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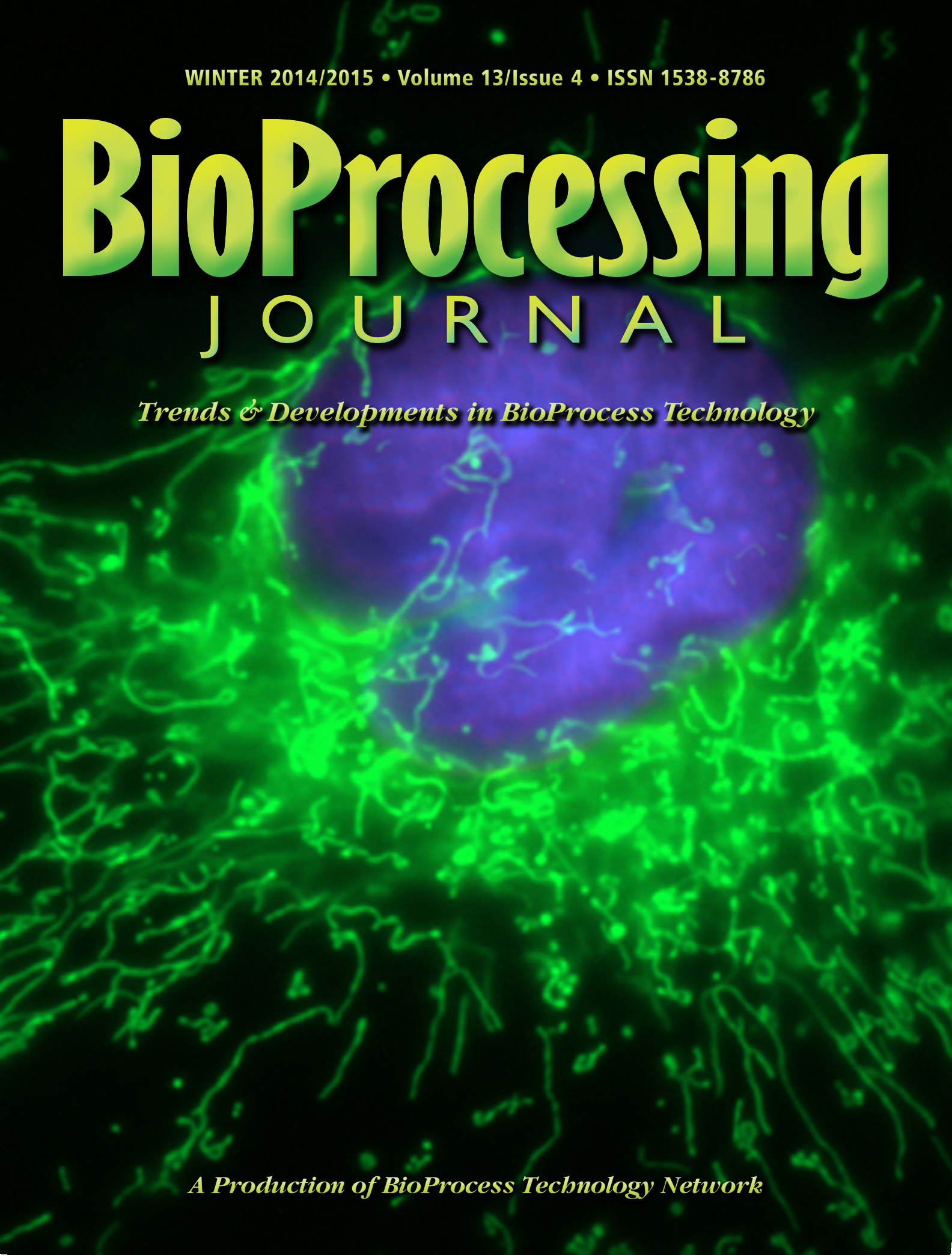

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TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Biopharmaceutical Manufacturing: *Historical and Future Trends in Titers, Yields, and Efficiency in Commercial-Scale Bioprocessing*

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Abstract

This article documents the progress, current state, and projected future trends in titer and yield as industrial and technological benchmarks for commercial-scale biopharmaceutical manufacture. Biopharmaceutical product commercial-scale manufacturing (bioprocessing) was benchmarked by tracking titers and yields over time, from the 1980s to the present, and further out ten years. This study compiled commercial-scale titer and yield data for a set of 39 major biopharmaceuticals, nearly all mammalian-expressed proteins, particularly, monoclonal antibody products. This included extensive searches of many potential data sources, including contacting knowledgeable bioprocessing professionals.

In the 1980s and early 1990s, average titers at commercial scale started out at < 0.5 g/L. The current average reported commercial-scale titer is 2.56 g/L. We also confirmed that the manufacture of commercial products has, over the years, undergone repeated cycles of technical production upgrades, with titers and yields increasing incrementally, even for the oldest products. BioPlan estimates that ≥3 g/L is now the industry standard titer for new bioprocesses being developed, with ≤7 g/L now presumed to be the general industry top-end titer level that, while not unusual, is not often achieved. In terms of yields, we found a 70% yield to be the current industry average yield, not the often-cited 75%. Improvements in downstream purification technologies (*e.g.*, as demonstrated by higher yields) have been fewer and adopted more slowly than upstream production.

Introduction

In biopharmaceutical manufacturing, titers, measured in mass (grams) of desired proteins per volume (liter) produced in the bioreactor, and yields, measured as percent of mass (grams) of purified product obtained vs. mass (grams) at the start of purification, are the key benchmarks that manufacturers use to determine operational efficiency and improvements in bioprocessing. Titer is essentially the amount of protein produced in each liter of bioreactor fluid. If the titer doubles, then all else being equal, only half as much fluid volume needs to be purified or half as many lots/batches are needed to produce the same amount of product. Thus, titer is a very important measure of the efficiency of a product's manufacturing, and related manufacturing costs. Similarly, yield can be considered how much (percent) of the protein coming out of the bioreactor is finally obtained after filtration and purification steps are completed. This is a measure of the efficiency a manufacturer has achieved in the downstream purification and filtration operations.

Biopharmaceuticals require highly complex and costly manufacturing.[1] A significant percentage of the high consumer cost of these products is due to their complex manufacturing. Bioprocessing efficiency can affect sales prices and, thus, access to these expensive products. Patients, governments, and manufacturers recognize the need to minimize costs, particularly, since marketed biopharmaceuticals will increasingly be competing on the basis of cost, particularly as biosimilar, biobetter, and biogeneric versions enter the market in coming years.[2, 3] Manufacturers must maximize manufacturing efficiencies to minimize costs, both to decrease costs (optimize profits) and sell their products in an increasingly competitive world market.

Since the 1980s, marketed biopharmaceuticals have

come to be dominated by recombinant proteins and antibodies, and related biomanufacturing has seen steady improvements. However, no clear analysis had been done to document current industry titers and yields, and how these have changed, nor has there been projection of future improvements. Various articles have reviewed progress and trends in commercial-scale bioprocessing since the advent of recombinant products in the 1980s, including concentrating on titers and/or yields.[4-8] However, none of these have compiled and analyzed titer or yield data for specific commercial biopharmaceutical products. A major problem is that titer and yield data for commercial biopharmaceutical products are rarely published. Thus, as discussed below, most of the titer and yield data collected for this analysis came from individuals' notes and recollections from conference presentations, posters, and discussions with colleagues.

In past decades, biomanufacturers were often primarily focused on simply getting their biologic on the market, with manufacturing efficiency not a priority. Also, there were relatively few models and little knowledge available regarding optimizing commercial-scale bioprocessing. Back in the 1980s and even 1990s, bioprocessing technology was rather primitive by current standards, and titers and yields at commercial scale tended to be rather low, compared with the current industry.

Because making changes in any pharmaceutical process is costly and difficult, requiring additional testing for supplemental approvals, once a bioprocess is defined in applications/approvals, companies are loathe to make changes. As such, commercial-scale manufacturing bioprocesses for marketed products can remain unchanged for years. However, established product manufacturing processes are often changed where significant cost-savings can be attained from updating bioprocessing and, particularly, where these process changes can be combined with facilities modifications or new construction, with multiple changes bundled in supplemental applications.[1] Thus, even the oldest legacy recombinant biopharmaceuticals (*e.g.*, from the 1980s and 1990s) are now being manufactured more efficiently, particularly, at higher titers, than when these bioprocesses originally came online.

To measure and benchmark trends in commercial-scale biopharmaceutical product manufacturing (bioprocessing), including tracking trends in titers and yields over time, from the 1980s to the present, and then to project out ten years (2024), we extensively collected all available (public domain/non-proprietary) titer and yield data for the commercial-scale manufacture of marketed recombinant proteins/antibodies. These titer and yield data are unique. Previously, no comparable efforts have been made to retrieve titer and yield data, nor to assess past, present and future improvements in commercial biopharmaceutical manufacturing.

This study concentrated on biopharmaceuticals with higher sales revenue, including major-selling products on track for biosimilar competition in coming years. Most of the products evaluated were monoclonal antibodies (mAbs), with 14 of these having attained blockbuster sales (>$1 billion). Besides having the highest revenue, recombinant monoclonal antibodies are the product class with by far the highest production volume, with antibodies generally requiring massive quantities of active agent to support relatively high and regularly repeated doses, with patients often consuming grams/year. Thus, monoclonal antibody products can require production of hundreds of pounds or even tons of protein. To date, this biomanufacturing is generally done in facilities anchored by very large banks of fixed ≥10,000 L stainless steel bioreactors.

Methodology

BioPlan undertook the task of retrieving and compiling all available titer and yield data, both present and past, for commercially-manufactured biopharmaceutical products. The goal was to define current and historical titer and yield trends, and develop projections for future improvements. Data collection concentrated on a core set of 35+ major biological therapeutics. These were mostly major-selling mAbs and other biosimilar candidates along with data for a few upcoming products manufactured at commercial-scale but not yet approved.

Product-specific titer and yield data were retrieved from all available sources, including publications and from extensive outreach and networking, and directly contacting bioprocessing professionals. Where product data were lacking, we used available bioprocessing information to estimate upstream titers and downstream yields and confirmed viability of these estimates through interviews with those familiar with historical processes. These estimates are included in the analysis. Other sources used included:

- *Biopharmaceutical Products in the US and European Markets, (BIOPHARMA)*, the only information resource/reference specializing in marketed biopharmaceuticals[1]
- Scientific literature—bibliographic databases such as *BIOSIS Citation Index* and *Web of Science*, and review of retrieved articles
- Google and other search engines
- Trade literature, including the websites of relevant publications
- Review of speaker presentations at bioprocessing-related conferences
- *Top 1000 Global Biopharmaceutical Facilities Index*[9]
- BioFacilities Newsletter[10]

Contributions of commercial-scale titer and yield data were most successfully obtained by networking. We contacted industry professionals and asked them to comment and report on non-proprietary, commercial-scale bioprocessing titer and yield data. These inquiries included:

- BioPlan Associates' 460 member Biotechnology Industry Council™ (BIC)
- Other subject matter experts (~130) identified as involved in the development or manufacture of specific products
- Messages posted to relevant online groups/lists

In addition, we used time-series titer and yield data from BioPlan Associates, Inc.'s *Annual Report and Survey of Biopharmaceutical Manufacturing*.[4] In recent years, this has included asking those surveyed (*e.g.*, 238 global respondents in this year's study) to report the average mammalian cell culture titers and yields attained at their facility at both clinical and commercial manufacturing scales.

Commercial titer and yield data for commercially-manufactured biopharmaceuticals are rarely published. Thus, much of the data collected were recollections by bioprocessing professionals from presentations. These data were generally not considered fully authoritative (*e.g.*, the original sources were unavailable for examination). However, the collective data (particularly concerning titers) are considered sufficient to enable modeling of trends in biopharmaceutical manufacturing efficiencies, which was the primary goal. Retrieved titer and yield data were scored by the authoritativeness of their sources. Overall, about one third of products evaluated required developing estimates, with external input or other support obtained before inclusion into the final data set.

Nearly all established marketed products had some information available indicating bioprocessing upgrades, with upgraded and/or new facilities reported. The BIOPHARMA database was a key source for this information.[1] This enabled the designation of "bioprocessing (re)design year" (or likely year of most recent incremental bioprocessing [re]design or upgrades) for specific products. Where good titer data were not retrieved, the average titer for that "bioprocessing (re)design year" (see Figure 1 and discussion below) were then taken into account in estimating current/2014 titers. The average "bioprocessing (re)design year" was early 2004. This compares to early 2006 as the average year for FDA approval for this set of products.

Other information was also developed for each product

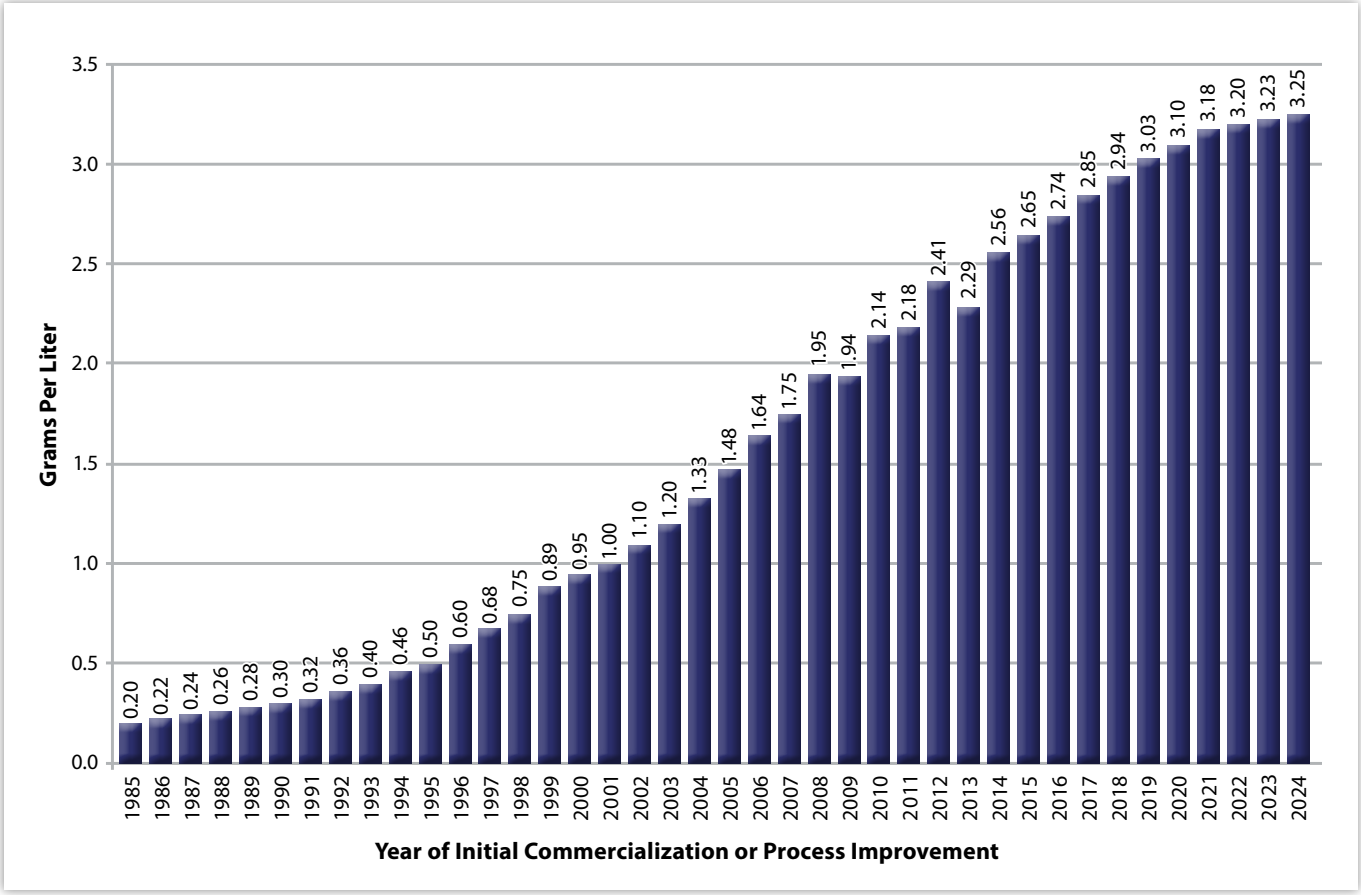

FIGURE 1. Average titer data and extrapolations, 1985–2024.
Source: *11th Annual Report*[4] data for 2006–2014, extrapolated to 1985 and forward to 2024.

including: cell line, bioprocessing description, downstream processing scheme, phase/stage of development (nearly all marketed), FDA approval date, 2013 annual sales[1], and the number of biosimilars and biobetters in development for each product.[2,3]

Trends in Titers Over Time

Titers and yields are basic indicators of bioprocessing efficiency. Generally speaking, the industry has presumed for a long time that titers have steadily, incrementally increased since the 1980s. Figure 1 shows averaged BioPlan survey-based/commercial-scale titer data for years 2008–2014, with extrapolations back to 1985 and forward to 2024, based on available data and feedback from bioprocessing experts. Nearly all available titer and yield data in Figure 1 are for mammalian cell-derived products (mostly mAbs) as they comprise most commercial-scale titers over time.

Note that average titers at commercial scale started out in the 1980s through the early 1990s at <0.5 g/L, a titer considered today to be unacceptable, particularly for any new bioprocess. From the 1980s to the present, average commercial-scale titers have increased a full order of magnitude. This exemplifies the major technological advances in biologics production in recent decades.

Average commercial-scale titers in the mid-1980s started out low (*e.g.*, 0.25 g/L) and increased at a fairly steady rate, with a slight increase in growth rates starting in the early 2000s. Average titer growth in more recent years is estimated to have been about 20% annually.

Increases in average reported commercial-scale titer were, are, and will continue to be driven by trends such as improved culture media and its optimization, expression systems and genetic engineering, cell line development/optimization, improved downstream processing, and modeling-based process de-bottlenecking. Higher titers are associated with increased cost-effectiveness and efficiency. In practice, titers only go up as technological improvements are adopted over time. Products in the development pipeline generally attain higher titers than licensed products with older bioprocesses, but titers for those licensed products increase during their lifecycle due to incremental technology upgrades, which are the norm.

From BioPlan's recent *11th Annual Report and Survey*, the current average reported titer at commercial-scale is 2.56 g/L, and 3.21 g/L for clinical-scale.[4] Commercial-scale titers have, and always will, trail behind clinical-scale titers, because clinical-scale products are generally newer products being made using the latest, more efficient bioprocesses. The projected five-year (2019) average commercial-scale titer, estimated at ≥3 g/L, is roughly about the same as the current reported average clinical stage titer. BioPlan estimates that ≥3 g/L is now the industry standard titer for new bioprocesses being developed.

For 2015 and beyond, BioPlan projects a slight slowing of growth in average titers (*e.g.*, to about 18% annually) as technological incremental improvements start hitting their upper limits, and an ever-increasing number of marketed, including older legacy products, remain at lower titers.

Current Titers and Five-Year Projections

Current (2014) and five-year (2019) titer projections for a set of 33 biologic products, with data generalized when necessary to protect intellectual property, are presented in Table 1, and are sorted by estimated titers.

- **Product Class.** Most are mAbs, along with related fusion proteins and antibody fragments.

TABLE 1. Estimated 2014 and 2019 upstream titers.

Product Class	Cell Line	Approval Decade	Titer (g/L)	
			2014	2019
mAb	CHO	2010	7.00	7.00
mAb	Mammalian*	2010	7.00	7.00
mAb	CHO	2010	6.60	7.00
mAb	CHO	2000	6.00	7.00
mAb	Mammalian*	1990	3.80	4.48
mAb	CHO	1990	3.50	3.50
mAb	Mammalian*	2010	3.06	3.61
mAb	NS0	2010	3.00	3.50
mAb	CHO	2010	2.90	3.42
Enzyme	Mammalian*	2000	2.76	3.26
mAb	NS0	2010	2.70	3.20
mAb	Mammalian*	2000	2.50	3.00
Coagulation Factor	CHO	2010	2.50	2.95
mAb	Mammalian*	2010	2.50	2.95
mAb	CHO	1990	2.26	2.67
Enzyme	CHO	2010	2.14	2.50
mAb	NS0	2000	2.00	2.50
mAb	NS0	2000	2.00	2.36
mAb	Mammalian*	2000	2.00	2.36
mAb	NS0	2010	1.90	2.25
mAb	Mammalian*	1990	1.90	2.25
mAb	CHO	2000	1.77	2.10
mAb	CHO	2010	1.71	1.30
mAb	CHO	2000	1.60	1.89
mAb	CHO	2010	1.50	1.80
mAb	CHO	2010	1.37	1.61
mAb	CHO	2000	1.28	1.26
mAb	CHO	2010	1.17	1.38
mAb	CHO	2010	0.94	1.10
mAb	CHO	1990	0.94	1.10
Enzyme	*E. coli*	2000	0.90	1.20
mAb	CHO	1980	0.50	0.74
Coagulation Factor	Mammalian*	2010	0.20	0.30

*Cell line type either unknown or generalized to avoid product information disclosure. Chinese hamster ovary (CHO); mouse myeloma (NS0); *Escherichia coli* (*E. coli*)

- **Cell Line.** The more commonly-used cell lines (CHO, NS0, and *E. coli*) are identified.
- **Approvals.** The decade of US approval.
- **Titer (g/L) 2014.** Data/estimates for current titers attained with each product class.
- **Titer (g/L) 2019.** Estimates for 2019 titer expected to be attained with each product class.

Figure 2 shows the distribution of 2014 titer data. Much variation in the distribution of current titers can be seen. For example, multiple new(er) products are reported to be manufactured at titers at or near 7 g/L. This may be an effective practical upper limit for titers now—and for some years to come—although there will be outliers surpassing this. High titers can create their own problems like increased protein aggregation and other quality issues. So it is incorrect to assume that all new(er) products will be manufactured at high titers, or that manufacturers will perpetually seek to increase titer. Many new products coming to market, including many biosimilars, will likely be manufactured at high(er) titers (*e.g.*, ≥4 g/L). But many, if not most, new products will still be manufactured in the 2–3 g/L range (with some even lower outliers). As illustrated below, a wide range in titers being attained with different products at any specific time is the norm.

The distribution of current commercial-scale titer data in Figure 2 shows average titers for products (n=39) closely matching the current ~2.5 g/L average industry mammalian titer reported by BioPlan's 2014 industry survey. Note that very few (typically only the newer products) are attaining titers ≥4 g/L, but those that do are in the rather high 6–7 g/L range. These reported specific titer data are generally averages while some may actually represent only the best results. No matter what, the exact titers and yields attained with any specific lot/batch can vary.

Many older products, such as those approved prior to year 2000, have current titers averaging in the 1–2 g/L range, which is pretty low by current standards. However, these titers are often significantly higher than when the products were first produced at commercial-scale, sometimes at a mere fraction of 1 g/L. Many older facilities were built to handle what are now considered low legacy titers and yields (*e.g.*, ≤0.5 g/L). Many of the highest-capacity facilities report that they are now actually operating cost-effectively even with these lower-level titers. This mostly involves older blockbuster antibody manufacturing, including the largest mAb production facilities anchored by banks of ≥10,000 L bioreactors.[9,10] These facilities have obviously evolved over decades by adapting their processes and/or upgrading their equipment and consumables to more

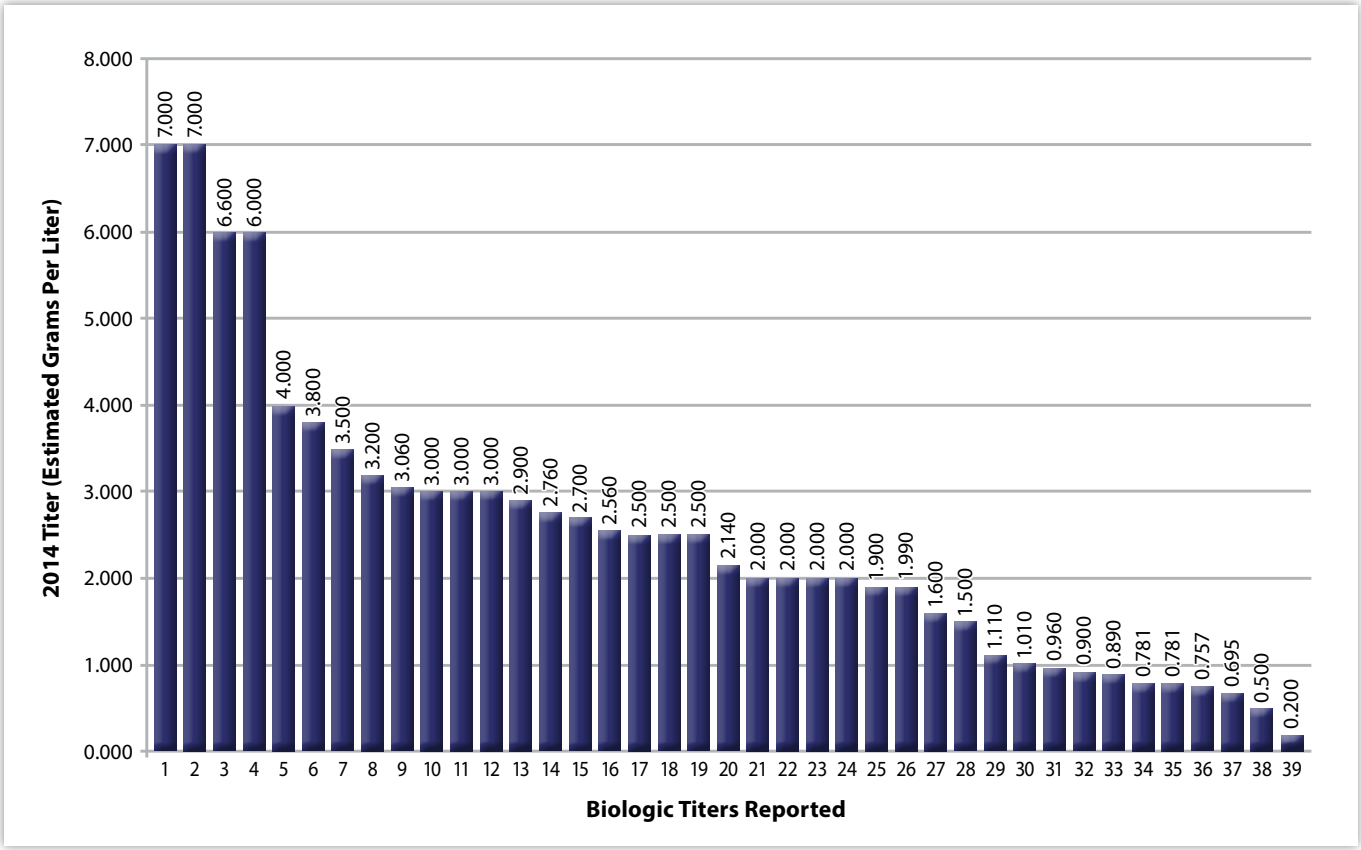

FIGURE 2. Distribution of current titers (n=39).

efficiently manage these 1–2 g/L titer ranges, particularly with downstream processing. In fact, some of the largest facilities report their downstream purification operations cannot handle antibody titers much over 3 g/L.

Trends in Yields, 1985-2014

Similar to titers, yields have also continued to increase, although fewer innovations have been available and adopted for downstream processing. And there isn't a lot of data available for making more detailed yield assessments. Yields are reported much less often, whether published or presented, as compared to titers. Yield data for specific products are difficult to obtain, and were available for relatively few specific products. In the past, an industry average yield of 75% (or 70–80%) has been widely adopted as the industry standard, and reported in the literature (*e.g.*, reference[5]).

However, an online survey undertaken in June 2014, with responses from 50 members of the Biotechnology Industry Council, revealed that the average downstream yield is approximately 69%.[11] From this internet study, with data tabulated by the year of initial production (Figure 3), we found that the average industry yield post-1985 was 64%, increasing to 69% for products approved between 2010–2014. These survey-based data were consistent with the yield data collected by this study's efforts. We did not identify a single product having >70% yield. Thus, we believe that 70% (rather than 75%) should be the current/2014 industry average yield for mammalian expression products, including mAbs. Note that yield data for the 1985–1994 range was not particularly comprehensive due to limited survey responses.

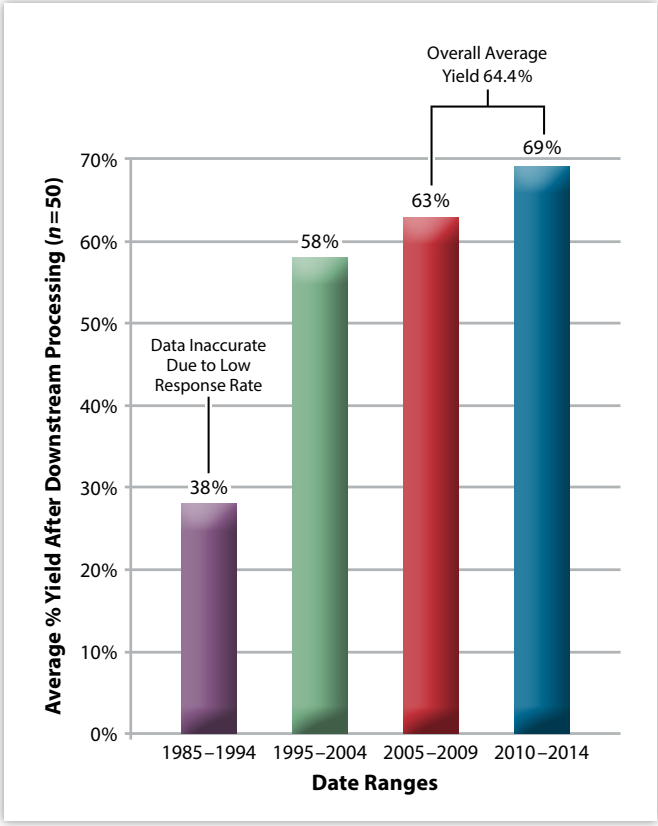

FIGURE 3. Industry average overall yield for final product.

Working with the data we were able to compile, it can be seen that yields have definitely not increased at the rapid rates that titers have, with yields (at best) doubling since the 1980s, while titers have increased about 10-fold. We project the industry average yield to increase by only a few percent in the next five years, with 70% seemingly a general limit with current commercial-scale purification technologies already adopted by the industry. Many advances have yet to be implemented at the largest scales.

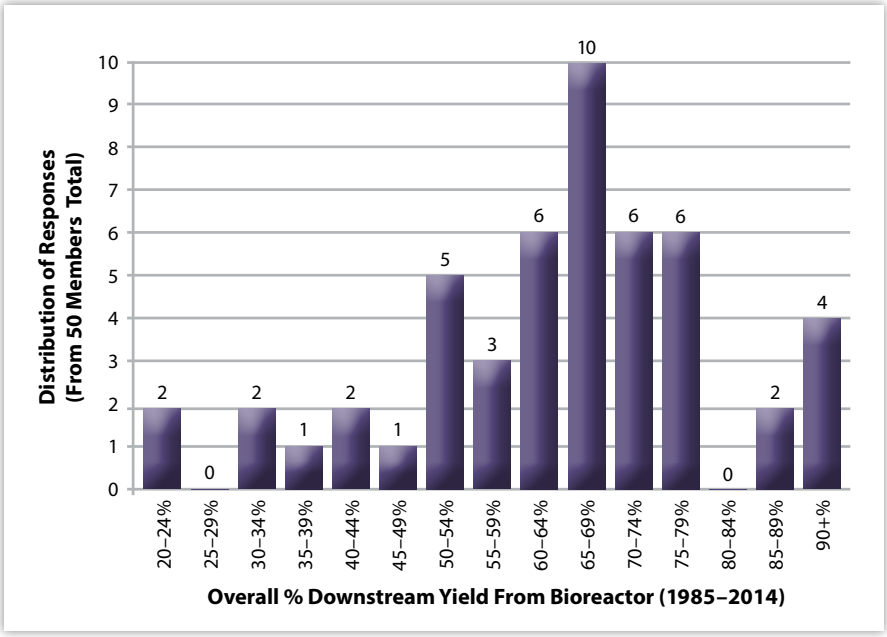

FIGURE 4. Distribution of responses, overall product yields (1985–2014).

The distribution of responses from the June 2014 internet survey of Biotechnology Industry Council members is shown in Figure 4. This indicates a significant grouping between 60–79%, with the highest number of responses between 65–69%. Outlier yield percentages were generally non-antibody products.

Expression Systems/Cell Lines Commercially Used

This study concentrates primarily on the yield and titer for mammalian-expressed recombinant

proteins products/antibodies. Table 2 shows the current distribution of expression systems for recombinant protein and antibody products approved in the US or EU (n=176).[1] The fact that the largest proportion of commercial products are produced by mammalian cell culture shows the relevance of concentrating on this expression system/class for this study of commercial bioprocessing yield and titer trends. It also affirms that the data and findings are exemplary and relevant to biopharmaceutical manufacturing in general, and other expression systems. Also, mammalian cell-expressed mAb products occupy the majority of the biopharmaceuticals market and have the highest production volumes, by far, which affirms the broad practical relevance of our mAb-oriented data and findings. We assume that non-mammalian commercial products (*e.g.*, microbially-expressed products) have similarly followed the titer and yield trends primarily reported here for recombinant mammalian products.

TABLE 2. Distribution of expression systems for recombinant proteins and antibodies currently approved in the US or EU.

Mammalian	
System Type	**# of Products on the Market**
CHO	60
Murine myeloma/hybridoma	11
Baby hamster kidney (BHK)	3
Human cells	6
Other	11
	Total: 91
Microbial	
System Type	**# of Products on the Market**
E. coli	53
Yeasts	21
Other	2
	Total: 76
Insect Cells	
System Type	**# of Products on the Market**
Spodoptera frugiperda (Sf21)	3
Trichoplusia ni (Hi-5)	1
	Total: 4
Animals	
System Type	**# of Products on the Market**
Transgenic goats	1
Transgenic rabbits	1
	Total: 2
Plants	
System Type	**# of Products on the Market**
Carrot cell culture	1
	Total: 1

Discussion and Conclusions

Bioprocessing Improvements with Older, Legacy Products

We confirmed that essentially every well-established, profitable product has its bioprocessing serially and incrementally upgraded, such as swapping-in improved vector constructs, cell lines, culture media and supplements, process de-bottlenecking, *etc*. We assumed that new facilities coming online, upgrades to existing facilities and bioprocesses, and using commercial-scale contract manufacturing organizations (CMOs) are often associated with such upgrades (*i.e.*, facilities batch their changes to minimize the costs associated with filing for supplemental approvals). Facilities and process upgrades, and working with CMOs were identified using *BIOPHARMA*[1], the *Top 1000 Global Biopharmaceutical Facilities Index*[9], and *BioFacilities Newsletter*.[10]

Note, there are often practical limits to which titer yields and bioprocessing can be improved. In order to significantly increase titer in a biologic that has been produced for some time, the process would require changes (*e.g.*, altered glycosylation or aggregate formation) and the resulting material, in essence, would be a biosimilar, requiring a costly regulatory approval process.

Facilities Implications of Titer and Yield Trends

When examining a facility's total bioprocessing capacities (cumulative bioreactor volume) in the context of titers and yields, it is clear that many older products are now being manufactured at low-capacity utilization levels. Particularly for legacy facilities producing blockbuster therapeutic antibodies that are facing biosimilar competition in coming years, there could well be a glut of excess capacity. This will quite likely affect the very largest legacy product manufacturing facilities. For example, with one individual blockbuster product, using available and reliable current titer, yield, and facility bioreactor capacity data, current capacity utilization is estimated at only about 10%. That means bioreactor capacity and other equipment are unused 90% of the time.

Although many of these large facilities have adapted to cost-effectively manufacturing their legacy products at low titers (*e.g.*, <1–2 g/L), this overcapacity may create problems. Some of these companies are now either idling or mothballing bioreactors, using them less frequently or are only filling them partially when used. Unless the excess capacity of these underutilized facilities, and particularly the legacy blockbuster antibody facilities, start manufacturing new products (those currently in late stages of development), we can expect more mothballing, decommissioning, or selling of these facilities. And/or an increasing number (some already are) of these largest biologics manufacturers, the major players, will offer their excess capacity for commercial-scale CMO services. This could have a disruptive impact on the biopharmaceutical CMO industry sector.

Conclusions related to titers and yields for biopharmaceutical

products currently manufactured at commercial scale supported by this study include:

- Data confirmed industry presumptions that bioprocessing efficiencies, particularly titers, generally increase over time, both for new products (new processes) and also for existing commercially-manufactured products to have their bioprocessing opportunistically upgraded periodically.
- Approximately 3 g/L is the current general industry average for new antibody and other mammalian commercial-scale manufacturing. About 7 g/L is now presumed to be the general industry top-end for titers for new commercial-scale bioprocesses. The industry average of 3 g/L estimate from this study for new commercial bioprocesses (products scaled-up for commercial manufacture) is consistent with the 2014 average commercial-scale titer of 2.56 g/L from the Annual Report.[4]
- Titers for commercial-scale bioprocessing vary greatly at any particular time (*e.g.*, 2014 titers ranged from 0.2–7.0 g/L).
- 70% yield was adopted as the current, recent past, and near-term future industry average or consensus yield. Improvements in downstream processing are fewer and are adopted more slowly than upstream.
- Titer and yield data, whether authoritative (*e.g.*, from a published source), reliably reported, and/or estimated based on best-available information, generally fit well within expected patterns. This includes titers for both new and older products, tracking the average titers attained when bioprocessing was presumed designed and/or last upgraded. Also, at any time, titers vary considerably over a wide range.
- Titer data are much more available, and more commonly reported, than yield data.
- Many facilities with the largest capacities (typically producing legacy mAbs) now have considerable underutilized bioreactor capacity, a result of cumulative technological and cost-saving improvements. Even so, established products have become less expensive to manufacture over time.
- The titer and yield data retrieved (in the public domain, *e.g.*, published or presented), particularly titer data, were sufficient overall to support modeling of bioprocessing, including projections concerning bioprocessing with upcoming biosimilars. However, most available data do not originate from authoritative (*e.g.*, published) sources. Keep in mind that such data should not be used to support bioprocessing design, investments, or other business decisions.
- Despite titers and yields being the most basic aspects of bioprocessing, and despite commercial-scale manufacture being the ultimate goal for bioprocessing, very few industry professionals are knowledgeable concerning actual titers and yields attained with commercial-scale manufacturing.

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[10] *BioFacilities*. BioPlan Associates. Free bi-monthly e-newsletter. www.bioplanassociates.com/publications/newsletters.htm.

[11] Online survey of 50 biopharmaceutical industry professionals, members of the Biotechnology Industry Council™ (BIC) who self-identified themselves as familiar with specific biological product yields between 1985 and 2014. (Note: For details, contact the authors below.)

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