T2+2™ Market Overview

Freeze-Drying for Biotechnology and Pharmaceuticals (Lyophilization)

July 24, 2009

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Lyophilization is a three-step freeze-drying process for removing nearly all the moisture from a target. The steps are "separate, but interdependent.[1]" First, the target is frozen. Next, the moisture in the target is removed via sublimation,[2] or the transitioning of a solid directly to a gas.[3] Approximately 90% of the target's moisture is removed in this step. Last, the target goes through a secondary drying stage.[4] Following lyophilization, the moisture content of the target is reduced to approximately 3% of its former amount, by weight.[5]

Lyophilization is frequently used in the biotechnology and pharmaceutical industries to both stabilize and increase the shelf-life of numerous vaccines, drugs, antibodies, and other biological materials.[6] Additionally, the process has been incorporated into certain microscopes, so that the effects of lyophilization and post-lyophilization melting can be observed directly.[7] While market sizes are hard to estimate, the following provides our estimates of the size and growth of the global lyophilization markets:

Market Niche Size			
Market Size in Dollars	***Growth Rate***	***Base Year***	***Detailed Basis for Estimate***
$250 million (cGMP lyophilizers)	10%-20%	2007	This estimate is taken from a *Biopharm International* article, and appears to be referencing only cGMP lyophilizers themselves and not ancillary items like glassware, polymer vials or other containers. The growth rate in the article is given as "double digit," thus yielding our 10%-20% range.[8]

[1] "Increasing lyophilization productivity, flexibility, and reliability using liquid nitrogen refrigeration: Part 1." November 1, 2007. *Biopharm International.* Goliath web site. http://goliath.ecnext.com/coms2/gi_0199-7220318/Increasing-lyophilization-productivity-flexibility-and.html (accessed July 24, 2009).
[2] Ibid.
[3] "Sublimation." Dictionary.com web site. http://dictionary.reference.com/browse/sublimation (accessed July 24, 2009).
[4] "Increasing lyophilization productivity, flexibility, and reliability using liquid nitrogen refrigeration: Part 1." November 1, 2007. *Biopharm International.* Goliath web site. http://goliath.ecnext.com/coms2/gi_0199-7220318/Increasing-lyophilization-productivity-flexibility-and.html (accessed July 24, 2009).
[5] "Lyophilization: Growing with Biotechnology." September 15, 2005. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1083&nc=1. (accessed July 24, 2009).
[6] "Product Technologies for Lyophilization." November 15, 2006. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1948&chid=3 (accessed July 24, 2009).
[7] "Lyostat 2 - Fully Integrated Freeze Drying Microscope." Biopharma Technology web site. http://www.lyophilizationtechnology.com/lyostat2.htm (accessed July 24, 2009).
[8] "Increasing lyophilization productivity, flexibility, and reliability using liquid nitrogen refrigeration: Part 1." November 1, 2007. *Biopharm International.* Goliath web site. http://goliath.ecnext.com/coms2/gi_0199-7220318/Increasing-lyophilization-productivity-flexibility-and.html (accessed July 24, 2009).

$60 million (laboratory lyophilizers)	6%-7%	2007	These estimates were taken from *Instrument Business Outlook*, and refer to smaller scale lyophilizers used for research rather than production.[9]
$1.3 billion (lyophilization services market)	10%-20%	2008	This estimate is given by merchant bank Clairvest Group. It is for lyophilization services provided by contract research organizations (CROs) to biotechnology and pharmaceutical companies. Clairvest also describes growth in the market as "double digit," again yielding our 10%-20% range.[10]

In addition to the above market estimates, we found that 151 million individual targets are expected to be lyophilized annually by 2010,[11] and that there was an installed base of over 3,000 cGMP lyophilizers as of 2007.[12] With regard to freeze-drying microscopes, while we could not find specific market size estimates, we did find that the Lyostat series of microscopes from Biopharma Technology (which, based on our research, appears to be the dominant freeze-drying microscope on the market) has been used in the formulation of over 470 biotechnology and pharmaceutical products.[13]

Market size and growth rate are a function of the number of people in the market and the anticipated rate of buying. As markets transition between emerging, growth, shakeout, mature, and declining, the basis for competition and the number of competitors usually changes, along with the factors influencing adoption of innovation. The number of and growth rate for customers suggests how many units might be sold.[14]

Our Current View on the Phase of the Market	
Today	***Trend***
Growth	Growth

[9] "Market profile: laboratory lyophilizers." December 31, 2007. *Instrument Business Outlook.* AllBusiness web site. http://www.allbusiness.com/pharmaceuticals-biotechnology/pharmaceuticals-industry/11414841-1.html (accessed July 24, 2009).
[10] "Clairvest Announces US$20 Million Investment in Lyophilization Services of New England." March 26, 2008. Reuters web site. http://www.reuters.com/article/pressRelease/idUS215065+26-Mar-2008+MW20080326 (accessed July 24, 2009).
[11] "Lyophilization: Growing with Biotechnology." September 15, 2005. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1083&nc=1. (accessed July 24, 2009).
[12] "Increasing lyophilization productivity, flexibility, and reliability using liquid nitrogen refrigeration: Part 1." November 1, 2007. *Biopharm International.* Goliath web site. http://goliath.ecnext.com/coms2/gi_0199-7220318/Increasing-lyophilization-productivity-flexibility-and.html (accessed July 24, 2009).
[13] Wood, Richard. "Empirical Data Help Freeze-Drying." Physicsworld web site. http://physicsworld.com/cws/article/indepth/32729 (accessed July 24, 2009).
[14] For a detailed discussion of the "innovativeness dimension," see Everett M. Rogers, *Diffusion of Innovations*, 4th ed. (New York: Free Press, 1995). For further readings related to market phases and innovation, see also James Utterback, *Mastering the Dynamics of Innovation* (Boston: Harvard Business School Press, 1996) and Vijay K. Jolly, *Commercializing New Technologies: Getting from Mind to Market* (Boston: Harvard Business School Press, 1997).

While the technology behind lyophilization appears to be mature and has been used for over 60 years,[15] the continuing robust growth of the biotechnology and pharmaceutical markets appears to be driving significant demand for lyophilization equipment. Between 2005 and 2012 it is expected that 25% of the 300 sterile products likely to be approved by the FDA will require lyophilization, as will 40% of the new molecular entities (NMEs).[16] This growth appears set to continue, as biologics, the pharmaceutical product class that is most likely to require lyophilization,[17] are expected to grow at a compound annual growth rate (CAGR) of 13% through 2010, [18] far outpacing the overall pharmaceutical industry growth rate of 5.5%.[19]

Markets can also be described in terms of the basis for competition (best technological performance, best value or the price/performance tradeoff that best matches the end-users' preferences, lowest cost, or best availability or the ability to get the product quickly). This dimension helps to define the context in which a commercialization strategy must be developed.

Basis for Competition in the Arena	
Today	***Trend***
Best Value	Best Value

According to our research, lyophilizers appear to be most often purchased by CROs, companies that perform outsourced drug research and development for biotech and pharmaceutical companies.[20,21] This is because it is often not cost-effective for these companies to make the capital investment in lyophilizers themselves.[22] This appears to indicate that price is the most important aspect of lyophilizers. However, given that these machines can cost over $3 million[23] and are quite complex,[24] we infer that performance

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[15] Wood, Richard. "Empirical Data Help Freeze-Drying." Physicsworld web site. http://physicsworld.com/cws/article/indepth/32729 (accessed July 24, 2009).
[16] "Lyophilization: Growing with Biotechnology." September 15, 2005. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1083&nc=1. (accessed July 24, 2009).
[17] Ibid.
[18] "Biologics Driving Growth to 2010." June 22, 2006. Pharmaceutical Business Review web site. http://www.pharmaceutical-business-review.com/comment/biologics_driving_growth_to_2010_comment (accessed July 24, 2009).
[19] "Pharmaceutical Market Trends, 2008 - 2012: key market forecasts & growth opportunities." Biopharm Knowledge Publishing web site. http://www.bioportfolio.com/cgi-bin/acatalog/Pharmaceutical_Market_Trends__2008_-_2012__key_market_forecasts___growth_opportunities.html#a1190 (accessed July 24, 2009).
[20] Bucur, Brian. "Low-Risk Lyophilization." PharmaManufacturing.com. http://www.pharmamanufacturing.com/articles/2009/036.html (accessed July 24, 2009).
[21] "Why Anteco?" Anteco Pharma web site. http://www.antecopharma.com/why-anteco (accessed July 24, 2009).
[22] Ibid.
[23] "Product Technologies for Lyophilization." November 15, 2006. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1948&chid=3 (accessed July 24, 2009).
[24] Jennings, Thomas A. "Lyophilization: Introduction and Basic Principals." 1999; Interpharm/CRC, p. 4. http://books.google.com/books?id=Zjuu-

must also play a considerable role in the purchase decision. Thus, it is most likely that competition in this market occurs based on value.

In each market there may be stakeholders and companies with significant market share that will influence the introduction of your technology. Some organizations or companies that will likely influence the introduction of this technology are the following:

Examples of Major Competitors in the Arena

Competitor	***Relevance***	***Web site***
FTS Systems	Developer of the SMART Freeze-Dryer Technology that is incorporated into the company's LyoStar lyophilization systems.[25]	http://www.ftssystems.com
Lyophilization Systems Inc.	Manufacturer of lyophilizers ranging for 3 to 300+ square feet.[26]	http://www.lyogroup.com/pages/3/index.htm
GEA Process Engineering	Has been manufacturing lyophilizers for over 50 years. Current lyophilizer brand is the Lyovac.[27]	http://www.niroinc.com
Serail	Lyophilizer manufacturer with over 40 years experience.[28]	http://www.serail.com/serail.htm
IMA Edwards	Manufacturer of the Lyomax and Lyofast lyophilizers, as well as a complete line of lyophilization-related products.[29]	http://www.imaedwards.com
Biopharma Technology	Based in the U.K. Manufacturer of the LyoStat II freeze-drying microscope as well as the LyoTherm II impedance analyzer. [30]	http://www.lyophilizationtechnology.com

Examples of Key Stakeholders or Networking Channels with Contact Information

Stakeholder	***Relevance***	***Contact Information***
International Society of Lyophilization – Freeze Drying (ISLFD)	Organization dedicated to the advancement of lyophilization and the support of lyophilization professionals.[31]	112A Bala Ave. Bala Cynwyd, PA 19004 Tel: 610-660-9665

pB5kWYC&pg=PA4&lpg=PA4&dq=lyophilization+complexity&source=bl&ots=d0RoNNyDAW&sig=eeFJpCEIWv89Mg8JIxZz46WnhtQ&hl=en&ei=zvRpStPjIMy_tgfC-8SnCw&sa=X&oi=book_result&ct=result&resnum=1 (accessed July 24, 2009).

[25] "SMART Freeze-Dryer Technology." FTS Systems web site. http://www.ftssystems.com/Smartfreezedryerstech.htm (accessed July 24, 2009).

[26] Lyophilization Systems Inc. web site. http://www.lyogroup.com/pages/3/index.htm (accessed July 24, 2009).

[27] "cGMP Lyophilizers and Lyophilization Systems." GEA Process Engineering web site. http://www.niroinc.com/pharma_systems/lyophilizers.asp (accessed July 24, 2009).

[28] Serail Inc. web site. http://www.serail.com/serail.htm (accessed July 24, 2009).

[29] IMA Edwards web site. http://www.imaedwards.com (accessed July 24, 2009).

[30] Biopharma Technologies web site. http://www.lyophilizationtechnology.com (accessed July 24, 2009).

[31] International Society of Lyophilization – Freeze Drying web site. http://www.islyophilization.org (accessed July 24, 2009).

		http://www.islyophilization.org
Biotechnology Industry Organization (BIO)	The world's largest biotechnology industry group, with over 1,200 members. [32]	1201 Maryland Avenue, SW Suite 900 Washington, DC 20024 Tel: 202-962-9200 http://www.bio.org
American Association of Pharmaceutical Scientists (AAPS)	Professional society with over 12,000 member researchers.[33]	2107 Wilson Blvd, Suite 700, Arlington, VA 22201-3042 Tel: 703-243-2800 http://www.aapspharmaceutica.com
International BioPharmaceutical Association (IBPA)	Group that brings together international CROs and biopharmaceutical companies. Provides services to all stakeholders in biopharmaceutical R&D.[34]	PMB 143 11521 N FM 620 #250 Austin TX 78726 Tel: 713-366-8062 http://www.ibpaalliance.org

Entry barriers are obstacles that remove customer segments from the market for some period of time. They limit the size of the addressable market in general or the market share that can be captured. These barriers must be overcome or avoided to have a successful market entry. Our work to date suggests the following entry barriers may prevent customer segments from buying this type of technology for some period of time.

Market Entry Barriers	
Name of Barrier	***Description/Why***
High Cost of Lyophilizers/Low Volume of Market	Lyophilizers are expensive pieces of equipment, with production models costing as much as $3 million. This is largely due to the redundancy that must be built into each machine, as any failure would ruin extremely expensive biological and pharmaceutical products.[35] Thus, while the market's dollar value makes it appear attractive, when one considers that there are only around 3,000 cGMP lyophilizers currently installed,[36] it becomes apparent that it is a very low volume market. This is likely a significant barrier to new lyophilizer manufacturers, as in such a low volume market it may be difficult to take significant share from established companies.

[32] "About BIO." Biotechnology Industry Organization web site. http://bio.org/aboutbio/ (accessed July 24, 2009).
[33] "Who we are." Amercan Association of Pharmaceutical Scientists web site. http://www.aapspharmaceutica.com/about/index.asp (accessed July 24, 2009).
[34] "Our Mission." International Biopharmaceutical Association web site. http://secure.ibpaalliance.org/index.html (accessed July 24, 2009).
[35] "Product Technologies for Lyophilization." November 15, 2006. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1948&chid=3 (accessed July 24, 2009).
[36] "Increasing lyophilization productivity, flexibility, and reliability using liquid nitrogen refrigeration: Part 1." November 1, 2007. *Biopharm International.* Goliath web site. http://goliath.ecnext.com/coms2/gi_0199-7220318/Increasing-lyophilization-productivity-flexibility-and.html (accessed July 24, 2009).

Regulation of Lyophilization	The U.S. Food & Drug Administration has issued guidelines on the inspection of lyophilized products and processes,[37] and since 2004 has been paying close attention to the use of the process in drug and vaccine manufacturing.[38] Lyophilization is also closely watched by European regulatory authorities, who have had concerns regarding sterility after the process is complete, as well as with residual moisture.[39] Such regulatory oversight and the exacting performance specifications it requires may serve to hinder the market.
Difficulties in Achieving Target Moisture Levels	The accuracy of the secondary drying step in lyophilization can vary, and often the desired level of moisture removal is not achieved. Enough moisture has to be removed to increase shelf-life, but removing too much can result in product instability.[40] Given the high cost of lyophilizers, such problems likely prevent potential end-users from making the significant capital investment.

While the market for lyophilizers is certainly growing, the market is not without challenges. There are still technical issues that need to be resolved in the process, and as long as the prices remain as high as they are, it is likely that biotech and pharmaceutical companies will continue to rely on CROs rather than purchasing their own lyophilizers,[41] which constrains the market.

Market drivers are forces that strengthen or weaken the importance of end-user needs over time. Practice level drivers are micro-economic; they affect the end-user directly. They influence the selection of substitutable goods and thus affect market share. Arena level drivers affect the organizations and industrial sectors in which the end-users work. They influence the overall demand for goods like this technology and its substitutes. They affect when and how much of the total addressable market is actually going to be in the market and buying.

Market Drivers	
Name of Driver	***Why Significant***
Growth in Biologics	Biologics, a class of materials used in pharmaceuticals that include monoclonal antibodies and recombinant proteins,[42] are expected to be one of the fastest

[37] "Lyophilization of Parenterals (7/93)." U.S. Food & Drug Administration web site. http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074909.htm (accessed July 24, 2009).
[38] Ludwig, Elisa. "Lyophilized products appear to be under FDA microscope." June, 2004. Entrepreneur.com web site. http://www.entrepreneur.com/tradejournals/article/120357126.html (accessed July 24, 2009).
[39] Ray, Louis and Florence Lhospice. "Lyophilization is not a freeze-dried technology." October 1, 2006. Pharmaceutical Technology Europe web site. http://www.ptemag.com/pharmtecheurope/Biopharmaceuticals/Lyophilization-is-not-a-freeze-dried-technology/ArticleStandard/Article/detail/390975?contextCategoryId=41896 (accessed July 24, 2009).
[40] "Product Technologies for Lyophilization." November 15, 2006. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1948&chid=3 (accessed July 24, 2009).
[41] "Why Anteco?" Anteco Pharma web site. http://www.antecopharma.com/why-anteco (accessed July 24, 2009).
[42] "Lyophilization: Growing with Biotechnology." September 15, 2005. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1083&nc=1. (accessed July 24, 2009).

	growing sectors of the pharmaceutical industry, growing more than twice as fast as the industry on the whole.[43] This growth is likely to continue driving demand for lyophilizers.[44]
Growth in CRO Activity	In 2008, CROs performed $20.4 billion worth of services for biotech and pharmaceutical companies, a number which is forecast to rise to $31 billion by 2012,[45] representing a CAGR of over 11%. As CROs are a large segment of lyophilizer end-users, this should be a positive driver for the market.
Development of Alternative Methods	Alternative processes to lyophilization are being developed, such the precipitation method developed by Roche for use in the manufacture of peptides. This method has allowed Roche to reduce its production costs.[46] If such alternate methods become widespread, they will likely slow the growth of the lyophilization market.

While the signs are generally positive for the lyophilization market, manufacturers need to be aware that due to the costs of lyophilization equipment, alternative processes are being evaluated.

Here are some additional data and sources that can help you better understand the market.

Name	*Description*
IBPA CRO Directory	The IBPA maintains a directory of CROs, many of whom use lyophilizers. The directory can be viewed at the following URL: http://www.ibpaalliance.org/assets/usrdocs/contract-research-companies.html
Lyophilization: Introduction and Basic Principals	Thomas A. Jennings text on lyophilization is available for free at Google Books. It can be viewed at the following URL: http://books.google.com/books?id=Zjuu-pB5kWYC&pg=PA4&lpg=PA4&dq=lyophilization+basic+principals&source=bl&ots=d0RoNPrwzV&sig=wa

[43] "Biologics Driving Growth to 2010." June 22, 2006. Pharmaceutical Business Review web site. http://www.pharmaceutical-business-review.com/comment/biologics_driving_growth_to_2010_comment (accessed July 24, 2009).
[44] "Lyophilization: Growing with Biotechnology." September 15, 2005. Genetic Engineering & Biotechnology News web site. http://www.genengnews.com/articles/chitem.aspx?aid=1083&nc=1. (accessed July 24, 2009).
[45] "Global Pharmaceutical Contract Manufacturing Market To Reach Over $31B By 2012 According To A New Report By Global Industry Analysts, Inc." October 23, 2008. Pharmaceutical Online website. http://www.pharmaceuticalonline.com/article.mvc/Global-Pharmaceutical-Contract-Manufacturing-0001 (accessed July 24, 2009).
[46] Jarvis, Lisa. "Changing Tides." July 17, 2006. *Chemical & Engineering News.* American Chemical Society web site. http://pubs.acs.org/email/cen/html/082806160414.html (accessed July 24, 2009).