

## **Diosynth Biotechnology – Riding the Biomanufacturing Wave**

### **Activities, Assets and Sale Figures**

Diosynth Biotechnology is a subsidiary of the Netherlands-based conglomerate Akzo Nobel, which deals with healthcare products, coatings and chemicals. Diosynth makes up part of the pharmaceuticals division of Akzo Nobel, along with sister firms Organon, Intervet and Nobilon.<sup>1</sup> Diosynth plays the role of the manufacturer. It is primarily involved in the provision of contract biopharmaceutical development and manufacturing services. Diosynth's biomanufacturing service focuses mainly on the production of recombinant proteins/peptides and DNA products from cell types such as the Chinese hamster ovary (CHO), *E. coli* and NS0 for therapeutic and vaccine applications.<sup>2</sup> It also has considerable expertise in contract biopharmaceutical development, also known in the industry as process development. Process development involves the design of specific chemo-genomic manufacturing systems, with the aim of optimizing the efficiency of the process.

Diosynth has only two facilities, one in Research Triangle Park (RTP), North Carolina and one in Oss, The Netherlands. The RTP facility is capable of small (100L) and intermediate (2000L) scale biomanufacturing processes, while the Oss facility can host large-scale processes (14,000-25,000L).<sup>3</sup> The firm is based in The Netherlands and its US headquarters is located in RTP.

Diosynth gained presence in RTP when Akzo Nobel acquired the US operations of Covance Biotechnology Service in June 2001 at a price tag of \$190 million. Prior to 2003, Diosynth's main focus was supplying Organon with active ingredients. Of late, Diosynth has bagged several manufacturing contracts with external US pharmaceutical companies, including contracts for ingredients in the production of Somavert for Pfizer, and Retavase for Johnson & Johnson.<sup>4</sup> While the firm generated \$593 million in 2002 sales, this figure is projected to double in the next two years. Its operations in the United States have been projected to generate \$130 million in revenue in 2003, up from \$110 million in 2001.<sup>5</sup>

### **Strategic Directions in the Last Four Years**

Diosynth has taken an expansionary path both in the United States and in the Netherlands. In 2002, the firm added 18,000 square ft of manufacturing space in its Oss facility.<sup>6</sup> In RTP, the company is set to invest \$100 million for purposes of expansion. This investment has the backing of parent firm Akzo Nobel.<sup>7</sup> Diosynth made plans in 2001 to buy 91.3 acres of land from the Research Triangle Foundation, which will allow the addition of 300,000 square feet of new manufacturing space. As of late 2003, the company has bought 79.6 acres of land of which only 25.8 acres are utilized.

The addition of new manufacturing space is in line with plans that are underway to shift the current focus of manufacturing in the RTP facility from that of being solely for clinical trials to that of full-scale production. Roger Lias, the vice president of business development for Diosynth RTP, predicts that Diosynth can aid in the commercial manufacturing of the same drugs they make for clinical trials.<sup>8</sup>

While Diosynth Biotechnology has the strong financial backing of Akzo Nobel in these expansions, there is no denying the fact that capital investment in an industry of the same nature as pharmaceuticals and drugs is often fraught with uncertainty. Diosynth could find itself plagued by the problems of excess capacity or eroding profit margins if market conditions are not forecasted properly. In order to evaluate its strategic direction of expanding manufacturing capability, we must understand more fully the specialized nature of biomanufacturing and also analyze the following factors:

- The demand for biomanufacturing in the near future
- The intensity of competition in the biomanufacturing sector

### **What is Biomanufacturing?**

Drug manufacturing in general occurs at the third stage of the medical biotechnology value chain, after the processes of discovery and product development. There is however some overlap with the stage of product development. Due to the scale and multitude of clinical trials, there is also a lucrative market in the supply of drugs manufactured solely for the various stages of clinical trials.<sup>9</sup> Where there is no overlap, manufacturing refers to scaled-up production in preparation for commercial sale of the drug.

Drugs in the biotechnology industry are derived from genomic and proteomic processes, and are fundamentally different from traditional pharmaceutical drugs. Biotechnology drugs often exploit processes that occur at the cellular level. Monoclonal Antibodies (mAbs), for example, work by utilizing certain proteins to change abnormal cell functions that are the root causes of illnesses. Because they work by mimicking natural processes, such proteins are created via processes such as mammalian cell culture for mAbs, or microbial fermentation for vaccines. Biomanufacturing is thus hugely differentiated from traditional pharmaceutical manufacturing, which instead involves the synthesis of various chemicals under controlled heat and pressure conditions.

### **Biomanufacturing as a Niche Market**

Cost is a key barrier to entry in the biomanufacturing market. As with all manufacturing activities, capital expenditure occupies a large proportion of initializing a biomanufacturing operation. Capital equipment represents about 40% of the cost of a new biomanufacturing facility. Typical equipment required include bioreactors and purifiers each of which could sell for \$250,000 to \$1 million.<sup>10</sup> A custom facility may cost between \$300-\$500 million to construct, equip and license.<sup>11</sup> Time is another factor. Because of the highly specialized and regulated processes, biomanufacturing workers often undergo extensive training packages. The time required for facility design, construction and validation is 3 to 5 years.<sup>12</sup>

Strict regulations add to the cost and time factors. There is a set of Good Manufacturing Practices (GMP) that manufacturers must adhere to in order to obtain a license for production.<sup>13</sup> Learning GMP systems and habits accounts for half of on-the-job training time, which averages nine months.<sup>14</sup> GMP standards are global and thus subject to the scrutiny of authorities from various countries, including the United States, Europe and Canada.<sup>15</sup>

These constraints impose a large burden on the profitability of the operations of biopharmaceutical firms. Patents are usually granted for a period of 17 years. This begins from the discovery stage of the value chain, upon discovery of a promising compound. The following table depicts the timeline of the idea-to-drug process.<sup>16</sup>

Table 1

Year	Stage/Phase	Probability of advancing to next stage
0	Discovery of a promising compound Patent clock begins ticking	
1–4	Pre-clinical testing Lab and animal tests	1/1,000 (.1%) of the promising compounds results in an Investigational New Drug (IND) submission
	Investigational New Drug (IND) application submitted to FDA	85% to Phase I clinical trials
4–6	Phase I clinical trials Assess safety and metabolism 30–50 volunteers	80% to Phase II clinical trials
6–8	Phase II clinical trials Assess efficacy and safety 100–300 volunteers	28% to Phase III clinical trials
8–12	Phase III clinical trials Assess efficacy and safety 1,000–5,000 volunteers	65% to New Drug Application (NDA) submission
12–14	New Drug Application 100,000 pages of data reviewed by FDA	90% of the NDAs are approved by FDA
14	Drug reaches market Post-market evaluation	
17	Patent expires	

Sources: Association of Clinical Research Professionals / Pharmaceutical Research and Manufacturers of America

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The ticking patent clock imposes an opportunity cost to time spent on setting up manufacturing facilities. Unable to meet the needs of patients wanting their products, smaller companies that have successfully obtained a New Drug Approval (NDA), but do not have existing in-house production capability, have lost millions of dollars in sales revenues.<sup>17</sup> On the other hand, companies with promising drugs awaiting an NDA would not want to commit to the high costs of setting up production prematurely. Therefore there exists a role for firms with readily available biomanufacturing capabilities to immediately assume production of the drug at the quickest possible time, in order to maximize sales revenues for the developer of the drug.

Given the nature and scope of drug discovery (see probabilities in above table), it is often not cost-effective for biotechnology firms involved in R&D to maintain teams that specialize in other functions such as manufacturing. Outsourcing the manufacturing stage would be a solution for these firms, in particular the small and medium biotechnology firms. ‘Access to the contract manufacturer’s expertise, experience and [GMP] compliance capabilities’ is one of the stated

reasons for outsourcing biopharma production.<sup>18</sup> On this thread, experienced biomanufacturers would also be seen as more desirable partners for outsourcing.

### **Biomanufacturing Demand – Capacity Crunch?**

One way to forecast demand for biomanufacturing services is to analyze the numbers of potential products in the discovery and product development stages of the biopharmaceutical pipeline. As of 2002, nearly 10% of existing drugs originated from biotechnology research, and close to 20% of R&D efforts in the drug industry were by biotech firms.<sup>19</sup> The number of approvals to commence manufacturing of biopharmaceutical products by the US Food and Drug Administration (FDA) was 110 between 1992-2002, up 200% from 1982-1992. According to the FDA and the Pharmaceutical Research and Manufacturers of America, there were more than 370 biopharmaceuticals in various stages of regulatory process in October 2002. The figure rises to 1,000 worldwide.<sup>20</sup> HighTech Business Decisions predicts that the commercial scale production of at least 50 new biopharmaceutical products will be required between 2008 and 2010.<sup>21</sup> Based on mammalian cell-culture alone, estimates of worldwide biomanufacturing capacity is between 400,000 to 450,000 liters, all of which were being utilized. Taking into account the swell of potential biopharmaceutical drugs in the pipeline, executives in the industry have estimated shortfalls of nearly a million liters of capacity for the US pipeline alone.<sup>22</sup> Existing non-biopharmaceutical manufacturing capacity has little impact on the alleviation of the shortage, because the facilities and skills for traditional pharmaceutical manufacturing and biopharmaceutical manufacturing are not readily interchangeable. Pfizer's contract with Diosynth to manufacture the active ingredient for growth hormone receptor antagonist Somavert is a case in point.<sup>23</sup>

### **Competition in the Biomanufacturing Sector**

Conventional economic wisdom tells us that rising demand will not result in rising prices if offset by sufficient competition in the sector. There are approximately 70 companies in the world offering contract manufacturing services, 50 of which are based in the United States.<sup>24</sup> Of these companies, some are large biotechnology firms such as Amgen or Biogen Idec, large pharmaceuticals such as GlaxoSmithKline (GSK) Biopharmaceuticals, both of which also carry out R&D and sales functions. Some are pure contract manufacturing organizations (CMOs) such as Lonza Custom Manufacturing or Diosynth Biotechnology. These players specialize mainly in mammalian cell-culture or microbial fermentation. The market for biopharmaceutical contract manufacturing is expected to grow from \$1.3 billion in 2003 to \$1.7 billion in 2004.<sup>25</sup>

Contractors are aware of the impending shortage; in 2001, 89% of contractors surveyed said that they were planning to expand operations.<sup>26</sup> Industry executives predict an expansion of 500,000 to 1 million liters between 2005 and 2006.<sup>27</sup> The productivity of the manufacturing process is steadily increasing. Expression rates have more than doubled. Major pharmaceuticals with underutilized biomanufacturing facilities are also actively marketing their excess capacity, including GSK and Abbott Laboratories. There have also been new entrants such as Cardinal Health, a contract sales organization (CSO).<sup>28</sup> The industry has been hard at work trying to ease the impending capacity crunch.

The large pharmaceutical or biotechnology firms may especially pose a threat to the CMOs in the contract biomanufacturing market. These large firms often offer R&D collaboration

opportunities to the pure R&D biotechnology firms, with options such as accessing their large databases of compounds. Collaboration in R&D often leads to manufacturing. Large firms also have the added advantage of being able to provide extensive distribution networks for the manufactured drugs. These are abilities that CMOs lack.

### **What advantage does Diosynth have?**

By virtue of the expanding biomanufacturing pie, Diosynth has taken the correct step of focusing on biomanufacturing and process development. It has also capitalized on the fact that it is a certified cGMP manufacturer. However, besides benefiting from general industry growth, Diosynth also enjoys some advantages by virtue of its function as a CMO.

While large biotechnology or pharmaceutical firms are able to provide add-on services, they lack the agility of smaller firms, given that most of their excess capacity and manufacturing knowledge is built upon their previous domestic production. Thus large firms may only be able to offer the specialized manufacture of certain proteins. Diosynth has had the advantage of working with a large variety of proteins in microbial fermentation and cell-culture bioreactor-based processes. This is one area of weakness for larger biopharmaceuticals and pharmaceutical firms. Manufacturing managers noted in a survey by HighTech Business Decisions that a CMO is considered 'more helpful' if they offer process development services.<sup>29</sup> Diosynth, given its breadth of experience is well poised to capture market share. As of late, Diosynth has developed a process, called DioRaSSP (Diosynth Rapid Solution Synthesis of Peptides), that will enable 'shorter development times and an increase of manufacturing flexibility, even at scales as high as hundreds of kilos.'<sup>30</sup>

Diosynth has also strategically positioned itself in terms of resources. Its strong financial backing by Akzo Nobel may also prove to be ammunition in its battle for market share. Smaller CMOs usually do not have the financial resources to build a manufacturing facility without having that investment underwritten by the customer.<sup>31</sup> Diosynth's location in RTP may also help it gain access to a limited pool of skilled biomanufacturing labor. This is due largely to the state initiatives of worker training with programs such as BioWorks, and also the agglomeration effects of surrounding biotechnology and pharmaceutical firms.

### **What implications does Diosynth's strategy have for the industry and jobs in North Carolina?**

Diosynth employs approximately 3,000 people worldwide, of which 595 personnel are based in RTP.<sup>32</sup> One implication of this strategy is a potential for an increased scale of production by Diosynth in RTP. Currently, the large-scale commercial manufacturing is done by the Netherlands plant. RTP handles small to medium sized biomanufacturing, primarily for clinical lots of US pharmaceutical firms. This contract could however follow through to the provision of biopharmaceutical ingredients for large-scale commercial drug production. Diosynth currently has spare land of 54 acres in RTP that could well facilitate the ramping up of production. We observe the emergence of a mutually beneficial relationship. Diosynth's expansion in RTP will provide more jobs for the North Carolina community, while the presence of other biotechnology firms, and extensive state training programs in biomanufacturing skills will provide Diosynth with the incentive to stay and expand its operations in North Carolina.

## References:

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<sup>3</sup> Diosynth Biotechnology: Leading the way to success in cGMP contract manufacturing, [http://www.diosynthbiotechnology.com/pdf/key\\_facts\\_brochure\\_11\\_19.pdf](http://www.diosynthbiotechnology.com/pdf/key_facts_brochure_11_19.pdf)

<sup>4</sup> Biospace (fn. 2)

<sup>5</sup> <http://triangle.bizjournals.com/triangle/stories/2003/09/15/story4.html>

<sup>6</sup> Ibid.

<sup>7</sup> <http://triangle.bizjournals.com/triangle/stories/2003/09/29/story1.html?t=printable>

<sup>8</sup> <http://www.bizjournals.com/triangle/stories/2002/06/03/story1.html?page=2>

<sup>9</sup> Jim Miller, Biomanufacturing Attracting Growing Interest, Outsourcing Outlook, 2003

<sup>10</sup> Inpharma. Dissecting the bioprocessing market with D&MD, [www.inpharma.com/news/news-NG.asp?n=26962-dissecting-the-bioprocessing](http://www.inpharma.com/news/news-NG.asp?n=26962-dissecting-the-bioprocessing)

<sup>11</sup> Window on the Workplace 2003: A training needs assessment for the biomanufacturing workforce, North Carolina Biotechnology Center, 2003

<sup>12</sup> Ibid.

<sup>13</sup> The Pharmaceutical Outsourcing Outlook 1998-2003, Reuters Business Insight, Pg 116

<sup>14</sup> “Window...” (fn. 11)

<sup>15</sup> <http://www.cgmp.com/universalGmps.htm>

<sup>16</sup> “Window...” (fn. 11)

<sup>17</sup> Ibid.

<sup>18</sup> Sandra Fox, Maximizing Outsourced Biopharma Production, [www.contractpharma.com](http://www.contractpharma.com), June 2004

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<sup>20</sup> “Window...” (fn. 11)

<sup>21</sup> HighTech Business Decisions <http://www.hightechdecisions.com>

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<sup>23</sup> Diosynth to make Somavert API for Pfizer, [www.inpharma.com](http://www.inpharma.com), June 3<sup>rd</sup> 2003

<sup>24</sup> Inpharma (fn. 10)

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