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European Biomanufacturing Efficiency Outstripping US
Outlook for Capacity Utilisation Through 2015

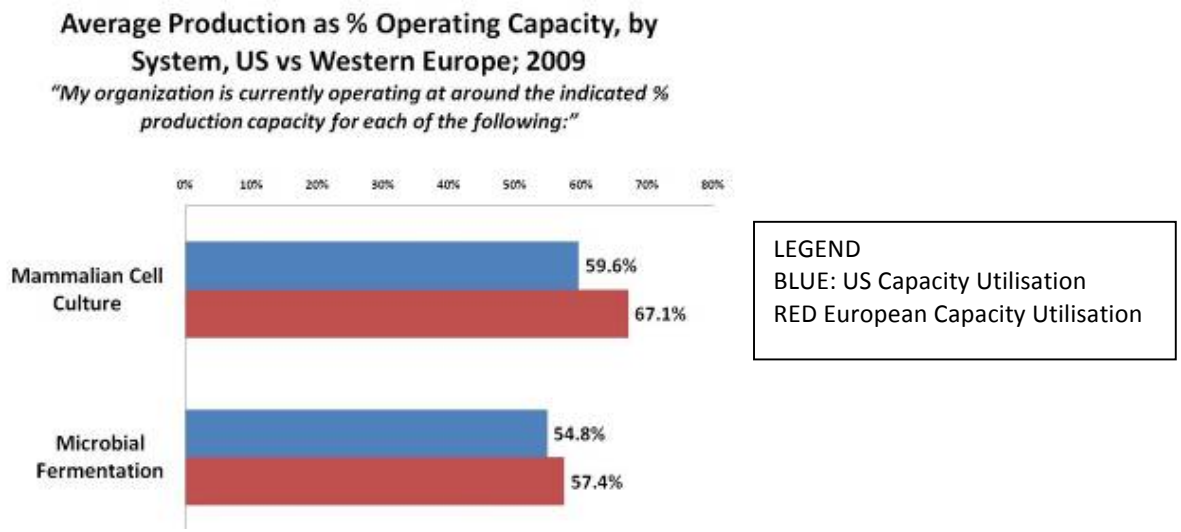
Introduction

European biopharmaceutical manufacturers are doing a better job at using available capacity than their US counterparts. In fact, last year in mammalian cell culture systems European biomanufacturers' 'capacity utilisation' rate was 67.1% compared to 59.6%, for US biomanufacturers. For microbial systems, European manufacturers report slightly greater capacity usage compared with US counterparts (57.4% vs. 54.8%, respectively).

These data, from the 7*th Annual Report and Survey of Biopharmaceutical Manufacturing* (BioPlan Associates, Inc), are among critical manufacturing issues probed through this annual study of 325 globally biomanufacturers and CMOs. A major finding was the 5-year capacity expansion trend comparisons between US and Western European biomanufacturers.

To put the data in context, the annual report provides a composite view and trend analysis from biopharmaceutical manufacturers and contract manufacturing organisations in 35 countries. It covers manufacturing issues including: Current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, employment and training.

Fig 1: Capacity Utilization by System, US vs. Western Europe



Source: 7th Annual Report and Survey of Biopharmaceutical Manufacturing (BioPlan Associates, Inc), Rockville MD April 2010

Similar patterns are evident from earlier years. In 2007, for example, Europeans reported higher microbial system capacity use (66%) than US manufacturers (53% in 2008).

Global Capacity Utilization Trends

Globally, capacity utilisation over the past year has remained unchanged for mammalian cell culture systems (at around 61%), and is virtually flat for microbial fermentation, as well (at around 56%). Since 2003, capacity utilization for mammalian cell culture systems has dropped significantly, by over 15.5 percentage points from 76.4% in 2003 to 60.9% in 2009.

Capacity utilisation is important for planners and investors as they determine whether biopharmaceutical manufacturing capacity will be available for the production of pipeline drugs that may be reaching approval. In 2003, there was insufficient capacity for the campaigns at the time, with the global industry's utilization rates exceeding 76%. This was a capacity-crunch time that led to facility build-outs by both biotherapeutic developers and contract manufacturers. The resulting expansions brought the utilisation rate down so that by 2006 it appeared that a stable capacity utilisation rate would be around 63%.

The biopharmaceutical segment has become increasingly adept at avoiding unanticipated high production demands that can create a capacity crunch. As a result, we saw a narrowing of the capacity utilization gap, which moved from an 18-percentage point spread between US total

industrial, and biopharmaceutical capacity utilization rates for mammalian cell culture systems in 2007, to an 8-percentage point gap in 2008, and then to a 13-point spread this past year.

Excess, 'flex' or buffer capacity is important in this business because the opportunity costs associated with *not* getting a company's product to market can be devastating. On the other hand, the cost of an idle biomanufacturing facility, and costly excess capacity is also actively avoided. So predicting one's own needs and overall industry capacity becomes a high-stakes game. Today, smoothed-out biopharmaceutical industry utilization rates are due primarily to improved planning by manufacturers, and the lack of any major blockbuster drugs that might absorb substantial industry capacity. The leveling-off in biomanufacturing capacity suggests that companies are using their existing capacity more efficiently, and are planning more effectively for shifts in demand for additional capacity. Some CMOs prefer to target higher utilization rates, upwards of 80%, because of the cost of idle capacity.

Part of the reasons for the decreased utilisation rates in recent years is the earlier build-outs, but more recently, higher yields in current systems have reduced the need for additional biomanufacturing capacity. Further, regulatory approval rates for new biopharmaceuticals, until recently, have been flat. Use of disposable bioreactor technologies for cell culture coupled with external perfusion may shift overall capacity towards cell culture production (MAb and otherwise).

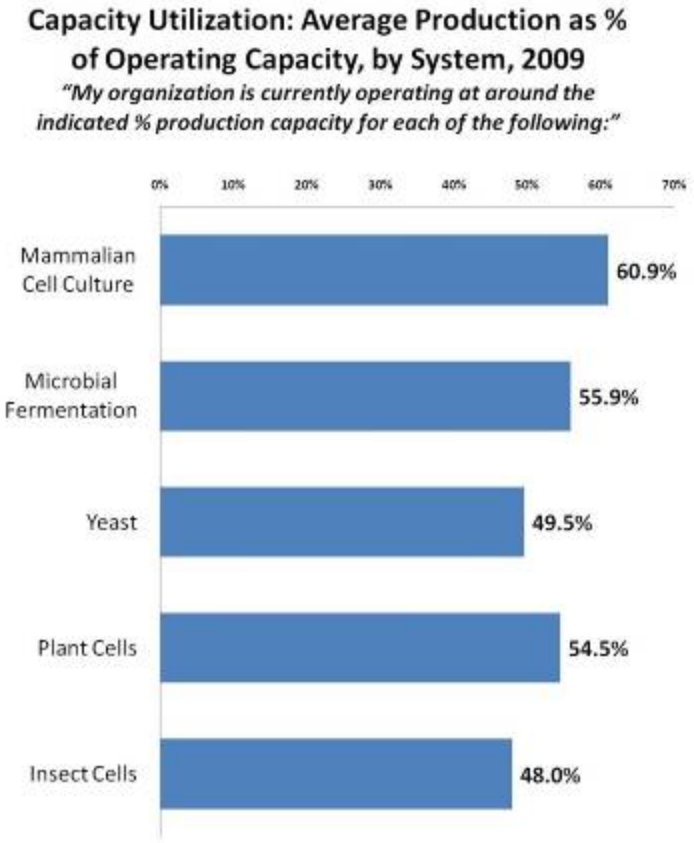
Comparison of Biopharma Utilisation Rates vs All Industries

We compared the biopharma industry data with overall US industrial production[1] and in February 2008 for all US industries, capacity utilisation rate was to 80.7 percent. By February 2009, that rate had fallen to 70.9%, and in February 2010, the rate had bounced back to 73.0%.

Our study showed that capacity utilisation for mammalian cell culture systems was at 60.9% globally. Microbial systems were at 55.9%, and yeast was at 49.5%. As in previous years, plant and insect systems were at a lower utilisation level than mammalian cell culture.

Fig 2: Capacity Utilization, By System, 2009

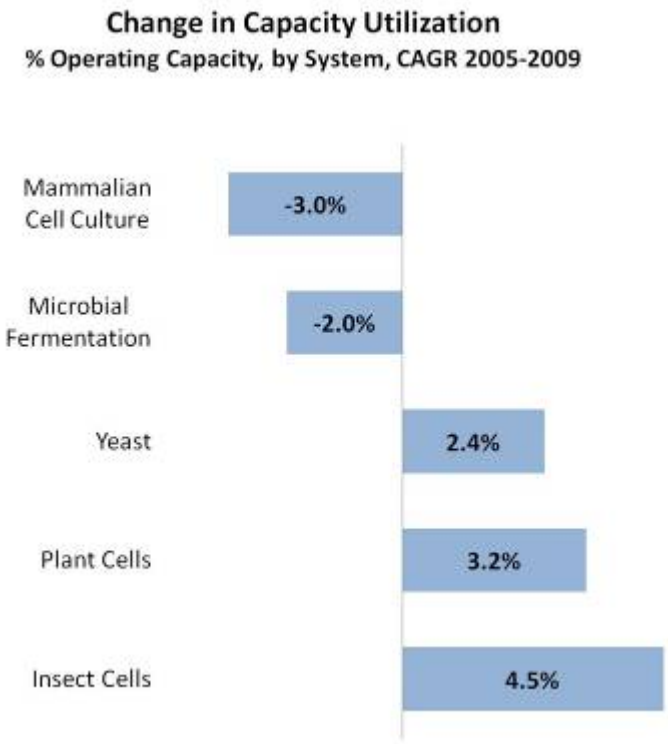
[1] US Federal Reserve Statistical Release; Industrial Production and Capacity Utilization: http://www.federalreserve.gov/releases/g17/current/default.htm



Average Growth Rate in Capacity Utilization, 2005-2009

Across all systems between 2003 and 2008, we find that utilisation has leveled off. The current economic situation has had a dramatic impact on global capacity utilisation for all industrial segments, and so it is having impact on biopharmaceutical products. Recent capacity utilisation changes have generally been small, a decrease of 2-3% for mammalian and microbial systems over the pasts three years. For the less common systems, such as plant, and insect, there has been an increase. But these tend to reflect larger swings due to fewer users, so these numbers may vary based on fluctuations at a relatively small number of facilities.

Fig 3: Change in Capacity Utilization, CAGR, 2005-2009



Current State of Capacity Utilisation

Budget concerns, over-capacity, improved manufacturing technologies, and disposables are only a few of the factors have converged to create a continuing surplus of both mammalian cell culture and microbial fermentation capacity. As the industry matures, and improvements in manufacturing technology continue, major biopharmaceutical companies with substantial mammalian cell culture capacity of their own (Amgen, Genentech, Pfizer/Wyeth, etc.) are likely to operate at less than industry-average capacity, despite having large production requirements.

Continuing from previous years, both large and mid-tier contract manufacturers, including Lonza (Basel, Switzerland), Boehringer Ingelheim (Biberach, Germany), Celltrion (Incheon, South Korea), and many others, may continue to experience capacity surplus. Despite the financial risks to CMOs of holding idle capacity, most have not begun to compete on price to reduce their supply.

Capacity Constraints: US vs. European Biomanufacturers

About 11% of U.S. respondents perceived "severe" or "significant" constraints, while 13.8% of Western European respondents did so. Further, more respondents at Western European facilities

were experiencing "moderate" constraints (21% vs. 14%). Last year there were some significant differences between the two groups. For example, 40.5% of Western European respondents in 2008 (study data collection period) indicated that they were experiencing "No constraints", while 50.3% of US respondents felt the same (a 10% spread). The percentages in both groups experiencing no constraints has been rising, but the gap has shifted, and a greater percentage of Western European biomanufacturers appear to be seeing no capacity constraints this year, compared to the two previous years, where more US companies were seeing no capacity constraints.

Fig. 4: Capacity Constraints, US vs. Europe, for 2010 Study

Expectations of Capacity Constraints in the Next Five Years

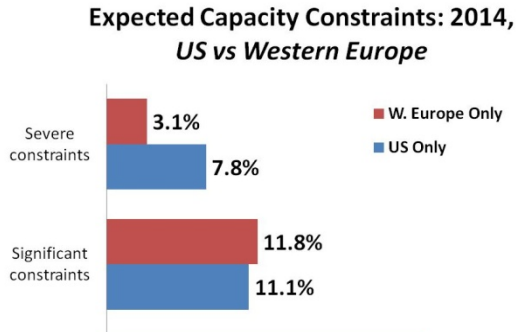
Respondents were asked to predict the extent their facility is likely to experience production capacity constraints (by 2014). Globally, respondents seemed moderately more concerned about upcoming capacity constraints on commercial-scale production vs clinical scale. This year, 23.6% expected either "significant" or "severe" constraints on commercial production systems in the next five years, compared to 18.8% and 15.3% for late-stage-clinical and early-stage-clinical systems.

The percentage of respondents expecting to experience at least *some* constraints in five years is significantly higher than what is being experienced today: 24%, 29% and 32% of respondents (commercial, late clinical, and early clinical, respectively), predicted that within five years they would continue to experience *no constraints*. This compares with 42%, 50%, and 51% of respondents today who are experiencing *no constraints* at those same scales. The industry appears to expect to use up this excess capacity by then.

Expected Capacity Constraints by 2014: U.S. vs Western Europe

This year we found relatively few differences between these segments regarding severity of constraints, although this year, less than half the percentage of Western European respondents indicated they expect severe constraints in five years (3.1% vs 7.8% for US). However, when aggregating projections of "significant" or "severe" constraint expectations, these segments remained relatively consistent (15% W Europe vs 19% in U.S). A significantly larger percentage of Western European respondents projected expectations of "no constraints" (37% vs 25.6% for US). This may suggest that Western European biomanufacturers are expecting less severe constraints in five years. Some industry observers have seen increased development of microbial/yeast based processes in the US where currently very few large scale fermentation facilities are available or being constructed. This may result in future constraints particularly in Europe, which has a significant larger number of production scale facilities for microbial and yeast based process.

Fig 5: Five-year Projections for Capacity Constraints: US vs Western Europe



Factors Creating Future Capacity Constraints

Respondents were asked to identify the major factors likely to constrain their organization's production capacity over the following five years. This year, the most frequently checked factors were "Facility constraints" (55.4%), "Physical capacity of downstream purification equipment" (41.7%), "Analytical testing and drug product release" (31.9%), and "Costs associated with downstream purification" (29.4%). Those who felt that they were "unlikely to see capacity

constraints in five years" were in a minority (10%). This compares with 21.4% of respondents last year who indicated they were unlikely to see capacity constraints in five years.

Despite the global economic downturn, scientific labor markets were seen as tightening somewhat. Expectations of constraints due to the "inability to hire new, experienced scientific staff" jumped from 15.9% of respondents last year to 22.7% this year. Much of the tightening in the market for experienced bioprocessing specialists may not be due to an actual shortage. Rather these specialists are increasingly being spread out over a growing number of biopharmaceutical companies worldwide, including dozens of new biosimilar entrants and many new companies in India, China and other developing countries worldwide.

Not surprisingly, downstream purification constraints and cost of purification bioprocessing are still among the biggest concerns. Barring a major purification technology breakthrough in the next few years we do not expect to see improvement in purification capacity deficiency, as well as a purification cost reduction resulting from such an improvement.

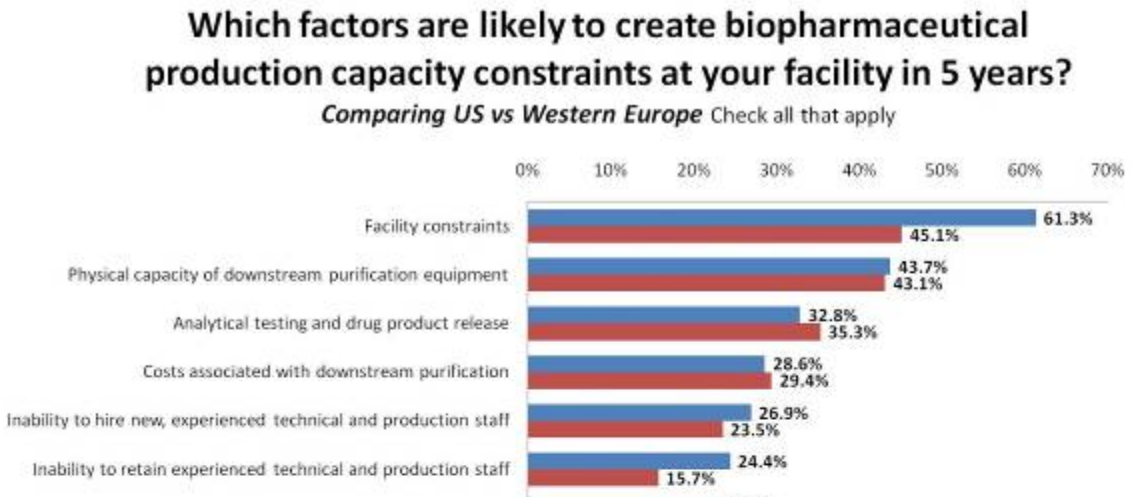
Factors Creating Capacity Constraints: US vs. Western European Respondents

Expectations regarding future capacity-constraint factors showed some significant differences between US and Western European manufacturers.

- "Facility constraints" represented the largest divergence in responses, (61.3% of US, vs 45.1% of Western European respondents).
- Concerns over *"Physical capacity of downstream purification equipment"* are now approximately equal -- noted by 43.1% of Western European respondents versus 43.7% of US respondents (Last year the figures were 27.3% W.E. and 47.9% U.S.).
- 24.4% of US respondents foresaw capacity constraints arising from the *"Inability to retain experienced technical and production staff,"* whereas only 15.7% of European respondents did so (Last year, 26.3% US and 12.4% Europe).
- Similarly, 19.3% of US respondents foresaw capacity constraints arising from the *"Inability to retain experienced scientific staff,"* whereas only 11.8% of European respondents did so (Last year, 21.7% US and 12.4% Europe). So employee retention issues in the US are relaxing this year, while they have remained a concern in Europe.

- On the other hand, *hiring* in Western Europe appears to be slightly more problematic than in the US. *"Inability to hire experienced technical and production staff,"* was indicated by 18.5% vs 19.6% of European respondents as a cause of capacity constraints.
- *"Inability to optimize my overall system, given my current technology and resources"* was a concern of 21.8% of US respondents, vs. only 15.7% of Western European respondents. This suggests US respondents may be more interested in novel technologies aimed at system optimization (perhaps better media formulations and/or expression systems).
- *"Production problems with downstream purification"* although not a major issue, appears to be a slightly greater problem with European respondents (15.7% vs 12.6% for US respondents).

Fig 6: Selected Factors Creating Future Capacity Constraints, US vs Western European Biomanufacturers



Key Areas to Address to Avoid Future Capacity Constraints

Globally, respondents indicated that to avoid significant future capacity constraints, the top area, for the fourth year running, involved downstream purification. This year, *"Develop better downstream purification technologies"* took the top spot with 55.9% of respondents feeling new technologies are required. Following was "*Develop more cost effective disposables"* with 44.6% indicating the area needing fixing. This was also a major concern in 2007 (39.6%) as well as in 2006.

"Optimize systems to improve downstream purification performance" was third on the list of areas to fix to avoid capacity problems (42.6%). This has been more or less consistent over the past 4 years, although on a slightly downward trend. However, when combined with the number one cited need being *development of new purification technologies*, purification clearly tops the list of capacity constraint concerns.

Avoiding Capacity Constraints: U.S. vs Western Europe

We compared responses from facilities in the US and Western Europe. The primary areas of differences in how capacity constraints can be avoided are show below.

Western European respondents were more likely to want improvements in these areas:

- Better downstream purification technologies (66.7% W. Europe, vs 52.9% in the US)
- Increase training in regulatory areas (very slightly higher: 15.7% W. Europe, vs 14.3% in the US)

US respondents were more likely to want improvements in these areas:

- Optimize systems to improve downstream performance (47.1% in the US vs 39.2% in W. Europe)
- Streamline FDA regulatory process (37.8% in the US vs 31.4% in W. Europe)
- Reduced scale-up and early-stage costs (34.5% in the US vs 23.5% in W. Europe)
- Fund more research to maximize production efficiencies (28.6% US vs 15.7% W. Europe)
- Manufacturing standards and industry benchmarking (27.7% in the US vs 19.6% in W. Europe)

- Better training and education in technical areas (22.7% in the US vs 13.7% in W. Europe)

This is generally similar to the pattern seen in 2008, and in 2007 as well. In 2008, "Optimize downstream purification performance", was indicated by 47.1% of US and 39.2% of W.E. facilities as a way to avoid constraints. "Streamline FDA regulatory process", was indicated by 37.8% of US facilities as a way to avoid constraints, versus 31.4% in Europe. The other discrepancies between the U.S. and Europe last year related to "Funding more research to maximize production efficiencies." 28.6% of US facilities indicated this as a way to avoid capacity constraints, while only 15.7% of European facilities agreed.

Planned Future Capacity Expansions

On average, respondents indicated that they plan to increase overall mammalian cell culture production capacity by 49%, *in total*, within the next five years (compared with 5-year projections of 57% expansion that was made the prior year projection). For microbial systems, respondents projected a 39% increase over the next five years (vs 34% the prior year). Thus, respondents' projections from last year regarding capacity increases have decreased significantly for mammalian systems (by 8 percentage points), but have increased by 4 percentage points for microbial systems.

Note that these numbers refer to the average percentage that each respondent is planning to increase capacity, not the percentage or number of industry production capacity liters that will be increased.

Planned Five-Year Capacity Expansions; US vs. Western European Manufacturers

This year Western European respondents projected they would see five-year capacity expansions for mammalian-cell systems of 67% on average, compared to 38% for US respondents. However, once again this year, compared to the previous two years, expansion plans, Western European facilities have clearly scaled back. Despite the recognition by respondents of excess capacity today, and in coming years, both US and European respondents, on average, indicated their five-year expansion plans were relatively stable over time.

Table 1

Western European vs US Biomanufacturers' 5-year projected Capacity Increase

	Mammalian Systems		Microbial Systems	
	Western European Biomanufacturers' 5-year projected increase	*US Biomanufacturers' 5-year projected increase*	*Western European Biomanufacturers' 5-year projected increase*	*US Biomanufacturers' 5-year projected increase*
2009	67%	38%	41%	37%
2008	62%	44%	28%	32
2007	66%	36%	44%	33%

Summary: Capacity and Industry Trends

There is likely to be sufficient capacity in both Western Europe and the US to meet production requirements for biopharmaceuticals over the next five years. Budgets for new capacity are being cut, and companies continue to consider CMO capabilities at the scale-up stage and beyond. With the increase in biopharmaceutical approvals[2], some industry capacity may be absorbed. Further, because blockbuster products, particularly monoclonal antibodies, can consume substantial installed capacity, the success or failure of one or two of potentially high volume products in development can significantly change the capacity utilization picture. However, this only affects those few with the largest capacity, and we are seeing fewer likely blockbuster products in the pipeline.

In addition, continued technology improvements in up and downstream production will likely change overall facility requirements for capacity. Thus, installed capacity may become a less important factor. Output and productivity may be measured differently in coming years as higher titers in bioreactors require less capacity for the same production. Disposable, single-use manufacturing is also changing how the industry measures efficiency and capacity. Most existing facilities today were designed for lower titer products; some with 20,000 L bioreactors. As titres continue to increase, and as new production technologies, improved cell lines and expression levels are introduced, and as improved media formulations and supplements improve bioreactor performance without additional installed capacity, the bottlenecks will continue to shift down-stream.

Biotherapeutic developers in both Western Europe, and in the US continue to predict that the physical capacity of downstream purification equipment will be the greatest constraint on capacity

in the near future, in part due to the improvement in titers. Though we have seen incremental improvements in purification technology, the industry is looking for significantly cheaper, 'lower-staff' improvements to reduce the problems associated with purification capacity. These are unlikely to occur rapidly.

References:

1) 7th Annual *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*, Annual, BioPlan Associates, April 2010 (see http://www.bioplanassociates.com/publications/bmcp.htm).
2) Rader, R.A., *BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets*, Biopharmaceutical online database, http://www.bioplanassociates.com/publications/pub_bpuseu.htm.

BIO

Eric S. Langer is president and managing partner at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing in Rockville, MD. He has over 20 years' experience in biotechnology and life sciences management and market assessment. He is an experienced medical and biotechnology market publisher, practitioner, strategist, researcher, and science writer. He has held senior management and marketing positions at biopharmaceutical supply companies, and teaches biotechnology marketing, marketing management, services marketing, and bioscience communication at Johns Hopkins University, American University, among others. He is co-founder and Managing Partner at BioPlan Associates Inc and has a degree in Chemistry from the University of Maryland and a Masters in International Business from American University.