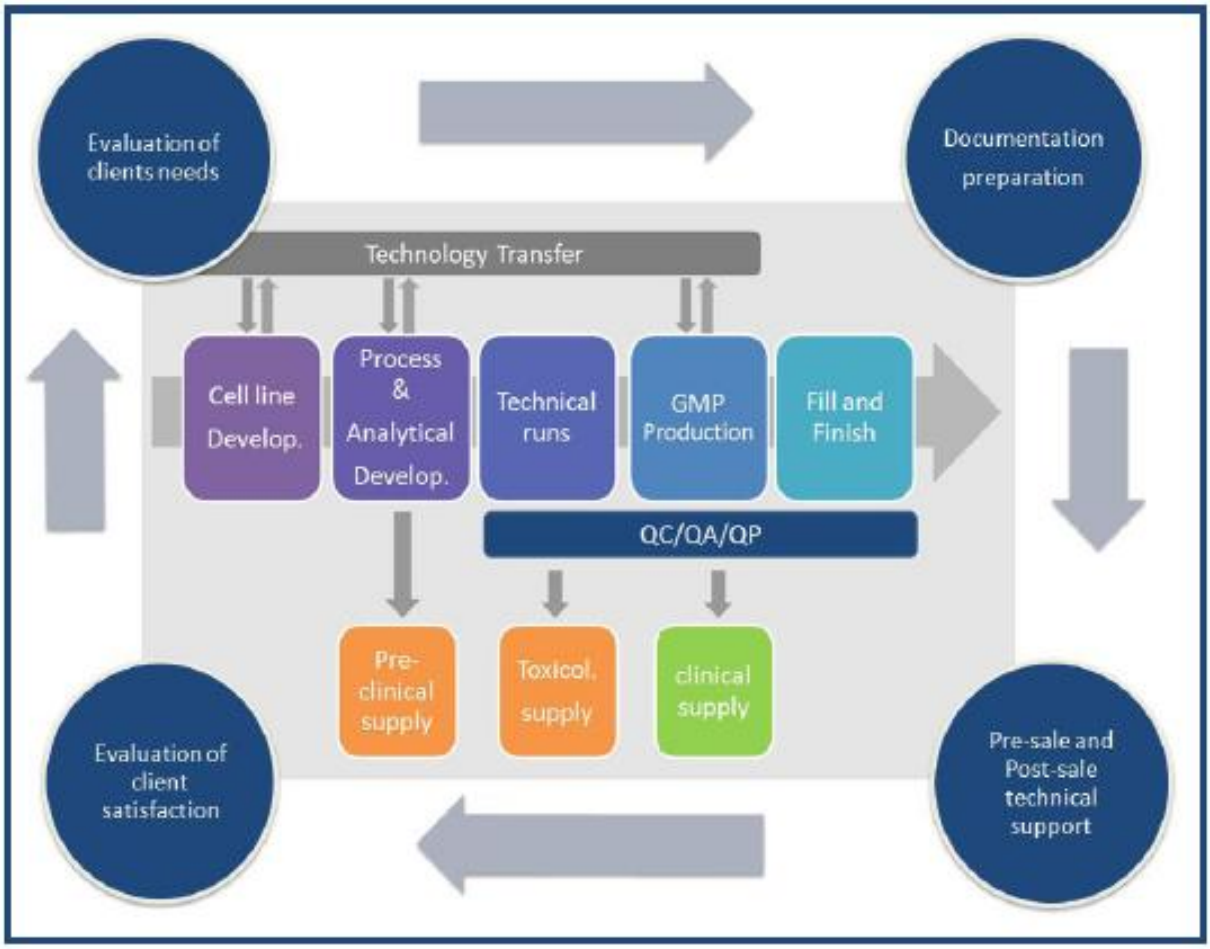


Figure3. Genibet's Business Model

Source: Company Reports – Investors, 2013

The inner rectangles are Genibet's core activities. Before explaining each of the rectangles it is important to emphasize that some companies contract Genibet to all these activities for a specific project, while others might just need one or two services from the rectangles. Besides, there is an action of technology transfer during the processes that can be done in cooperation with the clients or in association with many other partners, namely IBET which is the private research institute that is Genibet's main shareholder. Technology transfer with respect to clients refers to exact knowledge transmission, for example temperature or pH at which cells must be treated. Partners such as IBET, CEVEC or Clean Cells intervene in the process with technology transfer when, for instance, Genibet does not have all the needed material for one of the activities.

The Cell Line Development stage is where the first cell cloning is done to access the ease of replication. After that there is the Process & Analytical Development which are the analytical methods used to check if the substance is within the stipulated rules required by the above mentioned authorities.

The Technical Runs are no more than technological experiments so that production can be started. Technical Runs are followed by GMP Production where the scale production is activated. After GMP Production there is the Fill and Finish stage, here small bottles and sacks are filled ready for infusion or to be injected on patients.

Pre-clinical supply are pre-clinical assays to be done on simple animals, which if go well allow the next stage - Toxical supply – pre-clinical final assays to be done on more complex animals. If these two stages of experiments show a positive response, it is possible to move to the Clinical supply that is production for human testing.

As it was said above, Genibet has great interaction with its partners during the process, mainly with IBET, since they strongly complement the activities. This multiple partnerships help Genibet creating value for its customers through since its scope of services gets bigger and this distinguishes the company from the other CMOs of the same size. These partners, being older than Genibet have a greater network and knowledge on the market from which Genibet also benefits. Besides, it is also important to mention that Genibet is creating relationships with European SMEs lying on:

- Complementary services
- Complementary markets or market segments

- Complementary technologies

8. SWOT Analysis

Strengths	Weaknesses
• Close relationship with IBET and its state-of-the-art technology • Access to IBET and other partner's network • Only Portuguese biopharmaceutical company • International recognition through exposure in different countries and projects • Customized manufacturing through technical through scrutiny of clients' needs • Staff reputation and remarkable knowledge • One-stop-shop service through joint projects with partners • Regulatory expertise	• Limited capacity on the mammalian production unit • Great dependency on IBET • Little track record so far – the company is relatively recent • Weak economic situation – long-term debt amounting to €2,3 million
Opportunities	**Threats**
• Exponential growth of potential biotech applications and its products on the industry • Increase in the number of outsourcing from companies with in-house capabilities •Annual growth on the Bio-CMO market up to 10%-15% for the next 5 years • CAGR around 14,2% for the next 5 years on the Mammalian segment • Forecasted growth where Genibet is present, EU and US • A large portion of the new bio technologies and ideas come from Universities (Genibet's clients) • Growth of Biosimilars over the next years • Reduced Fill & Finish offer for phases I-II • Existence of incentives for technological innovation (subsidies)	• Industry highly regulated by authorities within a fast-paced changing environment • Market is over supplied, pushing the prices down – Chinese and Indian companies are entering the CMO industry • Economic crisis that persists in Europe • Great competition among the greatly fragmented industry as well as with the big pharmaceutics and CROs

Figure 4. Genibet's SWOT Analysis

Source: Analysis carried out for the purpose of this Thesis and adapted from Company Reports and In-Depth Interviews

9. Industry Analysis

a) Biopharmaceutical Industry Landscape– Market size and growth

Biopharmaceuticals differ from pharmaceuticals in terms of controlling quality and production. In what concerns R&D, pharmaceuticals focus their work on products modified by chemical processes, while biopharmaceuticals target natural substances and produce drugs that are modified through biological platforms. The second has higher probability of negative effects that have to be reduced, such as the variability of biological starting materials, contamination and instability of the active ingredients.

The industry is characterized by its uncertainty once only few drugs that are discovered attain the commercialization stage. It is estimated that the percentage of chemicals/biologics that come into the market is only 0,1. Although, biopharmaceuticals run a higher risk, they are able to deliver valuable benefits comparing with the existing drugs.

The global biopharmaceutical industry is currently worth over $145 billion (60% mammalian and 40% microbial), compared to $140 billion in 2011 and it s estimated that the industry should exceed $167 billion in 2015. In 2011 the number of biologics in the pipeline that were presumable to be approved soon, was bigger than 1200 in Europe.

The biopharmaceutical market is growing at a much higher rate than the pharmaceuticals', 15% and 7% respectively. This evident growth is the reason why the big pharmaceutical companies recently invested or even acquired biotech companies so that they too have a presence on the world of biologics. The research firm EvaluatePharma estimates that the industry will lose as much as $267 billion as a repercussion of patents expiring until 2020. Thus, the biosimilars market is likely to continue the spread in the EU.

As a consequence the leading players are focusing their means on Marketing and R&D with the purpose of leveraging their profits. Moreover, in 2011 the market value of biosimilars was worth $16.4 billion and the predictions point this market to be worth $200 billion by 2020.

b) CMO's

During the last years, the demand for biopharmaceutical contract manufacturing services increased at a compound annual rate of 13% per year and its market was worth approximately $3 billion in 2013. Contract manufacturing services became a crucial strategic choice for pharmaceutical and biopharmaceutical companies due to some underlying factors. For instance, the primary reason is to limit risks and cut down the global investment required to develop a new drug. On one hand the smaller biotechnology companies do not have capital access to invest in equipment and capacity to produce in large scale for the market or for phases I-II while the large ones try to improve its rationalization of assets and profitability.

The relevant part (28%) of companies that have in-house capabilities but still outsource production does it for specific reasons such as to benefit from production scales, lower costs, focus on core competencies, reach markets in different parts of the globe and access production technologies. As the pharmaceutical/biopharmaceutical companies are increasingly conveying parts of their value chain to CMOs, they are now considered strategic partners in terms of expertise and know-how (See Exhibit 5).

The rate at which biotech based drugs is growing is two times bigger than that of traditional drugs and almost 35% of the current drugs in the development stage of the pipeline worldwide are biologics.

However, biopharmaceuticals have to deal with challenges at a technical level as well as with strong investments. Moreover, since the CMOs act during the first stages of drug's development, they stand up to an industry over supplied resulting from the slowness in the number of authorized biologics and also from an increase of manufacturing productivity. Nonetheless, in 2013 there was still a growth on the outsourcing of biopharmaceutical manufacturing demand.

The sort of CMO players vary, they can be pharmaceutical companies with excess of capacity, small players that focus on targeted forms of the manufacturing system/niche biological platforms and CROs (contract research organizations) trying to increase their size in the market.

Although there are different types of bio-CMOs, their value chains follow similar activities. In order to start and to sign the agreement contract, the company and the

client have to establish the goals enclosed in the partnership and stipulate what needs to be outsourced regarding resources – Contracting.

Equally important is the R&D and Technology transfer, where the client needs to transmit the product research and development done so far so that it can be manufactured using the right technology. After the objectives are clearly established, the Production (Manufacturing) starts with upstream and downstream optimization and production – pre-development, screening, cell line construction, cGMP cell line construction, cGMP cell banking, process development, analytical services, scale up, cGMP manufacturing and regulatory support. The next stage is where the CMO hands over to the client the finished product and from then on it is expected that the two develop the relationship making the necessary adjustments to switch or add capacity.

c) CMO Customers

In what concerns the customers of CMO's industry, they can be distinguished in four groups: Large biopharmaceutical companies, Medium-Small and Virtual biopharmaceutical companies, Biopharmaceutical Start-ups, Clinical/Research groups. While the Large companies outsource production to maximize productivity and focus on core competencies, the smaller ones usually do not have the required capacity to perform production. These companies also do not have proficiency to manufacture biopharmaceuticals nor the means to build cGMP facilities.

Start-ups specialize just in inventing new drugs and therefore they are financially limited to produce its discovering. All the processes from development until regulatory issues are left for experts on the respective areas.

Finally there are the Clinical/research groups that, similarly to the Start-ups, have monetary limitations to produce and lack the knowledge about regulation. Yet, there are many Clinical/research groups that pass to the clinical trial phase specially those working in advanced therapies and tissue regeneration.

d) CMO Market Distribution

The market of Contract Manufacturing Organizations can be segmented by its geography, the type of production (mammalian or microbial based) and by its use (clinical studies or final production).

In 2013 the earnings of the overall CMO market was approximately $ 41,2 billion while in 2017 the same market shall be worth around $ 62,8 billion. Starting by the Geographic Segmentation, the majority of revenues are originated in the US, Latin America, Europe, India and China. The US and Europe shall lose weight on the market between 2012 and 2017 to the other regions above mentioned (see Exhibit 6). This is due to the fact that developing countries are growing at a much higher rate and therefore it is expectable that the bigger CMOs allocate their production on those regions in the future.

In what concerns the type of production, as mentioned above, it can be Mammalian-based or Microbial-based manufactured. The Mammalian-based manufacturing accounts for two-thirds of the CMOs Market and has a higher revenue growth rate comparing with the Microbial-based manufacturing (see Exhibit 7). Unlike the Microbial Contract Manufacturing Market that is mature and stable, significant growth is expected in the first segment (a 14,2% CAGR between 2011-2018).

Besides, the advanced technologies, the noteworthy prosperity of mAbs in oncology and the fact that there are only a minority of companies with the convenient know-how and production facilities show a bright future for this segment.

Lastly, regarding CMOs segmentation by its use, services are offered for clinical study usage or for entire final production. The final production segment that comprises manufacturing for commercialization (Phase III), accounts for 85% of the overall CMO industry and was expected to grow by 12,5% between 2012 and 2017, reaching $54,7 billion by 2017.

On the other hand, the increase of the global CMO market for clinical trials (Phases I-II) is expected to be only 8% for the same period, amounting $ 8,2 billion in 2017.

10. Competitors Analysis

a) Main Players Audit

The players in the biopharmaceutical CMO market are very scattered since distinction can be made based on:

- The extension of services provided, which can go from analytical services and development, regulatory advice, medicines development and manufacturing for phases I,II and III
- Company's dimension concerning staff and production facilities/platforms

In general bigger biopharmaceutical CMOs act globally since they are technologically steady in many areas. In addition, as they own larger manufacturing capacities, units are more spread around the world and it is possible to offer a great variety of services that can go from drug development, full analytical services, analytical development and production for clinical trials from phase I-III, while small companies are usually only able to focus on one or two competencies.

Among the large ones, which are Genibet's indirect competitors, are Rentschler, Lonza, Catalent, Boehringer Ingelheim, Patheon and Royal DSM.

Company	**Indirect competitors – Large size**
Rentschler	Its focus is on only one animal cell culture. This company is currently increasing its capacity.
Lonza	The company is a good example of one that takes part in every biological manufacturing platforms. Being the biggest CMO worldwide, it is already present is 5 regions. Its revenues amounted to $ 3,6 billion in 2013.
Catalent	It is one of the big fice bio/pharma CMOs that had up to $ 500 million of revenues, $ 1,6 billion in 2013, with 8300 employees.
Boehringer	The group is one of the world's leading pharmaceutical companies, being the largest privately held owning 135

	affiliates spread by 47 countries. By 2013 its revenues were of $1,5 billion.
Patheon and Royal DSM	The two companies recently merged in a $ 2,65 billion deal, turning into the second world's largest CMO. It has now three main businesses: fine chemicals and API production, pharmaceutical services that include contract manufacturing and proprietary products and technologies.

Figure 5. Indirect Competitors' Table

Source: Author from Industry Reports and In-depth Interviews

Regarding Genibet's direct competitors, from which the majority have bigger capacities and higher market shares in the biopharmaceutical industry (>1%), it is possible to name twelve that dedicate to the production of therapeutic proteins from animal cell culture. Few of them make bacterial fermentation and fill & finish. There more small bio-CMOs that can be considered Genibet's competitors but not as similar as the twelve referred below (see Exhibit 8).

Country of Origin	**Company – small/medium size**
US	• Florida Biologix • Vista Biologicals • University of Alabama at Birmingham • The University of Iowa
Germany	• EUFETS • SellWiss Pharma Biotechnology BioUETIKON (also Irish) • Biomeva

Scotland	• Angel Biotechnology
England	• Clinical biomanufacturing facility – University of Oxford • Cobra biopharmaceuticals • Eden Biodesign

Figure 6. Small/Medium Competitors' Table

Source: Author from in-depth Interviews

b) Competitive intensity – Applying Porter's 5 Forces

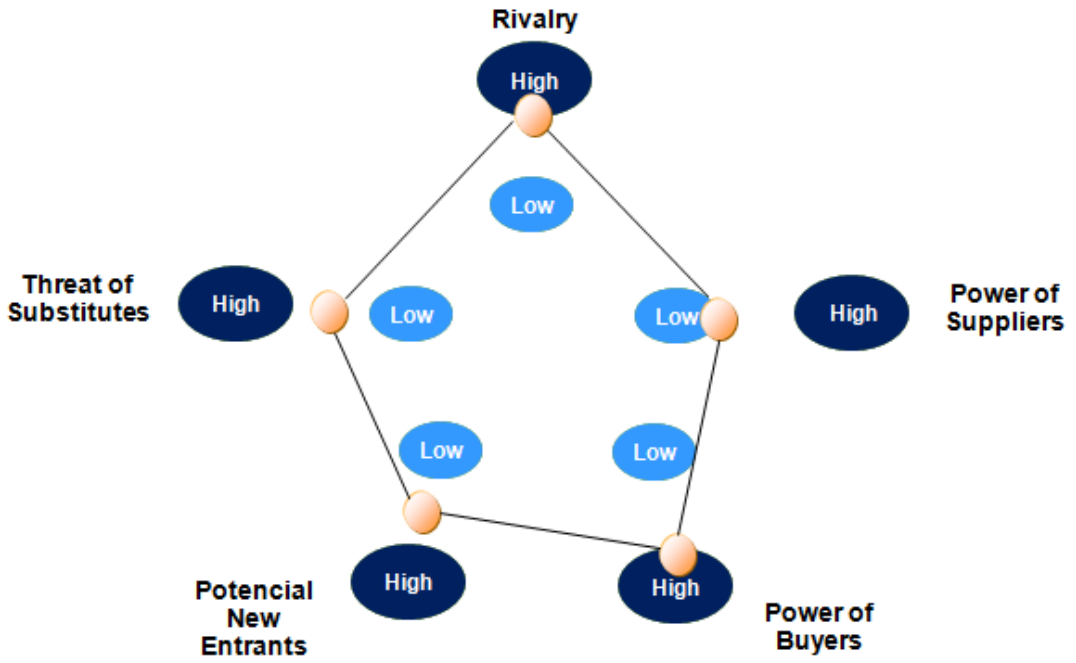


Figure 7. Porter's 5 Forces Analysis

Source: Analysis carried out for the purpose of this Thesis and adapted from the Industry Analysis

Rivalry in the industry – The existent rivalry is high. The CMO industry is significantly fragmented since there are a lot of small/medium sized companies, meaning that it is highly competitive. All these CMOs work hard towards competitive

advantage by providing a wider set of services, by specializing on regulatory affairs and by being flexible.

Power of Suppliers – The suppliers can be divided in two, raw materials suppliers and equipment suppliers.
The acquisition of raw materials is done based on each project needs. Usually on the bio-CMO industry the raw materials are relatively standardized and therefore, the level of negotiation power by the suppliers' side is low.
On the other hand, equipment suppliers have a higher power if negotiation that can be considered moderated. Due to the need that this equipment is technological advanced, the industry of its manufacturing shows a great know-how, resulting in few suppliers that can set higher prices.
Balancing the two types of suppliers and their negotiation powers, the supplier power is low/medium. However, there are switching costs for companies on changing its suppliers; qualification and bureaucracy attached are very time consuming which can affect companies' performance.

Power of Buyers – The power of buyers is greatly influenced by its dimension and capacity. For instance, big biopharmaceutical companies have high power over CMOs, whereas start-ups and clinical research groups have little negotiation power.
As in general, the biopharmaceutical industry has many small participants, there is a risk that the large buyers make use of backward integrations.

Potential New Entrants – The threat of new player's entrance into the industry is medium. Despite the considerable number of boundaries to enter the industry of bio-CMO (government control, patented technologies, economic resources, staff expertise, cumulative knowledge and customer contact networking.), it is possible for big pharmaceutics to acquire biopharmaceutical companies and entering the market automatically.

Threat of Substitutes –The primary substitute is the potential increase of capacity on the biopharmaceutical companies themselves, meaning that they can start producing their own medicines instead of outsourcing production. However, what recent events demonstrate is that the opposite is happening; many companies with in-house

capabilities outsource production order to optimize the value chain processes. If contract manufacturing is increasing and the CMOs' knowledgeable and experience human resources mean high switching costs, the threat of substitutes is low.

The analysis indicates that price competition is unlikely since, although there is a growing rivalry among the CMOs, the industry is profitable and also growing enough to compensate it.

11. Market Determinants and Forthcoming Tendencies

Even thought bio-CMO industry is relatively new, its importance is already noticeable and the years ahead are likely to be of growth and change.

To begin with, there is a rising demand for biologics due to their innovative nature of treating serious diseases such as cancer, diabetes and HIV. Joining this increasing hope held on biologic drugs and since they are considerably more complicated to indentify and produce than traditional pharmaceuticals, the demand for CMOs' services is also increasing. The demand for biologics has a predicted annual market growth of 15%, wherein the CAGR for the bio-CMO market lies on 10%-15%.

The high demand for CMOs services is a consequence of several factors such as CMOs' ability to rapidly answer to the industry changes. Moreover, the unpredictability of the market leads the drug companies to invest less in new producing systems. Outsourcing production to CMOs is then the best option when capital optimization is needed to launch new products. Besides, there is the benefit on time, gained by pharmaceutical/biopharmaceutical firms that choose not to develop manufacturing practices and leave the process for experts.

Time is efficiently saved once CMOs own immense knowledge regarding the analytical process development, production and regulatory issues. But the advantages of outsourcing do not end here; producing costs represent a large portion of pharmaceutical and biopharmaceutical companies' total operational expenditures (23%) and shareholders are pressuring for costs to be reduced. If so, economies of scale can take place for most of these firms.

Predictions point out an increasing demand bio-CMO outsourcing in EU and U.S, accompanied by a growing adherence from CMOs to engage even more in one-stop-

shop services that allow a greater offering range in what concerns biopharmaceuticals' pipeline covering. All these elements result in solid strategies of alliances between drug makers and CMOs which bring win-win scenarios.

Although the future landscape seems very positive, there are some concerns too.

Firstly, as the number of competitors increase, the pressure for prices go down also increase resulting in lower margins. Contributing for these price reductions are countries like India and Chine where CM services cost half of what they cost in European countries. In addition, there are a lot of generic companies entering the industry and, on top of that, CROs and large bio/pharma firms are also seeking to enter the market. CROs are including manufacturing practices through vertical integration and the big drug makers by joint ventures or acquisitions that enable them to increase production capacity.

Another concern might be the exposure to risk in which CMOs incur because of customers that request performance based contracts on pricing structures, forcing CMOs to reach dealt KPIs. This issue is also linked to contract manufacturing companies' financial situation, funding for biotechnology start-ups is a challenge as a consequence of the persistent economic downturn leading to a smaller quantity of biopharmaceuticals in progress and consequently, reduced demand for CMO services.

Finally, still on the concerns, there is regulation which on the drug industry is highly strict. This influences companies' the cost structures and also adds pressure on prices.

All in all, on one hand the industry is facing excessive supply of CMOs capacity but on the other hand, the demand for outsourcing biopharmaceutical production is still growing at a 15% rate and it is expected to be growing for the next years. Moreover, the mammalian segment within the biopharmaceutical market will help support the contract manufacturing industry (CAGR of 14,2% until 2018).

In short, the industry continues to be appealing due to the growth predictions but it will get more challenging as well.

a) What distinguishes a CMO – Critical Elements

After the industry analysis it is possible to evaluate the factors that contribute the most for bio-CMOs' success.

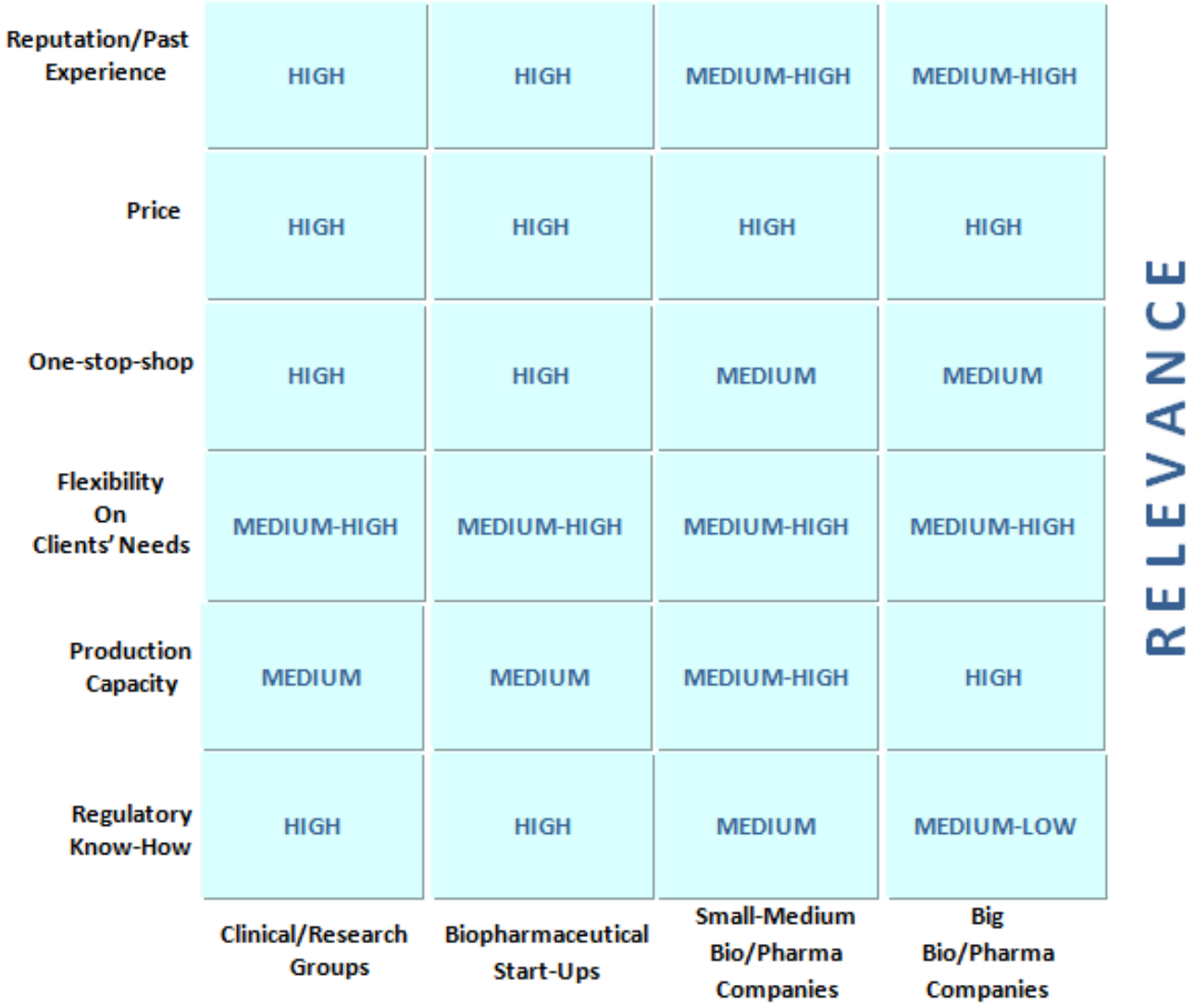


Figure 8. Success Factors of bio-CMOs

Source: Author's adaptation from Industry Reports and In-depth Interviews

Genibet belongs to the group of Clinical and Research Groups due to its manufacturing capacities and size. Regarding the Critical Elements elected as success ones, the company is well positioned.

Firstly, it is important to mention that most relevant factor of all is **Quality**, not included on the Exhibit for being an unconditional prerequisite for pharmaceutical and biopharmaceutical markets.

Genibet's facilities were built strictly according to the requirements of the industry.

In what concerns **Reputation and Past Experience,** the straight bonds with IBET since its early beginnings, helped Genibet creating notoriety on the market much faster than if the company would have had to set for itself. The relationship brought, however, benefits for both sides since the two groups function as complements in many projects. After the leveraging derived from the relationship with IBET, the company was able to keep building experience and name by selecting valuable staff and by maintaining exceptional relations with regulatory authorities.

Also, Genibet specialized in regulatory issues, training technicians to find adequate solutions on the field for each client – **Regulatory Know-How**. In both areas the company is well positioned since the relevance is high on the industry both for reputation and knowledge on regulatory issues.

Besides, the vast network of partners worldwide enable Genibet to offer a integrated **One-Stop-Shop** service to its customers, that might go from Process Development, Analytical Methods Development, Quality Control Analysis, Regulatory Consultancy and Production – Clinical Trials. In addition, the partnerships work as complements for the majority of relevant projects Genibet engages in, as each company/group has a certain set of resources needed for one client order. This allows the company to be extremely **Flexible** for specific needs.

In what concerns **Price,** Genibet offers competitive prices due to its simple internal organization.

12. Main Challenges

Geographic Targets

As seen before, the company has, in the present, businesses South Korea, United States and Europe. As any start-up, the goal is to grow in the future and have a sustained geographic expansion. Through the industry analysis and in-depth interviews done in

order to understand Genibet's priorities, it is possible to identify new markets and improve services offered on the existing ones:

Mexico – It is a potential market for Genibet to enter since the biopharmaceutical industry has been growing its importance in the country for the last decade. There are already over 130 companies, start-ups and research groups specialized in biotechnology and the industry currently employs more than 0,2% of the Mexican total population. Besides, the country is now politically stable the Government is promoting the attractiveness on this market through numerous initiatives.

Brazil – Along with Mexico, in Brazil the biopharmaceutical industry is experiencing considerable growing and the Government is also supporting this growth. Moreover, Brazil has straight commercial relationships with Portugal in many other industries and the fact that, the language and culture is similar, certainly facilitates transactions and partnerships. A lot of Genibet's partners already have links with Brazilian enterprises.

United States – Being a western country, the values and norms are similar to the Portuguese ones and, although the language is quite different, it is a language a language that Genibet's staff is very familiar with. Moreover, the US is the region where Biotechnology is developed the most, having the largest portion on the biopharmaceutical market (42%) and so there are great opportunities for growth. The biggest advantages here are that Portugal has low labor costs in comparison with the US and also, there is a positive political link that have been easing business with the country for some years now.
IBET has a huge network of partners in the US and it is important to mention that Genibet has recently established contact with a venture capital from Boston – Flagship VetureLabs – that work as innovations incubator. Genibet will provide services to one of the new projects of this company, and has already the Bacterial unit fully occupied on last 4 months of 2014 and first 6 months of 2015.

South Korea – The growth of the biopharmaceutical industry on Asia is clear, being the continent where the market shares will grow the most in the future. There are some South Korean CMO competitors but owning much less expertise on regulatory issues than Genibet, The country is positioned as the 12th regarding patents detention and

biomedical funds. However there are some concerns regarding the difference in languages, the distance between Portugal and such countries and also the difficulties on transportation.

Europe – It has the same regional trading bloc, same currencies, similar law and all the countries are relatively close to Portugal. After the United States, Europe is the biggest market in biopharmaceuticals. The growth of the industry is expected at a CAGR of 9,5%, which is positive but smaller than in the past since Europe is currently facing stability.

The challenge for Genibet is, on the short-run, to stabilize and toughen its financial situation by growing importance on the countries where it is already present – Europe, U.S and South Korea. The next step would be to increase the presence on the same countries by increasing the number of partners there, as well as expand partnerships to Brazil.
On the long-term, the goal is to increase capacity and consequently the current services provided, so that the company is able to enter Mexico and Asian countries.
Besides the geographical expansion and sales growth, Genibet aims to increase its clients' satisfaction level by being even more open to discuss innovative products, production developments and time barriers.

Consumer Targets

The present segments Genibet is targeting are Clinical and Research groups and Biopharmaceutical start-ups, that the company intends to maintain. Accordingly to the analysis done, the direction in which Genibet is going regarding segments is the right one assessing by its current producing capacities that meet these groups' necessities.
Usually Clinical and Research Groups as well as Bio-Start-ups focus on the area of Advanced Therapy, fields where the company is being evolving and investing, particularly on Animal Cell and Viral Units for these therapies.
Other segments are not reachable by Genibet since their manufacturing needs are typically much bigger than the company's capacity. However it is possible to have

determined projects with small/medium/large biopharmaceuticals, such as for instance the collaboration it has with Novartis Institute and with Laboratorios Leti.

Production Targets

The services offered include:

- Master and Working Cell Bank Production for Microbial (50 liters)
- Master and Working Cell Bank Production for Bacterial (50 liters)
- Master and Working Cell Bank Production for Animal Cells (50 liters)
- Master and Working Cell Bank Production for Viral Seed Stock (50 liters)

The predictions show that the Mammalian segment will have a compound annual growth rate of 14,2% in the coming years and so, the challenge that arises for Genibet would be to expand the animal/mammalian cell unit and invest even more in technical know-how on this area.

Pricing

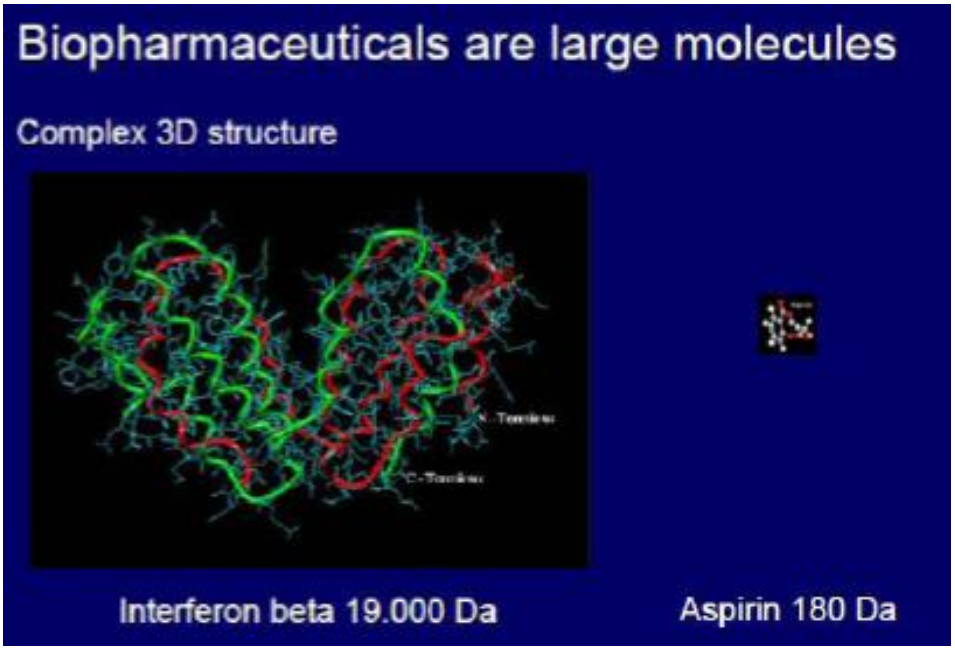
In what concerns pricing, Genibet stipulates prices given its variable costs and set margins. It is extremely difficult for the company to benchmark direct competitors on pricing due to the highly fragmented industry of existing small players. The markup margins of Genibet are relatively high, allowing profitability in all the services offered. From the industry analysis done, price poses a challenge in regards to keep margins, as the overall industry prices will tend to go down because of the new entrants.

Although Genibet faces a highly fragmented industry full of small, medium and large size competitors, and the future facilities' expansion is challenged by a current weak credit environment, it was possible to understand from the analysis done on Genibet that small CMO's also face great opportunities of growth and prosperity.

Furthermore, the company chooses to keep its position in the marketplace at the same time that it tries to find answers for the difficulties. Were the concerns on competition and financing more critical on the short-run? Or will they persist and get more accentuated? Were the geographical, client and production target options the best Genibet could have done so far?

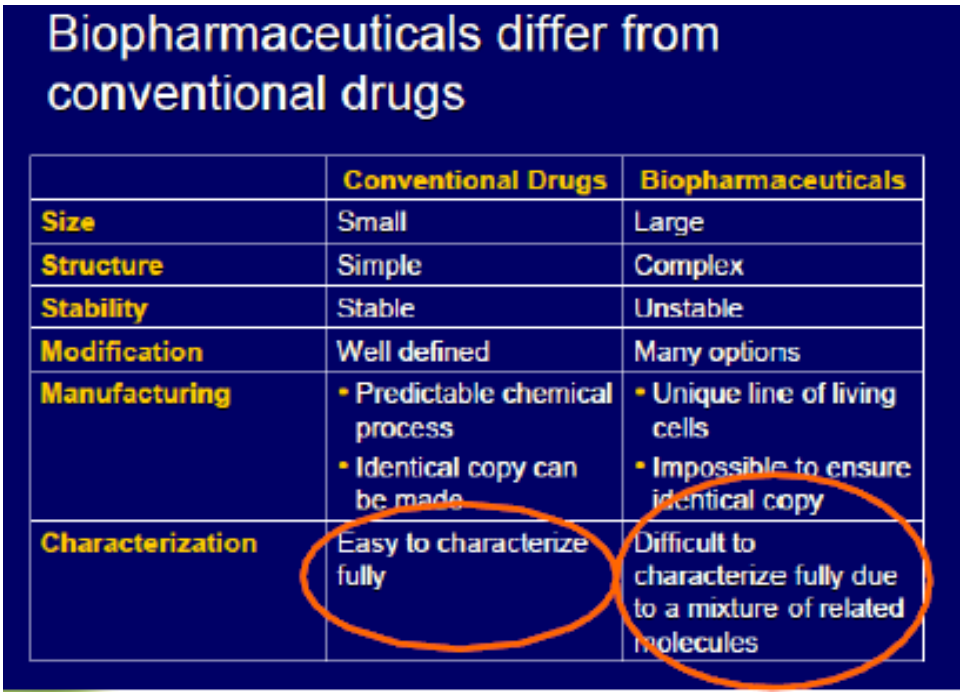
III. EXHIBITS

Exhibit 1 – Biopharmaceuticals Complexity



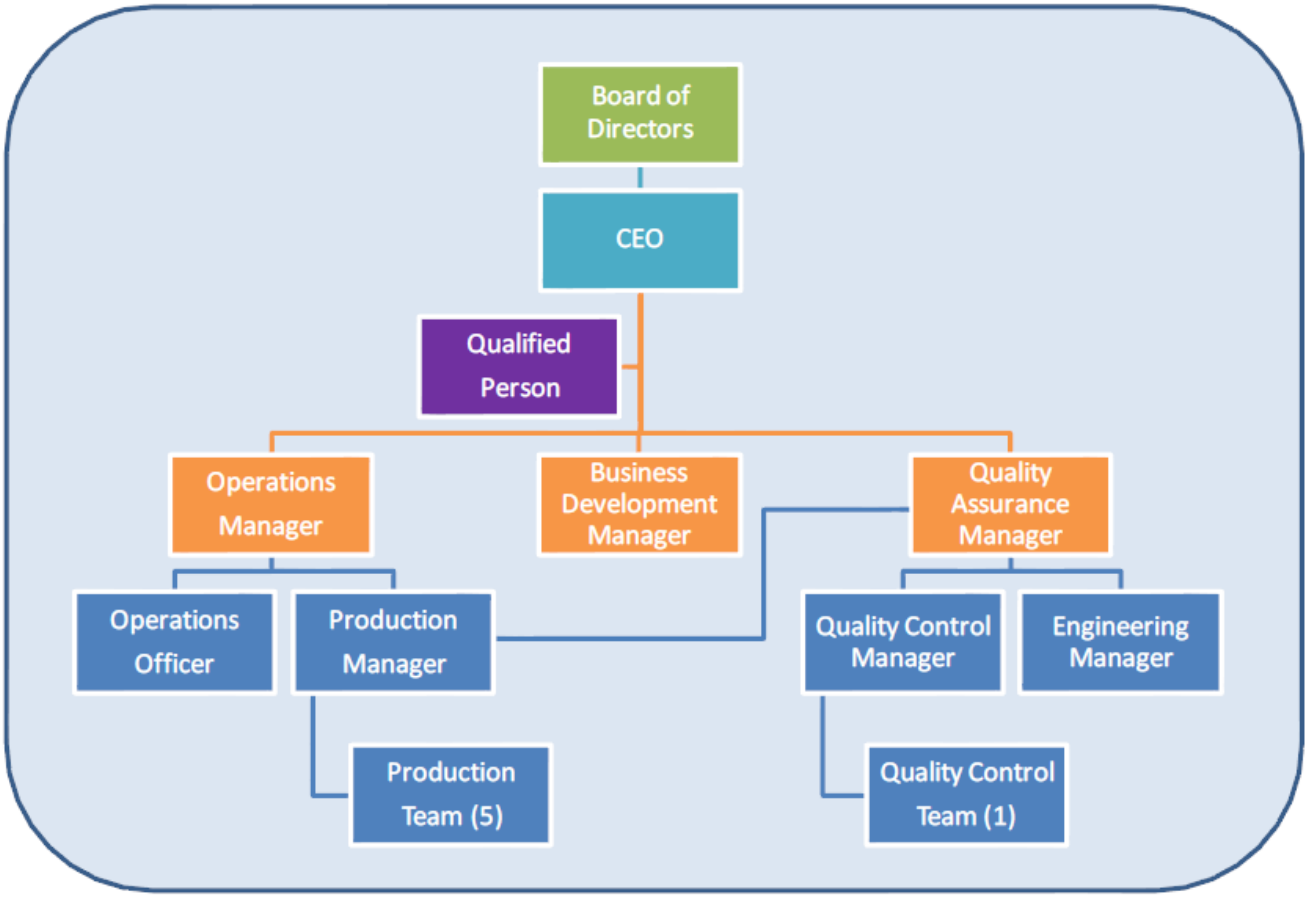
Source: Company Reports – ATM Production and Regulatory

Exhibit 2 – Biopharmaceuticals versus Conventional Drugs



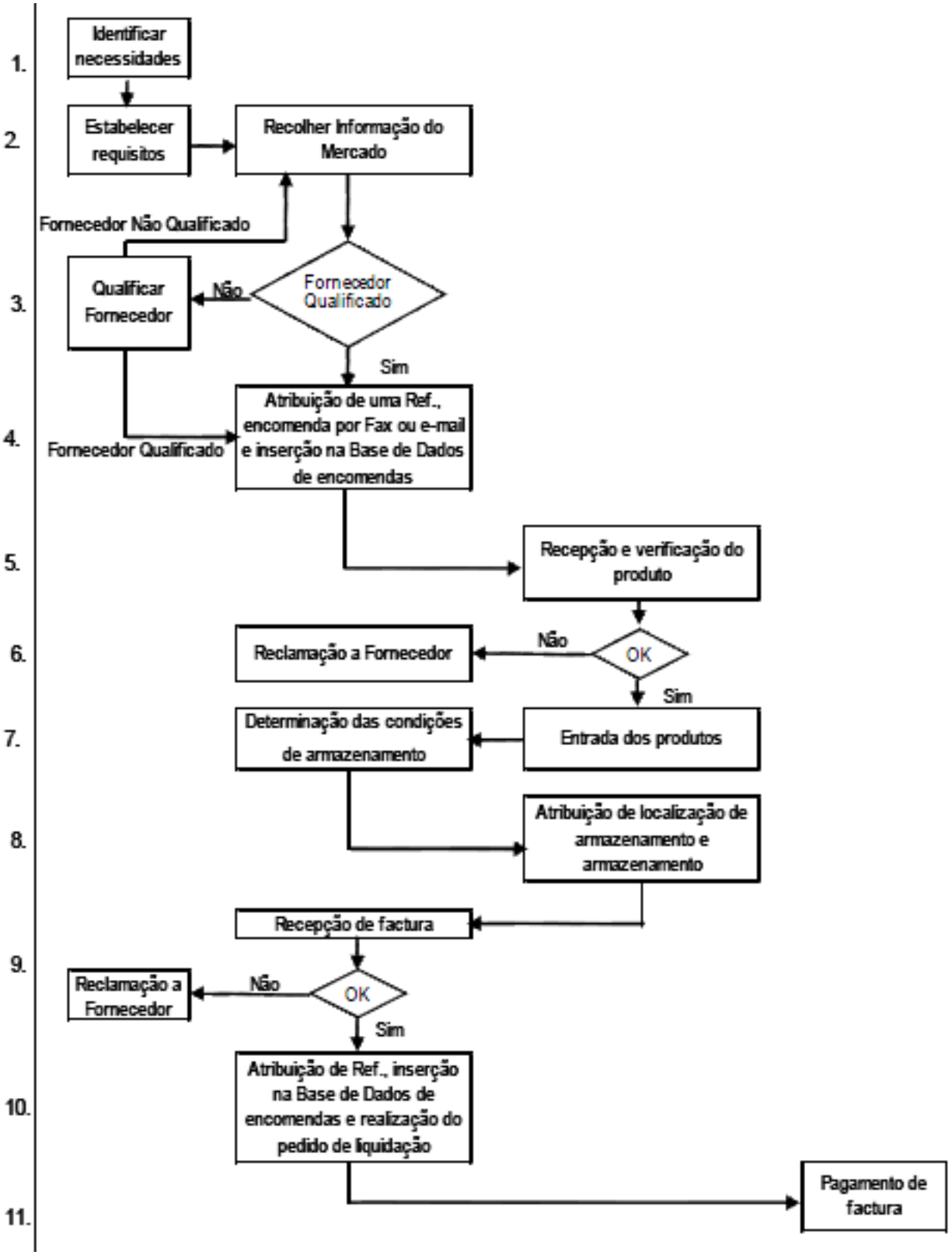
Source: Company Reports – ATM Production and Regulatory

Exhibit 3 – Genibet's Current Organizational Chart



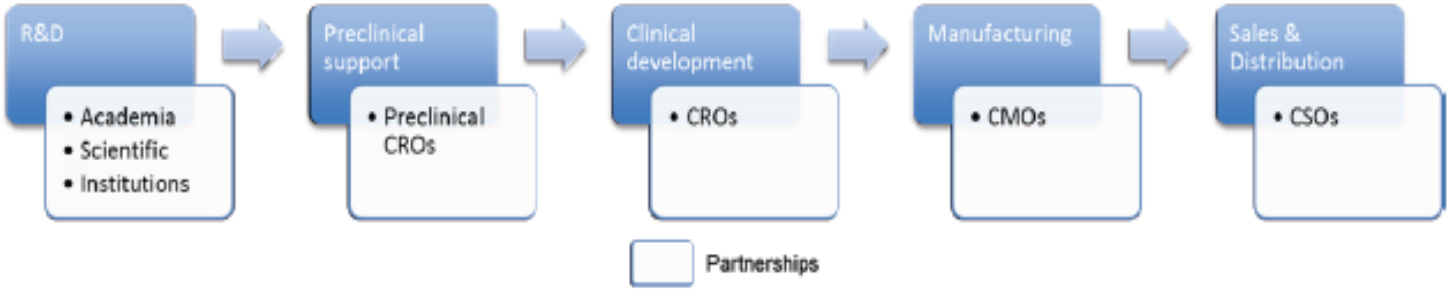
Source: Company Reports – Investors, 2013

Exhibit 4 – Genibet's Supply Flowchart



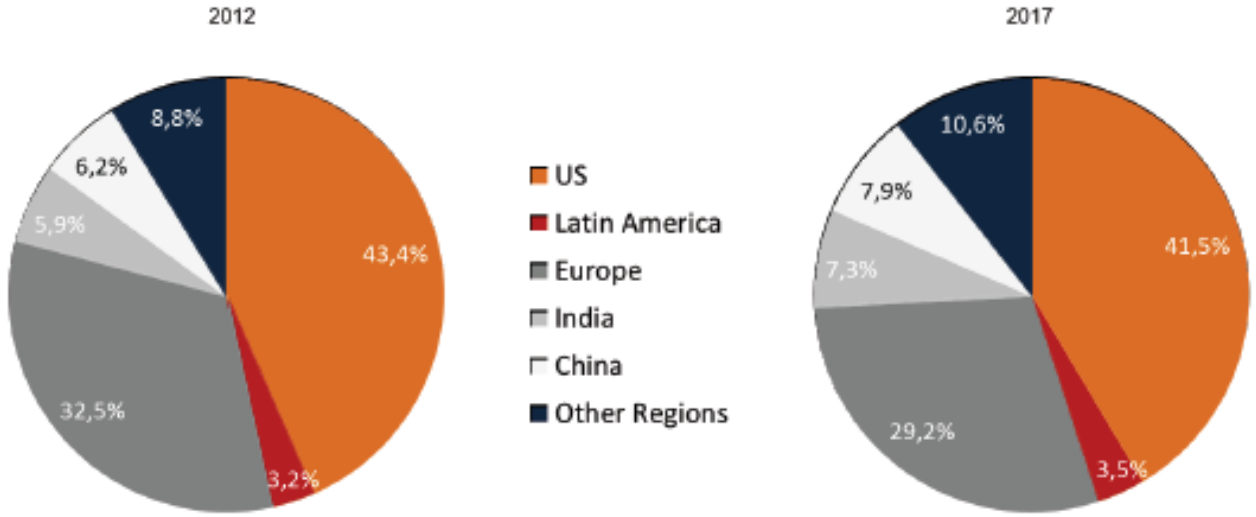
Source: Company Reports – Genibet, 26 Janneiro 2010

Exhibit 5 – Outsourcing as a driver



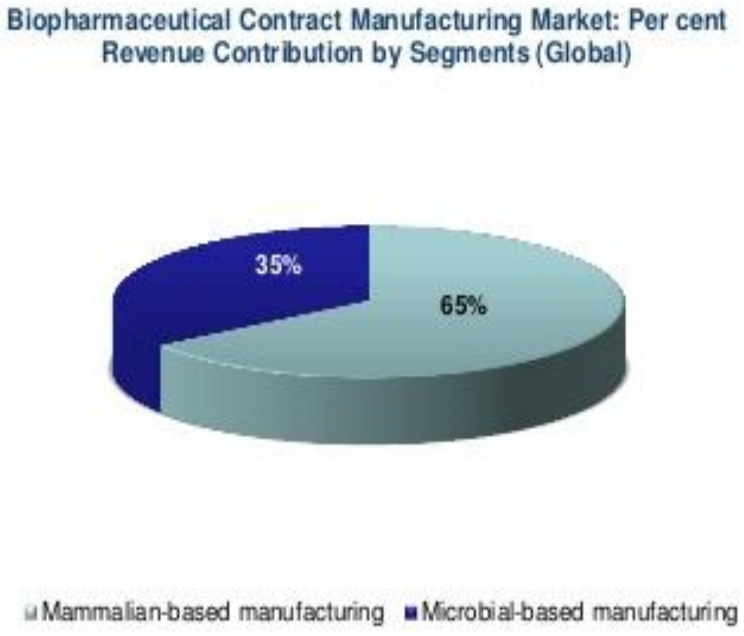
Source: Industry Reports

Exhibit 6 – Global CMO by Geographic Market



Source: Industry Reports

Exhibit 7 – Biopharmaceutical Contract Manufacturing Market: Segment Analysis



Biopharmaceutical Contract Manufacturing Market: Per cent Revenue Contribution by Segments (Global)

Segment	Revenue (%)	Revenue Growth Rate (%)
Mammalian-based manufacturing	65	5-6
Microbial-based manufacturing	35	2-3

Source: Industry Reports

Exhibit 8 – Genibet's Competitors: Small Bio-CMOs

Company	Production platforms and respective capacity sizes			
	Microbial	Animal cells	Viral	Fill and Finish
1. Bibitec (G)		100L		
2. APCETH (G)		Yes		
3. ProBioGen (G)		500L		
4. Eufets (G)		Yes	Yes	Yes
5. Vibalogics (G)	30L	30L	30L	Semi -autom.
6. Scil proteins (G)	1000L			
7. Biomeva (G)	10-1000L			
8. Celonics (G)		20-1000L		
9. Glycotope (G)		10-250L		Semi -autom.
10. Miltenyi (G)	200L	200L		
11. PharmedArtis (G)	350L	350L		
12. Wacker Biotech (G)	300L			
13. Angel Biotechnology (UK)	750L	750L		
14. Eden Biodesign (UK)	Yes	Yes		
15. Cobra bio (UK)	Yes	Yes	Yes	Yes
16. Eurogentec (B)	500L			
17. PX Therapeutics (F)	100L	200L		
18. 3P Biopharmaceuticals (S)	Yes	Yes		
19. Aret a international (I)		Yes		
20. Novasep (B)	Yes	Yes	Yes	Yes
21. BioUETIKON (G)		Yes		
22. SynCo Bio Partners (H)	1000L	100L		
23. Pharmacell (H)		Yes		
24. MaSTherCell (B)		Yes		
25. Genethon (F)			Yes	
26. Ark Therapeutics (Fin)			Yes	

Source: Company Reports – Investors 2013

IV. TEACHING NOTES

1. Introduction

The Case Study presented about Genibet – A Biopharmaceutical Contract Manufacturing Start-Up - provides means to link applicable theory with the case. Thus, it may be used for class discussions in courses such and Healthcare management, Strategy, Pharmaceutical Entrepreneurship, etc, together with suggested questions that might generate possible solutions for the challenges the company faces or will face.

Therefore, the teaching notes are for teacher's usage and they include many guidelines describing how the class discussion should be conducted. It is important to mention that, the teaching notes, functions as overall guidance since the questions can be differently interpreted by different students. The discussion in class may pursue different ways as interpretations are diversified and that can be an advantage if solutions are improved as a consequence.

The Case Study Genibet – A Biopharmaceutical Contract Manufacturing Start-Up – is being developed in the end of 2014 and so it is normal if, in the coming years, new up-to-date ways of analyzing and debating the case arise. Furthermore, supplementary information about the company and its environment may also appear as it is a fast growing industry.

2. Case Synopsis

Genibet is a Portuguese small company founded in 2006. Its main activity is the manufacturing of biopharmaceutical products for other companies, working as a Contract Manufacturing Organization under GMP (Good Manufacturing Practices) conditions. The products manufactured by Genibet are only for pre-clinical stages as well as for phases I-II of the biopharmaceuticals' pipeline.

Since its foundation and, as part of its strategy, the company has been concentrated on building state-of-the-art facilities, unique on the Iberian Peninsula so far, and on the regulatory permissions of these units and activities. For this purpose, the company strongly invests in training its employees resulting in a very skilled staff. Besides, Genibet has been also searching for a geographical expansion, so that it can serve better its clients. Therefore, the company has done this by establishing numerous partnerships worldwide from which the most important one is with IBET – Insituto de Biologia Experimental e Tecnológica. Not only has the company benefited from the technical and scientific complementary support of IBET, but also it has had access to cutting edge technologies and a great network of contacts on the industry.

By creating a Platform of Preferential Partners (European SMEs) – Clen Cells, Eurotrials and CEVEC – Genibet aimed to add value for its clients in a sense that these partnerships allow the company access to complementary technologies and services. The scope of the company's services gets bigger and this differentiates Genibet from the competitors.

Moreover, the company is also proud of its achievements on the area of research grants for research projects. It has a very well succeeded record within the European FP7 framework and within the National Grant system for the industry – QREN. These grants won by Genibet are worth more than 4.300.000 Euros, including past and current projects.

Well specialized little CMOs like Genibet have important opportunities now and in the future and the company considers that the business activity's development will lead to sustained growth in the long-term. However, as it is expectable, the company faced some challenges such as the present credit environment which limits some possibilities of facilities' expansion, the highly fragmented industry that brings along several competitors, among other technicalities.

Nonetheless, Genibet chose to maintain its position in the market. Were these concerns more critical on the short-run? Will the persist and get more accentuated? Were the geographical, client and production target options the best Genibet could have done so far?

3. Teaching Objectives

The Case Study presented about Genibet allows the students the possibility to evaluate important topics that were learnt in classes during the Master's Degree as well as the opportunity for them to make practical use of the knowledge acquired on a resolution of company's real challenge.

The objective of the case was to provide an example of a small company that, even though the present economical situation of its country of origin, developed an original business model that allowed growth and sustainability. Students may apply several frameworks and other strategic solutions by addressing subjects such as market potential, partnerships and production constraints. Therefore, Porter's Value Chain, the PEST analysis and the CAGE's framework are some examples of the tools that can be use to answer the suggested questions.

All the information and data needed to solve the case is provided on the case or on the exhibits.

Through a deep reading of the presented case, a student should be able to understand:

- The current situation of Genibet and its Business Model
- The importance of such a business initiative due to the growing importance of biotechnology
- How is it possible for CMO to add value and be competitive
- The urge for such companies to be recognized and spread worldwide
- The difficulty and special attention needed when analyzing an industry so highly fragmented
- The numerous aspects that shall be taken into account when intending to expand the project, such as the financial and funding aspects as well as analyzing the potential markets threats and opportunities
- The relevance of partnerships in regards to industry experience, market knowledge, reputation, network and access to state-of-the-art technologies
- The advantages and disadvantages of an intense competition in the bio-CMO industry

4. Assignment Questions

Assignment questions were developed to aid students analyze the case and provide the instructor guidelines throughout the discussion.

1) How do you think Genibet creates value?
2) Do you think there is a risk/concern for the client when outsourcing these services from Genibet? How can it be alleviated for both sides?
3) Genibet is presently targeting Europe as its first priority regarding Geographic Markets, then U.S and South Korea. Besides, new markets were identified on the case. Perform a CAGE framework on these current and potential markets including:
    - Cultural, administrative, geographic and economic distance
4) What are the advantages of the partnership established with IBET? In there any conflict that may appear in the long run?

5. Analysis and Discussion

1) How do you think Genibet creates value?

To conduct the analysis on how the company creates value, we will use The Porter's Value Chain framework to identify the way in which Genibet changes the business inputs so that they have greater value than the original cost of creating those outputs.
The bigger the value a company creates, the more profitable it will likely to be and the greater is its competitive advantage.

Taking into account Genibet's small dimension and the stage of life in which the company is, the value chain analysis will be adjusted and not all the areas on figure 5 will be covered. Furthermore there are areas that will be more deeply analyzed since they are the ones that add more value to the chain: R&D, Technology Transfer, Production, Quality, Marketing, Sales and After Sales services.

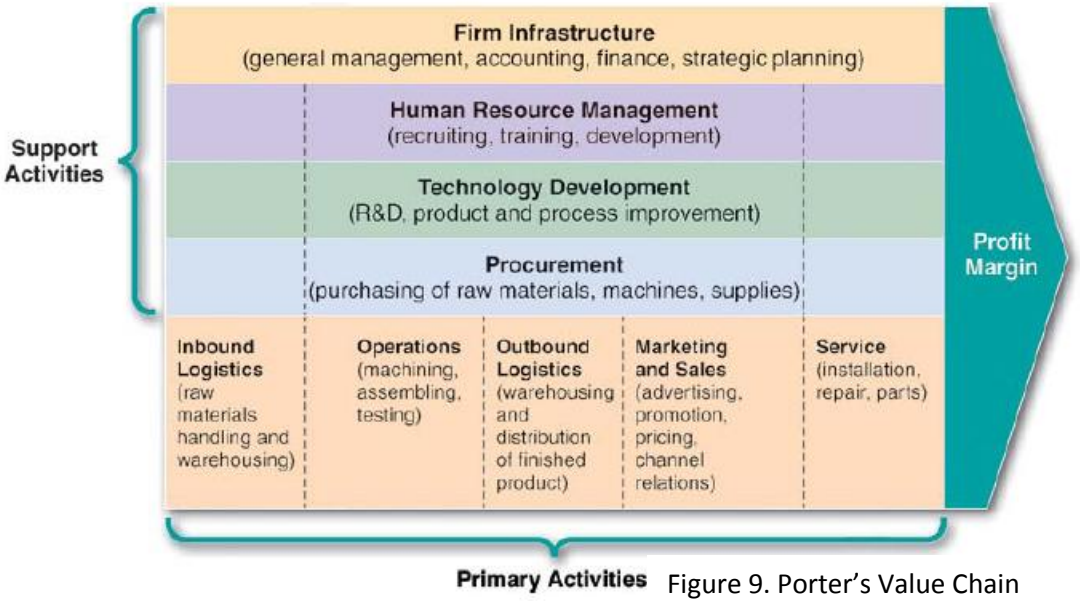


Figure 9. Porter's Value Chain

Source: Company's Reports

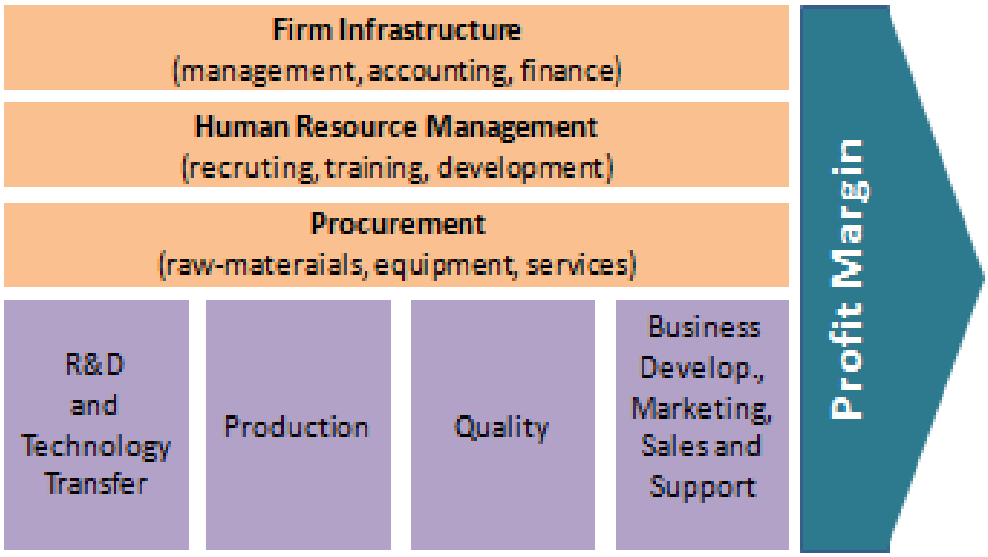


Figure 10. Genibet's Value Chain

Source: Author's adaptation from Company's Reports and In-depth Interviews

Firm Infrastructure (general management accounting and finance)

Genibet has an Administrative Council composed by five elements that are nominated in a shareholder's General-meeting. Part of this Administrative Council is a Executive Director that coordinates the different activity areas.

Being on a strict partnership with IBET, the company's accounting is part of IBET's accounting and, therefore there is not an organized accounting management.

Human Resource Management (recruiting, training and development)

Genibet's current organizational chart (see Exhibit 3) shows clearly the company's dependence upon part-time human resources.
In a company where the business is based on technology transferring between the clients and Genibet, this factor can be a weakness because there can be a lack of critical human mass to evaluate the quality of the clients' data and for to dominate the several processes the company engages in.
On the other hand, the staff allocated to production is sometimes too little to assure all the production needed and that may incur in long extra hours of work. The fact that Genibet trains its employees in a way that every process is carefully done and in the most possible productive way, helps reducing the time needed for each step of manufacturing at the same time that it allows less errors to occur.
Besides, another move that Genibet has been using to help with the lack of skilled staff to work on production is the "usage" of IBET's technicians which are currently not paid for Genibet.
In addition there is not a formal Human Resources Management and so there are no formal procedures for recruiting staff, a system of career development nor a performance assessment system. The recruitment process is done based on the technical needs the company finds on its path and the staff training is done "on the job", meaning that it is done by the few Genibet's seniors.

Procurement (purchasing of raw-materials, equipments and supplies)

Genibet's management of materials in what concerns purchasing management, stock reception, stock conditions and suppliers assessment is defined by implemented procedures. The acquisition of raw-materials, disposable materials and reagents is done accordingly to each project that might require different types of materials. These needs are assessed by Production and Quality Control departments and registered on a data base.

R&D and Technology Transfer

The main service Genibet provides to its clients is manufacturing biopharmaceuticals without any single failure, according to the stipulations made on the first phase – Evaluation of clients's needs and Cell Line Development. Here, the company receives technical information from the client and evaluates the strength of the first results done on the laboratories. This is the most important step on the overall process since it requires experienced human resources that will influence the rest of the project.
If the first tests performed with the clients' information runs without any problem-engineering runs- , Genibet is able to make its proposal on the remaining part of the process. Otherwise, Genibet may propose itself a solution and includes this research – more engineering runs - as an extra cost. Usually all the projects approved on this phase are done in partnership with IBET. As figure2 shows, all the process must be accompanied by the client, although the technology transfer is mostly done on the initial phase.

Production

Genibet occupies part of IBET's facilities. It has four manufacturing units specialized in microbial, cell culture and viral process development as well as cGMP manufacturing services to research groups, biotech and pharma companies for Phase I and II clinical trials:

The Bacterial Unit – Dedicated to the production of antibody fragments, vaccines (protein and carbohydrates), proteins, plasmid DNA, RNA and phages.

The Animal Cell Culture Unit – This unit allows the performance of animal cell banks and preparation of cells for cell therapy.

The Viral Unit – The unit comprises two production areas and it is devoted to filling and finishing of clinical batches and viral vectors for gene therapy and vaccines may also be produced for phases I-II of the clinical trials.

The Fill and Finish Unit - in this unit semi-automatic filling of small vial series are performed. It works as a complement of the Bacterial and Animal Cell Culture Units since is for the filling of the products manufactured on those units or by other CMOs.

There are many factors that are worth mentioning regarding Genibet's manufacturing facilities such as the fact that they were constructed with the latest technologies; the fact that a large part of the equipments are disposable allowing Genibet to easily change its rooms for different project and great compliance all the units own with the international regulatory requirements for the biopharmaceutical industry.
It was the first company in Portugal with clean rooms (cGMP) for the production of biopharmaceuticals and also, it was the first to produce for clinical trials, innovative products.
In what concerns production, Genibet is leveraged by the vast proficiency in virology, molecular biology, cell and bacterial culture of its main shareholder and host, IBET.
Besides IBET, the company focuses on maintaining a strong network of complementary partnerships for the R&D and Clinical Trials. .
Besides its main core competency, which is the manufacturing of such products, Genibet distinguishes in the market for its expertise on regulatory issues since many times the clients do not know how to handle them.

Quality

The first goal on Genibet's Quality System is to make sure all the quality requirements are kept so that the company is trustable for authorities, clients and investors. Genibet's Quality System includes all the aspects needed to reach the Quality objectives, by applying the cGMP rules there is a guarantee of compliance with all the legislations.

The system has been audited several times in all its units and only received good comments and approvals.

However, it is critical that this department works in line with all the other systems (finance, commercial, human resources) so that it gets more efficient and cohesive.

Business Development, Marketing, Sales and Support

Currently Genibet does not own a properly organized work of Business Development, Marketing and Sales because of its dimension. The clients and projects have been arriving through the IBET's contacts and more recently the contacts Genibet have been acquiring too.

Nonetheless, as the company intends to grow and expand its services worldwide, the Business Development is something that is starting to be thought about.

Taking into account the youth of Genibet and its dimension, the first step regarding Business Development would be to know even better the business, to gain even more visibility on the market and gather more clients for its network as well as maintaining the existing ones through an attendance during and after the service.

2) Do you think there is a risk/concern for the client when outsourcing these services from Genibet? How can it be alleviated for both sides?

Genibet's clients may sometimes be concerned about the fact that the company will have access to their chemical formulas as technology knowledge. Opportunistic behaviors could ultimately happen as a result:

- Genibet could begin manufacturing and trading the same goods to the market as soon as the project ends, becoming one of the client's competitors
- Genibet could share these confidential information with others

Nonetheless, if Genibet would start proceeding like this, it would only incur in short-run gains. In the long term, its reputation would be injured leading to bankruptcy, as well as it would extend the damages to its main partner IBET. Thus, the company is interested in

building long lasting relationships, based on confidence and regular contact. Blanchette (2004) believed that the greater the effort the client puts on the relationship settled with the supplier, the more improved results they may expect.

Besides, the client also has to show some commitment to the relationship with the supplier and, as Genibet increases its manufacturing capacity to satisfy client's needs, there is a risk transferred from client to supplier. Thus, Genibet's clients shall also compromise with the company until the end of each project.

One possible solution to avoid these kinds of insecurities for both sides but especially for Genibet's clients is to protect relevant information and technology transfer through confidentiality contracts. Thereby, the rights for both client and supplier can be secured and it helps also on the first stages of the project – goals setting, manufacturing processes stipulation, schedules and its tolerance, among other.

3) **As analyzed on the Case Study, Genibet is presently targeting Europe as its first priority regarding Geographic Markets, the U.S and South Korea. Besides, new markets were identified on the case. Perform a CAGE framework on these current and potential markets including:**

CAGE Analysis	Cultural Distance	Administrative Distance	Geographic Distance	Economic Distance
Europe	• Different languages • Western culture – same values and norms	• Same regional commercial bloc • Common currency and law • Easiness on doing business	• Little physical distance • No land boundaries • Ease of transportation	• Stable growth • Europe as the 2nd biggest market in bipharmaceuticals • Lower costs of labor in Portugal
United States	• Different languages • Western culture – same values and norms	• Same regional commercial bloc • Easiness on doing business • Political positive relationship • Reduced long-term risk	• Considerable physical distance • Ease of transportation	• Few flexible entreprises • Stable growth • U.S as the largest market in bipharmaceuticals • Lower costs of labor in Portugal
Latine America	• Similar languages • Colonia l strong links with Brazil	• Mexico is polically stable • Venezuela presents some risk on the long-run • Political positive reltionships with Brazil and Venezuela	• Considerable physical distance • Not so good transportantion • Good ties betweem Brazil and Portugal	• Government initiatives that incentive the growth and allure of this industry, especially in Brazil and Mexico
Asia	• Different languages • Colonial strong links with China and India	• South Korean and India are politically stable • Chine presents some risk on the long-run • Political positie relationships with China	• Big physical distance • Not so good transportation	• Foreign investments in India are now less because of the low govern,ment coordination • South Korean and China walking towards leadership, with higher competition in China

Figure 11. CAGE Analysis

Source: Authors adaptation from International Markets Analysis and In-depth Interviews

4) **What are the advantages of the partnership established with IBET? In there any conflict that may appear in the long run?**

Genibet is a consequence from a spin-off from IBET, a non lucrative research institute focused on biotechnology, which is also Genibet's main shareholder. IBET felt the need of having a GMP unit in order to complement its Pilot Unit of fermentation and purification. This relationship is fundamental to leverage both businesses and brought numerous benefits to the company:

- Access to cutting edge technologies
- Training the staff in original production processes in an industry where technologies are always evolving
- Make use of the broad network of IBET (Universities, biopharma companies, research groups and CROs), built by the institute over the years
- Benefit from IBET's reputation in the marketplace as well as building its own
- Offer complementary services
- Shares costs and risks

Through this partnership, Genibet was allowed to access to IBET's list of clients. The fact that the research institute already held a vast range of customers, including companies like Novartis and Eurotrials, enabled Genibet to be known as a trustworthy and solid partner. As a consequence, since the company's entrance in the market, many companies showed interest in working and establishing partnerships with Genibet.
The two not only work as complementary partners on the services needed on each different project, but complement other partners too, that share their knowledge and technologies on the business practices.

Trough these web-partnerships, Genibet is able to offer a set of integrated services – One-stop-shop services – at once, such as process development (with IBET), GMP production, analytical development (with Clean Cells), regulatory expertise (with Eurotrials) and fill-and-finish. Furthermore they have developed logistics for their products' distribution to the customers and Genibet is allowed to share the risks, costs and liabilities of the projects with IBET so that it does not have to carry the weight of the investments all by itself.

It is relevant to mention as an example, a recent project that illustrates the interaction between Genibet and IBET. A Spanish customer contacted IBET regarding the manufacturing of an oncolytic virus (virus used to treat pancreas' cancer) since they only had a rudimentary manufacturing process so far. IBET developed then the manufacturing process for an large scale and Genibet produced the virus to be used in clinical trials in Spain.

The fact that part of Genibet's activities is based on the cutting edge research developed by IBET – integrated solution for clients - is a system that allows great competitiveness on the global market. However, this is only possible if the two teams work closely and there is a high level of communication between the two, as well as the share of strategic decisions one may take.

The only conflicts that may result from the partnership are lack of communication and divergent strategies as Genibet becomes more mature and financially independent.

If both sides do not clearly communicate their goals there might be a risk of misunderstanding. As the parties can carry distinct objectives or strategies, they can fail to achieve a range of mutual agreeable goals.

Conclusions

The elaboration of this Case Study was enriching for myself as well as for Genibet, in a sense that it allowed a deeper analysis of the company and improvements on analysis done in the past. It allowed a more structured outlook of the industry and also of the company's internal factors.

However, as in every Master Thesis, there were some limitations of the study conducted. Firstly, the period of time in which the Case Study was built was not long and it may have lead to the loss of important details. Besides, as the number of the company's employees is little and they are on a phase where there is a lot of work, it was not possible to talk with other members of the staff besides the CEO – Teresa Alves. This could have been beneficial for the case since it would allow more perspectives on the same matter to be incorporated and eventually could have lead to a more accurate outcome.

Finally, the fact that Biotechnology is a complex subject and I am not an expert on the area can also be seen as a limitation since the industry requires a lot of study and precision.

Further Research

Biotechnology is a relatively recent subject and is constantly developing every day, leading to a situation of continuous research.

For further research, it is recommended for Genibet to pursue the industry trends mainly with regards to innovation and alternatives to traditional drugs. Genibet was founded not long ago and it would be interesting so check on how the company has moved until this point of time. Furthermore, upcoming research could be directed not only to the existing but, especially for the potential customers in a way that Genibet could anticipate their needs better. If the needs and wants are better identified, future research would be improved and it would also lead to more justified and cohesive partnerships.

Lastly, the company is highly focused on offering differentiated services. However, as seen on the case, the industry is very fragmented with many small players and predictions of more entering the market. As a consequence, future research is also

suggested to make a deeper analysis on the present research about recent diseases and treatment needs as well as on those that have higher success chances through Genibet's competitive advantage – expertise and facilities.

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