This article explores the availability of manufacturing capacity for biopharmaceutical products.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Biotech Manufacturing: Is the Crisis Real?

by Jeffery N. Odum

***"Clogged Pipeline…Manufacturing shortage putting squeeze* on surging success of protein-based drugs."**
– *Boston Globe,* January 30, 2001

***"The scarcity of manufacturing resources will become biotechnology's* next growth rate-limiting factor…for the next several years."**
– *Biomanufacturing Strategies, Contract Pharma,* Nov/Dec 2000

***"The explosion in the number of biotechnology products coming into the* market indicates that the need for manufacturing capacity for biopharmaceuticals will be great."**
– *High Tech Business Decisions,* 1999 Contract Market Survey

There have been many headlines, reports, and presentations that have asked the questions about the availability of manufacturing capacity for biopharmaceutical products. There also have been many answers given that say yes, the shortage is real. But while the opinions have been put forward, many individuals within the industry still ask, "Is the crisis real?"

The focus of this article will be to look specifically at the manufacturing capacity demand question for the biopharmaceutical industry. The analysis is based on current available data regarding the product pipeline and products in clinical trials. It will investigate the manufacturing classifications of approved drugs to focus on a specific market segment for the overall analysis. From the available data, predictions will be developed for future capacity needs based on probable drug approvals for the next five years.

Background

There has been much discussion and press in recent months regarding the explosion of biopharmaceutical drug products entering the clinical pipeline. Along with this information come reports that also discuss a pending shortfall of manufacturing capacity that could severely impact the industry over the next few years.[1,4]

It is documented through many sources that a firm making the decision to embark on a capital program to develop new manufacturing capacity is looking at a time period of potentially 36 to 60 months before a "new" facility will be able to produce marketable product.[2] The factors that go into this timeline include time for facility design, equipment procurement, construction, validation, and licensing. Therefore, the identification of manufacturing needs does not result in a quick, "overnight" solution to the problem.

There are also a number of new production technologies that are entering the manufacturing arena that hold much promise for the future. These include the areas of gene therapy and transgenics. Despite recent hype (good and bad) over the genomic research successes and gene therapy products, the first successful, commercially viable product is probably years away. Transgenic technologies in both plants and animals hold promise as well. One of the key advantages touted by the transgenic producers is the large volume that can be produced from the plant or animal host. But issues of scale-up costs, downstream recovery, and public perception of a lack of regulatory control must be ad-

Category	Pre-Clinical	Clinical Trials	Pre Reg.	Reg.	Total
Biopharmaceuticals (Including biologicals)	756	325	24	5	1,110

Table A. Worldwide biopharmaceutical product pipeline.

dressed before any serious production scale operations are embraced by the industry.[3]

In order to focus on the predominant human therapeutic technologies that comprise the majority of current marketed products, these technologies have not been considered in this study.

Market Strength

The biotech industry entered 2001 in a very strong position. After many years of promise, the industry has produced outstanding results in terms of products approved and overall sales volume. Since 1996, product approvals have increased approximately 30% annually, while approval times have decreased.[5] By the end of March 2000, an estimated 1,100 products were in the worldwide product pipeline – *Table A*.[6]

The strength of the market in the United States is reflected by the fact that there are more than 350 products in pivotal trials.[7] From a market capitalization perspective, the fact that there were 19 new companies that went public in 1999-2000, raising more than $2.2 billion in funding is also a sign of growth. At the close of 1999, total industry revenue exceeded $22 billion in the United States alone – the highest level in the history of the industry.[8]

This same story is reflected overseas as well. In Europe, there were 173 new biotech companies formed in 2000. Industry revenues reached 5.4 billion Euros, an increase of 45% from the previous year.[8]

The industry has produced some key drug products, some of which have been classified as "blockbuster" drugs by the folks on Wall Street based on their sales volume. The most recent data ending in 1999, indicates the top 10 biotech drugs on the market had a combined annual sales volume of approximately $9.0 billion.[9] Overall, industry sales/revenue for 2000 increased 11% to $31 billion.[10]

Product Pipeline

The pipeline for new drug products is strong. Based on current information from the FDA, PhRMA, and other sources, the estimated number of products in various stages of clinical trials is approximately 380 – *Table B*. This figure represents a significant increase over previous years, especially in terms of the products reaching late stage clinical production.

Along with this upward movement in the pipeline volume, the approval-to-market for biopharmaceutical products also has seen significant improvement. By 1996, product approvals had increased to an average of 12 per year. Today, that level is approaching 20 per year. For use in this analysis, this rate is assumed to increase at a very conservative base rate of 3% per year through the end of the decade.

The historical trends of product approvals for cell culture and microbial products also provide support data and lend substantiation to forecast trends showing increases in product approvals over the next five years. In addition, technology improvements have made Monoclonal Antibodies (MAbs) more attractive. Also, mature products are finding new life as new indications are being developed, thus increasing the interest and use of these products in many areas.

Figure 1 provides a graphical representation of new product approvals. Based on industry data, the trends support the view of strength in the pipeline well into the coming years.

Based on conversations with individuals from numerous biotech companies, there are many firms that have found it

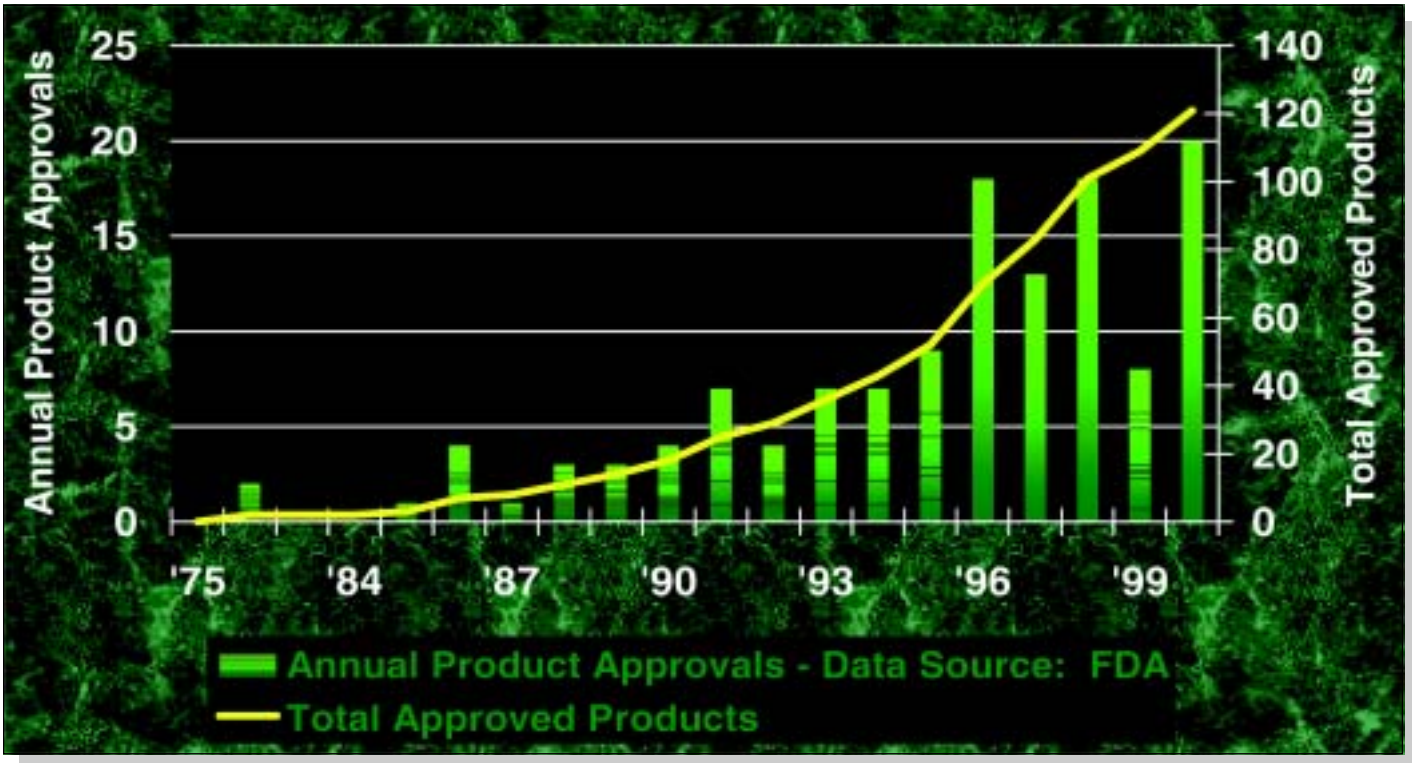


Figure 1. Annual biotechnology product approvals from 1975-2000.

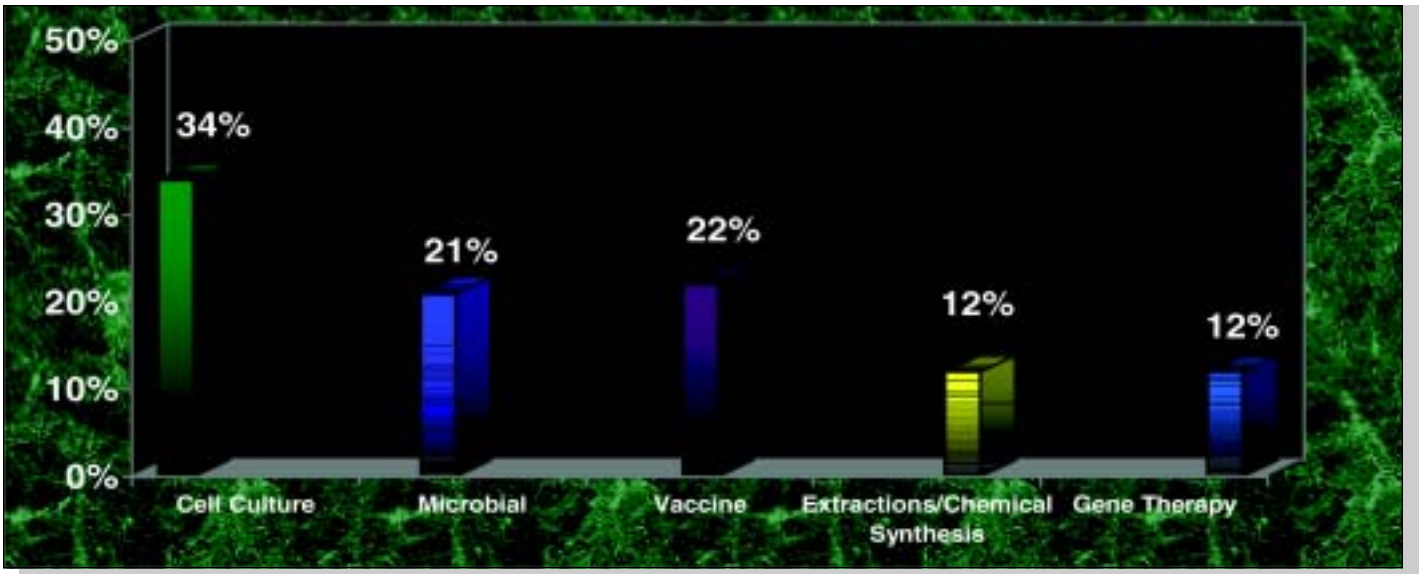


Figure 2. Manufacturing classification of drugs approved and currently in clinical trials.

difficult to secure outsource manufacturing space for their current production needs. Potential loss of control, higher long-term costs, and lack of sufficient capacity are all contributing factors. Also, firms have been successful in developing new products to keep the pipeline full, but many have been unwilling or unable to take the risk of sinking large amounts of capital into the development of a production facility based on early clinical results. The result finds many companies scrambling for manufacturing space. When products are eventually approved, there is a significant time lag (generally 3-5 years) before a facility can be brought on line for production. Since this has such a significant impact on overall profitability, firms are now finding themselves in somewhat of a bidding war over the limited amount of available contract manufacturing space, thus making a bad situation more difficult.

The biotechnology industry's very strong and improving financial picture, coupled with a healthy pipeline of new products to supply the market, an improving regulatory approval forecast, and a lack of capacity to produce products for the marketplace could become a significant limitation to the industry's growth potential.

Analysis Assumptions

This market analysis was performed to identify key manufacturing technologies in order to target the one area which shows the highest growth potential in the next five years, and therefore, the most likely area where the capacity shortfall would be seen. The analysis was based on the historical data available from CBER, PhRMA, BIO, and corporate sources.

Figure 2 shows the technology breakdown of the pharmaceuticals that were approved and in clinical trials by the year 2000. The largest market share is represented by the products derived from mammalian cell culture production, including monoclonal antibodies. This segment is anticipated to grow in the future due to technological advances (processes becoming better understood and scaleable) and cost reductions (eliminating/replacing expensive animal-derived additives in culture growth media). It is this segment that will be the focus of this analysis.

Another reason for the anticipated continued growth in the cell culture segment is the ability of mammalian cell hosts to produce highly complex, biologically active molecules. Unlike microbial hosts such as *E. coli* and yeast, mammalian cells have the sophisticated internal cellular machinery to perform post-translation modifications such as glycolysation of the product protein.

An important subset of cell culture products is monoclonal antibodies. The humanizing of monoclonal antibodies has led to greater utility and promise for MAb-based products. Through the end of 1999, there were 110 MAb products in development between Phase 1 clinical trials and license application and 10 previously approved for commercial use. With an estimated five to six products per year approved, the total number of commercially approved MAb products could climb to 50 by 2006.

Based on all of these factors, the manufacturing of mammalian cell culture products is probably the most promising opportunity for growth over the next five years. Microbial-based products will continue to be a significant segment of the

Category	Phase I	Phase II	Phase III	PLA NDA	Market	Total
All Cell Culture Derived (including MAb)	76	64	26	9	21	196
Others: Microbial/transgenic, etc.	66	54	26	5	33	184
Totals (cell culture + others)	142	118	52	14	54	380

Table B. Products in clinical trials by phase.

Product	Company	Type	Expression System	Sales
Epogen®	Amgen	EPO	Cell Culture	$1,760 mm
Neupogen®	Amgen	G-CSF	Microbial	$1,260 mm
Humalin®	Lilly (Genentech)	Insulin	Microbial	$1,332 mm
Intron-A®	Schering-Plough (Biogen)	INF-a-2b	Microbial	$1,100 mm
Avonex®	Biogen	INF- b -1a	Cell Culture	$ 621 mm
Cerezyme™	Genzyme	Imiglуerase	Cell Culture	$ 478 mm
ReoPro®	Centocor	MAb	Cell Culture	$ 447 mm
Embrel®	Immunex	TNF receptor	Cell Culture	$367 mm
Gonal-F®	Serono	RFSH	Cell Culture	$349 mm
Remicade®	Centocor	MAb	Cell Culture	$ 317 mm
Rituxin ®	Genentech/IDEC	MAb	Cell Culture	$ 279 mm
Activase®	Genentech	TPA	Cell Culture	$ 236 mm
Protropin®+ Nutropin®	Genentech	HGH	Microbial	$ 214 mm
Herceptin®	Genentech	MAb	Cell Culture	$ 188 mm
Synagis®	MedImmune	MAb	Cell Culture	$151 mm
Ribif®	Serono	INF- b	N/A	$143 mm
Serostim®	Serono	RhGH	N/A	$137 mm

Source: Company Annual Reports and News Releases

Table C. Top biotech drugs on the market – 1999.

market, but the growth of new products is expected to grow at a slower pace than mammalian cell products. Therefore, the balance of this analysis focuses on the growth expected in mammalian cell culture product manufacturing.

Analysis Methodology

History is a strong predictor of what the future may hold. It is this belief that forms the basis for this analysis. In order to look at forecasted capacity needs for the industry, some assumptions must be made on the probability of product approval coming out of the clinical pipeline. There are a number of historical parameters that can be used for this effort. One widely recognized source is **Parexel's Pharmaceutical R & D Statistical Sourcebook**. This reference provides probabilities of products advancing to the next stage of clinical trials and finally into the market. This data will be used for the analysis. They are:

- 3% growth in new cell culture products per year entering clinical trials
- 80% will pass Phase I
- 28% will pass Phase II

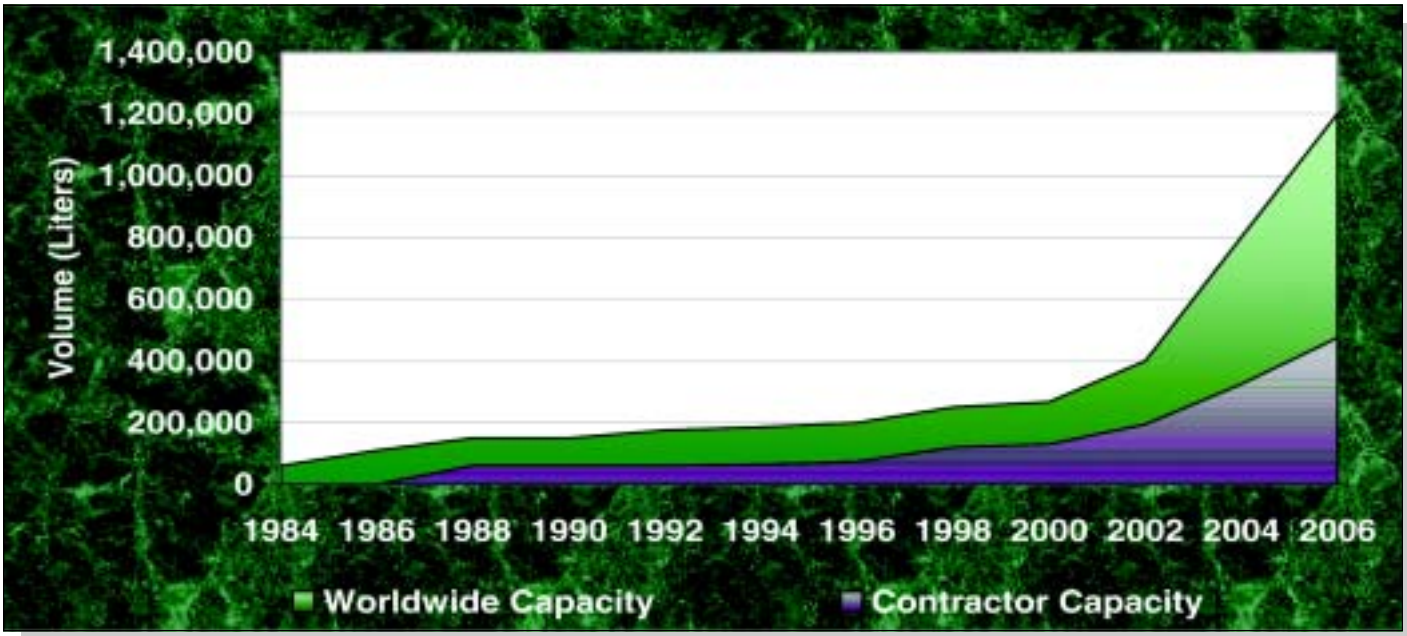


Figure 3. Worldwide cell culture capacity.

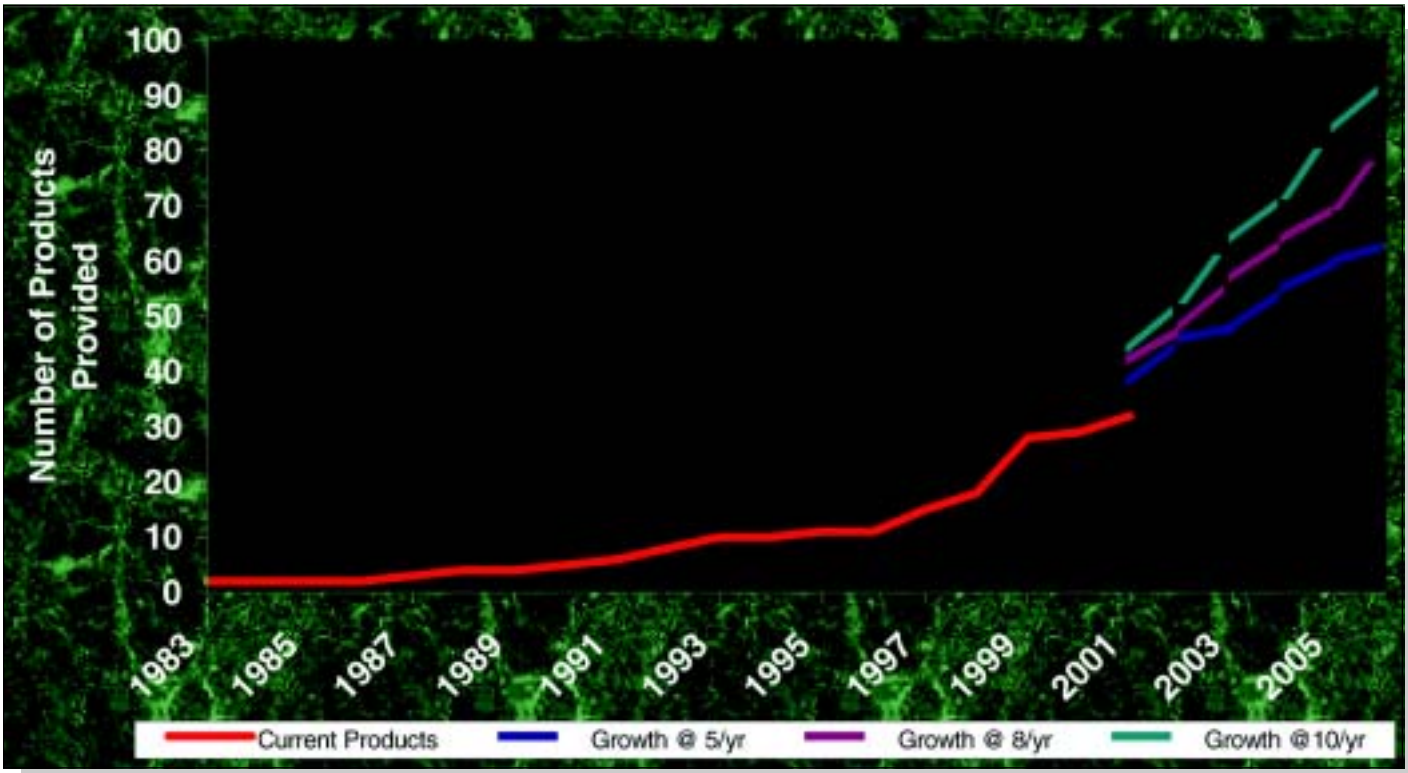


Figure 4. Approved cell culture products with projected growth.

- 65% will pass Phase III
- 90% will become registered products for launch

A key data element for the analysis is the current level of manufacturing capacity being utilized by the industry. While there is some information available related to corporate capacity, most firms do not make this public information. For this analysis, a model was created based on the historic bioreactor capacity required for producing the 20 leading US biopharmaceutical products on the market today – *Table C*. This information was derived from available public information on sales volume and dosage size, discussions with the manufacturing companies, and information from companies on the size of facilities.

The model was formulated to calculate future bioreactor capacity required. The known bioreactor capacity (in liters) was divided by the number of approved cell culture products. The composite capacity was calculated to be approximately 100,000L per product. In other words, 100,000L of bioreactor capacity is required to support a single cell culture based product. Numerous factors could influence that number: product titer, yield, campaign length, production method, etc. However, that information is highly confidential and generally unavailable. Thus, the model was implemented.

Using the projected product approvals through clinical trials, the historical industry trends of approvals, and the analysis of current capacity, a forecast of projected growth based on Liters of working volume was developed. This is illustrated in Figure 3.

Figure 4 projects the number of approved products by the year 2006 based on the probabilities stated earlier. Future capabilities required are based on three possible scenarios: conservative (5 product approvals/yr), likely (8/yr), and optimistic (10/yr).

Based on the analysis of this study, the shortfall that is indicated could have a negative impact on the industry. This could be seen in terms of decreased product approvals caused by the fact that firms will not have the ability to produce clinical materials in sufficient quantities. Figure 5 represents a short-term view of how great that impact could be. To put Figure 5 into a physical perspective, the capacity shortfall in the year 2006 is estimated to be in the range of 200,000-900,000 liters depending upon the number of products approved. Taken at an average of 500,000 liters, this represents the equivalent of five production facilities in relative size to the largest commercial production site in operation today. Putting this into terms of bioreactors, 500,000L is 50 x 10,000L bioreactors.

How Did We Get Here?

There are a number of issues that have potentially contributed to the current situation that is described throughout this article. These include:

- The dramatic increase in product approvals was not foreseen by the industry. Conservatism was the driver for many companies when it came to decisions related to capital expenditures for new facilities to produce yet-to-be-approved products.
- The large bio/pharma manufacturers were the only firms willing or able to spend money on capital expansion in the 1980s and 1990s.
- The industry's first attempt at launching the contract manufacturing segment of the industry in the 1980s was unsuccessful.

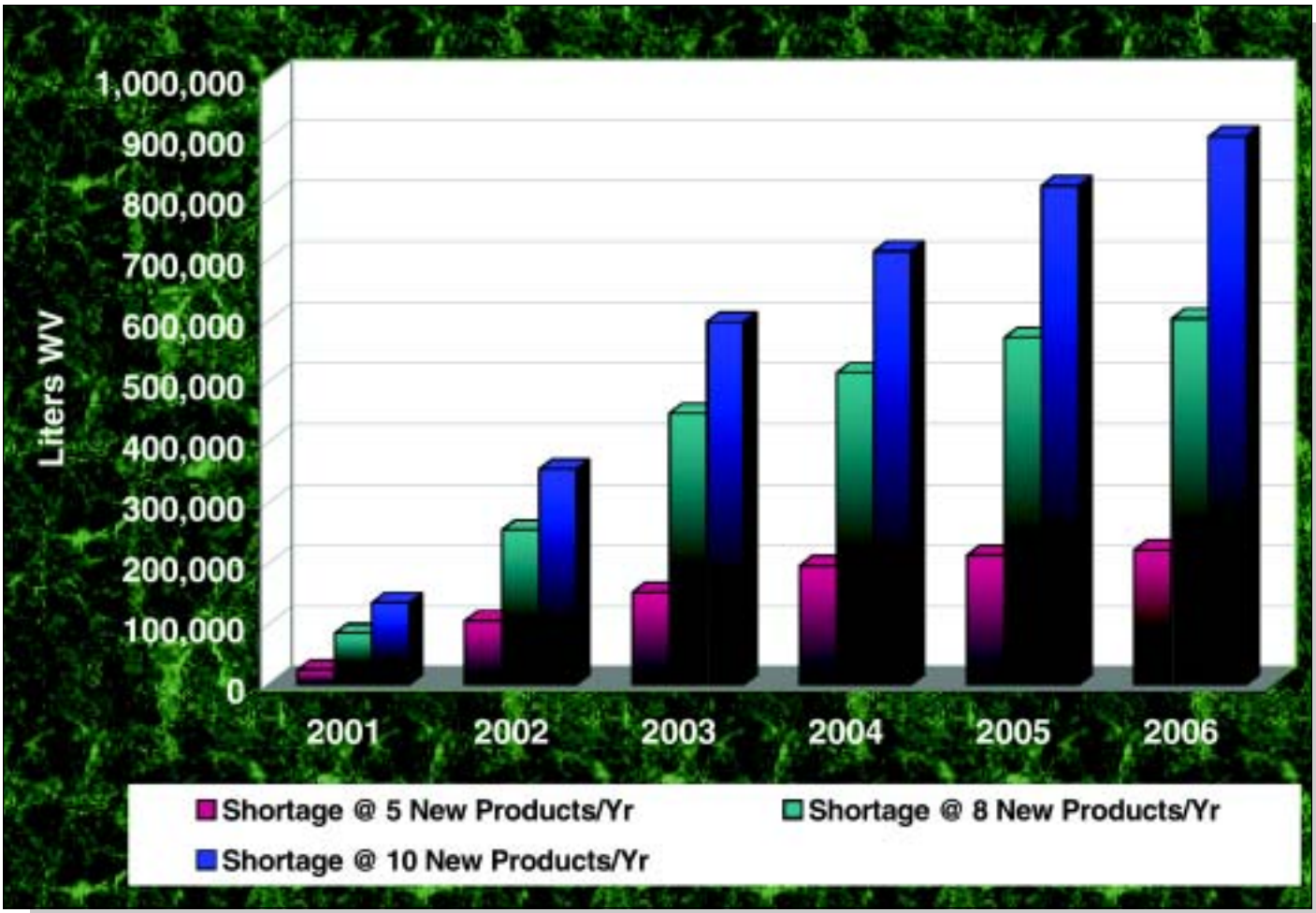


Figure 5. Capacity shortfall.

- The favorable regulatory environment in the FDA that has made outsourcing a more acceptable production philosophy was unforeseen.

- Companies were unwilling to sacrifice capital for bricks-and-mortar to reduce research and development funding.

- The success of raising venture capital for capital expansions in the biotech industry was not predicted.

Another impact could be seen in the costs associated with taking a product through clinical trials. The current trend that is being seen in the contract manufacturing industry indicates that firms are paying higher costs to secure the available space. In many cases, the contract manufacturers also are charging reservation fees to simply secure future capacity needs. This can easily be seen as a "sellers market" that could lead to increased production costs.

How Significant is the Problem?

Assume that the forecasted shortfall is 500,000L of capacity. This would be the equivalent of 50 x 10,000L scale bioreactors. One analysis that has been conducted using available industry facility data shows that one-liter of production capacity equates roughly to seven square feet of production space. Taking this assumption, the 500,000L would equate to 3,500,000 square feet of manufacturing space.

Based on a database of "typical" cell culture facility costs, we will assume that $950/SF is a reasonable assumption in today's market for the completion of GMP manufacturing space. This would be the cost for classified manufacturing space, without general office or laboratory support. These assumptions would show a $3,325,000,000 facility cost projection for the 500,000L capacity shortfall.

A general "rule of thumb" that has been used in the industry states that one square foot of capacity can produce roughly $1,000 of product annually. Therefore, the square footage gap developed in our analysis represents $3,500,000,000 of product annually. The "typical" biotech product market size is in a range of $50 - $500 million. Assuming an average market size of $200 million per product, this gap represents approximately 17 products that might not have a place to be manufactured.

Another approach would be to look at dosage size and patient populations. Typical therapeutic products have dose sizes in a range of 2-5g per patient on an annual basis. For analysis purposes, let's assume a patient population to be 50,000 individuals. This would equal a total annual production requirement for a product at an average of 150 kg. If you assume an average bioreactor yield of 500-1000 mg/L and a purification yield of 50%, the resulting capacity requirement would be in the range of 300,000L needed to produce 100 kg of bulk product. This analysis approach results in an estimated requirement of 450,000L to meet production needs.

Conclusions

The predicted shortfall of manufacturing space does seem to be very real. Whether you view the problem in terms of capital expenditures or number of products vying for manufacturing space, the impact to the industry can be well seen over the next five to seven years.

How the industry will react to this situation is yet to be seen. There are numerous firms, including Lonza, Biogen, and Boehringer-Ingelheim that have current expansion plans in various stages of progress. How soon they can bring capacity on-line will determine how severe the impact of the shortfall may be. Clearly, firms that have excess capacity in the near term will be in an enviable position.

There is also a potential concern from some industry sources that recognition of this shortfall could trigger a rapid response that could result in a future "glut" of manufacturing capacity. Whether this comes to pass will remain to be seen. However, the shortage, at least in the near term, is very real.

References

1. ***Biotech 2001,*** Burrill & Company, 2001.
2. ***Sterile Product Facility Project Management and Design,*** Jeff Odum, InterPharm Press, 1997.
3. ***Biotech 2001,*** Burrill & Company, 2001.
4. ***The State of Biologics Manufacturing,*** David T. Molowa, J.P. Morgan, March, 2001.
5. Food & Drug Administration
6. ***Pharmaceutical R&D Statistical Source Book,*** Parexel, 2000.
7. ***Search for Cures,*** Pharmaceutical Research and Manufacturers of America, July, 2001.
8. *Convergence – The Biotechnology Industry Report*, Ernst & Young, April, 2001.
9. Medical Ad News, July 2000.
10. ***Biotech 2001,*** Burrill & Company, 2001.

The author would like to acknowledge the assistance of Dr. Kim Nelson and Allan Bream, both of CRB, for the data they contributed to this study.

About the Author

Jeffery N. Odum is the Biotech Team Leader and Senior Project Manager for CRB Consulting Engineers' Southeast Regional Office in Cary, North Carolina. He has more than 22 years of professional engineering and construction experience that has been primarily focused on process-driven technology projects. The last 12 years have been focused on the biotech and pharmaceutical industries with key assignments in both engineering and construction management. Odum is an active member of ISPE where he serves as Chairperson of the Publications/Internet Committee, and member of the Training Committee developing training tools for the Society. Odum has authored numerous articles on GMP compliance and design and construction issues, and is the author of an industry reference guide, *Sterile Product Facility Design and Project Management*, published by Interpharm Press.

CRB, 1225 Crescent Green, Suite 300, Cary, NC 27511.

This article presents the major regulatory, design, operational, and economic differences between high purity waters employed in biopharmaceutical production and in microelectronics fabrication.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Comparison of High Purity Water for Microelectronic and Biopharmaceutical Facilities

by Andrew Baird, Kirsten Sommer, PE, and Ralph Williams, PE

Introduction

To appreciate technical influences and possible future trends, design engineers and operators of biopharmaceutical high purity water systems may find it beneficial to compare systems for their industry with those of the microelectronics industry. Each industry has unique strengths that may be leveraged by the other industry.

Highly purified water is utilized in both the biopharmaceutical and microelectronics industries. The former uses high purity waters for production, processing, formulation, cleaning, and rinsing. Biopharm operators are primarily concerned with microbial, chemical, and endotoxin contaminants that may compromise standards of safety, efficacy, strength, purity, and quality of a drug. There are two commonly used grades of pharmaceutical bulk water: Water For Injection (WFI) and Purified Water (PW). In microelectronics, high purity water is typically called UltraPure Water (UPW). Microchip fabricators are concerned with particulate, ionic, and organic contamination detrimental to the integrity of microchip circuitry. The majority of UPW is used for wafer cleaning, rinsing, and process equipment component cleaning.

Regulatory Environment

Biopharmaceutical communities mandate their own water regulations: Europe,[1] Japan,[2] and the United States[3] each publish official documents listing drugs with directions for specific quality attributes. These publications are known as pharmacopoeia (derived from the Greek word *pharmakopoios,* drug maker). Pharmacopoeial standards regulate water grades, specific quality parameters and test procedures. They do not specify operating conditions or the application for each grade of water. A European draft paper gives some guidance for water quality for pharmaceutical operations.[4]

In the United States and Europe WFI(s) (*Aqua ad iniectabilia)* and PW (*Aqua purificata*) are known as compendial waters; e.g. minimum requirements are set forth in the current edition of Official Monographs in the United States Pharmacopoeia (USP 24) and European Pharmacopoeia Third Edition Supplement 2000. In the US, the FDA enforces implementation of these regulations adopted through the federal codification system. In Europe, the European Agency for the Evaluation of Medicinal Products (EMEA) implements standards in member states code systems.

In addition to the United States Pharmacopoeia, Title 21 of US Code of Federal Regulations (CFR) Parts 210 and 211, otherwise known as current Good Manufacturing Practices,[5] provide some guidance, and the FDA Guide to Inspections of High Purity Water Systems[6] gives information for the design and operation of compendial water systems. However, the information presented in these documents is not intended to be an engineering design guide. Certain design approaches are evaluated or implied. Individual users must interpret this information and justify their design to the FDA during the validation process. Misinterpretations have led to systems not being validated or approved by the FDA. The ISPE Baseline® Water and Steam Systems Guide[7] was developed to assist engineers in designing water systems to attain FDA compliance without excessive design or one-upmanship engineering solutions.

For the microelectronics industry, quality parameters are discretionary by the owner and are not regulated. Each manufacturing operation develops internal quality specifications based upon processing requirements with benchmarking to American Society for Testing and Materials (ASTM), Semiconductor Equipment and Materials International (SEMI), Balazs Labs, Sematech, and other industry sources. An example is ASTM D5127-99, Standard Guide for Ultrapure Water used in the Electronics and Semiconductor Industry, which presents recommendations for water quality for various product types.

The requirement to design compendial water systems to attain legally enforced standards has far reaching consequences. When designing

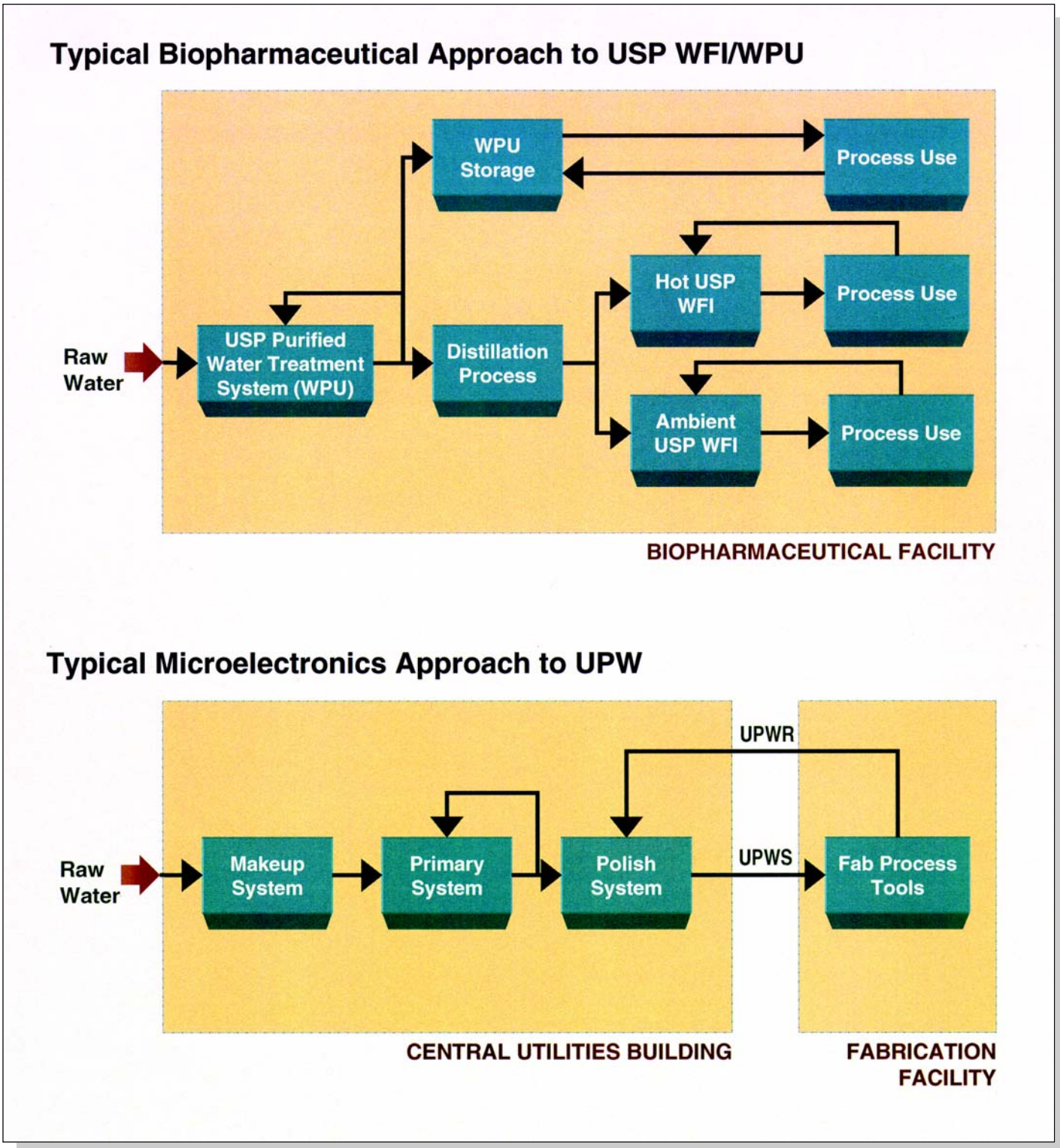


Figure 1. High purity water approaches – biopharmaceutical and microelectronics.

water systems, engineers and operators tend to concentrate on solutions that have a proven validatory track record. The biopharm industry is consequently slow to respond to developments in equipment and analytical innovations. A new design approach will require validation. Validation is an enhanced process of commissioning and testing by establishing documentary evidence for critical equipment and process parameters.

Validation occurs in three formal stages: Installational Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Qualifications are executed according to acceptance criteria defined in individual protocols. The installational qualification demonstrates that the system has been installed in accordance with design drawings, specifications, and the manufacturer's recommendations. The OQ demonstrates that the system or equipment operates consis-

tently as specified by meeting design requirements for control of operating parameters. The PQ demonstrates that the system or equipment performs consistently as specified by meeting process requirements and parameters under simulated production conditions. In order to evaluate the effect of seasonal variation on potable water supply, it may take at least one year to execute a PQ. In the race to market, manufacturers cannot afford to delay production schedules to evaluate new

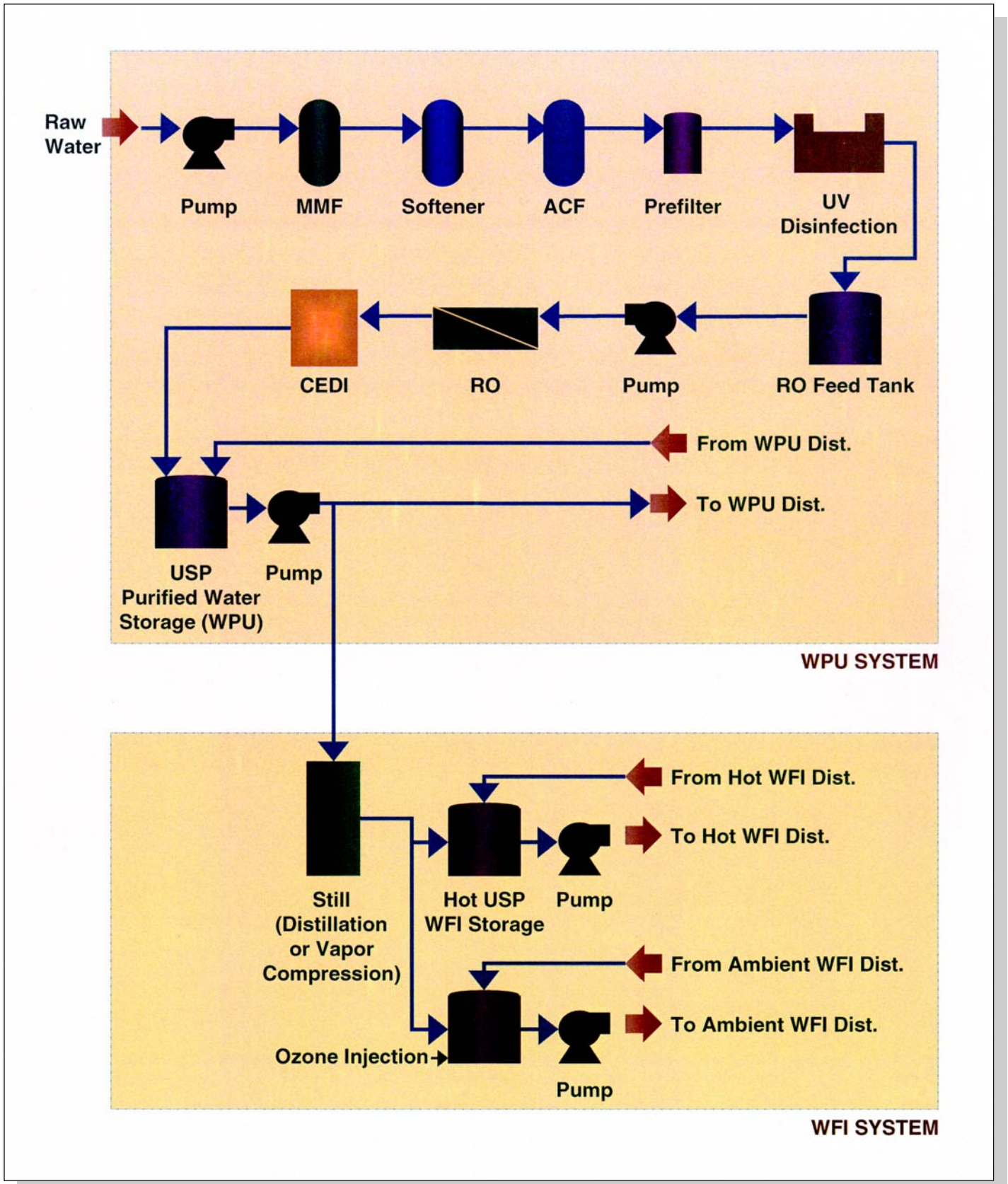


Figure 2. USP WFI/PW system design typical approaches.

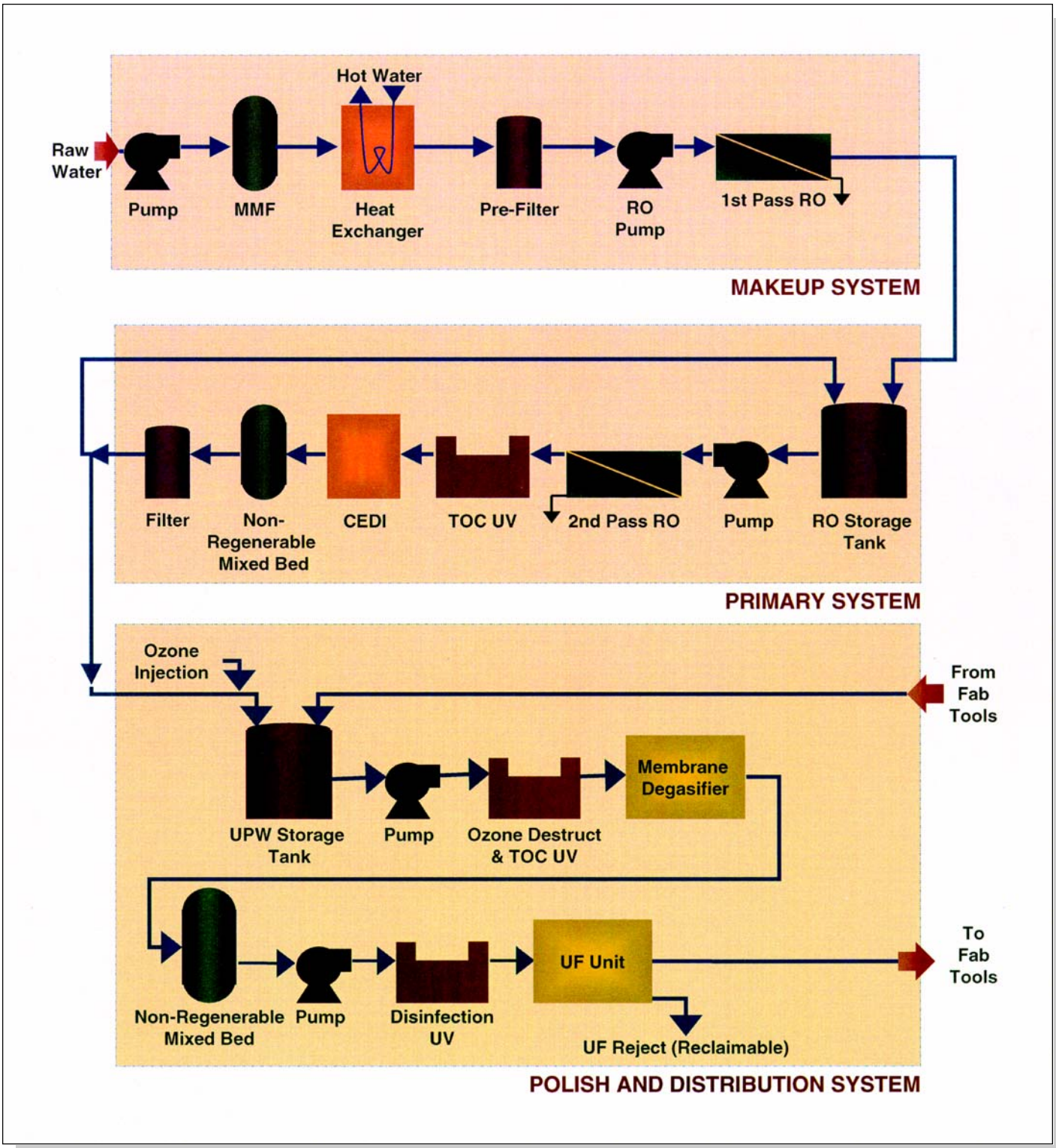


Figure 3. UPW system design typical approaches.

equipment or an innovative design. Design changes to an existing validated system must be revalidated to prove that the new system is equivalent to the original. The impetus to change a system already providing consistently high quality water is low, despite the fact that an improvement may result in decreased operating cost or more efficient operation.

Because microelectronics firms independently develop their quality specifications and are not bound to design/construction guidelines, they are free to test various water treatment technologies and analytical approaches. This led to a great deal of water treatment innovation in the 1980s and 90s that has proved beneficial to both the microelectronics and the pharmaceutical industries. Although this innovation has slowed in recent years, microelectronics firms continue to pilot test and work with component manufacturers. This culture of technology growth, flexibility, and the lack of regulation does lead to problems including quality specifications that are unattainable and unmeasurable, comparison of performance

> ***The process of identifying the necessary capacity for a given biopharmaceutical or microelectronics plant is very similar.***

between the systems is difficult, and there is little component and equipment standardization. Validation of a UPW system is an owner-prescribed process of commissioning and testing.

Water Quality Specifications

The biopharm industry sets operating specifications to achieve regulatory standards rather than product requirements. Because of the complexity of biological and biochemical entities, apart from microbial concerns, producers have generally devoted little attention to quality of water actually required by the process. Perhaps process performance could be enhanced with water of a quality higher than regulations. In general, users rely upon compendial standards for production method and dosage form to determine the type of water required. Operating limits are set to reduce the risk of dropping below the regulated level into a noncompliance situation. Users are willing to pay for the high cost of WFI/PW systems to consistently generate high quality water because of the risk of lost product to market in the event of lack of compliance.

Water quality specifications for microelectronics systems tend to aim toward best-achievable and best-measurable levels of contaminant control. The strong and measurable correlation between UPW quality and product yields provides adequate incentive to pay for expensive, highly reliable, and effective water treatment systems. The UPW system for a semiconductor manufacturer is usually the most expensive utility system in a new factory.

For US pharmaceutical applications, the current standard is USP 24, (previously USP 23) which eliminated individual ion and metals levels in favor of conductivity and Total Organic Carbon (TOC) for both WFI and PW. In addition, WFI is required to have an endotoxin level of less than 0.25 EU/ml - *Table A*. The USP Monographs do not specify microbial limits. Instead, water systems are monitored to confirm they operate within their design specifications and produce water of acceptable quality. Recommended appropriate action levels are described in Table A. Action levels should represent product quality concerns and the ability to effectively manage the treatment process. Conductivity and total TOC are commonly measured online, and endotoxins and bacteria are measured offline. Methods for offline and online measurement are documented by USP.

In contrast, microelectronics specifications will generally not include an endotoxin requirement, but cover resistivity, TOC, bacteria, particles, Dissolved Oxygen (DO), silica, anions/cations, and metals. Gross contaminants such as resistivity, TOC, particles, DO, silica, and sodium are measured online continuously, while specific contaminants such as halogens, inorganic, and organic species are measured individually offline. Specifications for ionics and metals are often driven by laboratory detection levels in the 10 to 100 parts-per trillion (ppt) range. Some manufacturers will even drive specifications below the detection levels and require sample concentration for testing although this is not yet a common practice. Analytical instruments and procedures are not regulated and can vary from site to site.

At present, particle measurement is restricted to UPW. As unobtrusive inline instrumentation becomes available and more reliable, this may find integration into USP requirements. Table A shows a comparison of maximum contaminant levels for various biopharmaceutical and microelectronic specifications. These specifications generally apply at the point-of-use.

Operational and Design Objectives

Design differences between biopharmaceutical and microelectronics water systems are better understood when one considers the operational objectives of the facilities. Of primary concern to biopharmaceuticals is that the high purity water system be successfully validated, and consistently produce water compliant with USP 24. This includes the overriding need for a high quality water supply and a distribution network that can be frequently sanitized for bacterial mitigation. Typical biopharmaceutical manufacturing operations occur one- or two-shifts per day with a 5-day-work week. For microelectronics, the primary objective of the water system is to create and distribute ultrapure water on a 24 hour 365 day basis with no shutdowns, while maintaining purity. While the biopharmaceutical firm is acutely aware of the impact of lost compliance, the microelectronics firm is concerned with any reduction in product yield.

For both industries, microbial-retentive filters are rarely used at the use-point. Instead, distribution loops are designed to minimize bacterial potential by sizing piping for turbulent flow. Turbulent flow is assured by maintaining a Reynolds number in excess of 2,500 (a more commonly specified level is 10,000) at the end of the supply headers. The debate continues over the effectiveness of reducing microbial contamination by increasing the water velocity beyond minimum turbulent levels.[8,9] Studies have demonstrated that raising the velocity beyond that required for minimum turbulence serves only to waste recirculated water capacity, restrict loop flexibility, and cost more to pump. In practice, when the process demands water, a requirement for turbulent flow results in supply velocities of between 3 and 5 Feet Per Second (fps), or as limited by the piping dynamic pressure losses.[10]

Figure 1 highlights the overall system configurations for a WFI and a UPW system. WFI source water is fed from a continuously circulated PW source and becomes WFI upon distillation or Reverse Osmosis (RO). WFI can be distributed either hot or at ambient temperatures. A UPW polish system is similarly fed from a circulated purified water source, the primary system, which in turn is fed by a pretreatment/makeup system.

Capacity, Scale, and Cost

The scale of water consumption can be vastly different between the two applications: a microelectronics plant may be as

Parameter	Units	Semiconductor Grade Water		Pharmaceutical Grade Water	
		Type E-1.1 ASTM D 5127-99	Typical Operating Owner Specified	Water for Injection USP 24	Purified Water USP 24
Total Organic Carbon	µg/l, ppb	2	2	500	500
Dissolved Oxygen	µg/l, ppb	1	1-20	na	na
Conductivity @ 25°C	µS/cm, Stage 1	na	na	≤1.3 Online	≤1.3 Online
Resistivity @ 25°C	Mohm-cm	18.2	18.2	0.77	0.77
Endotoxin	EU/ml	0.03	na	0.25	na
Bacteria		10 cfu/l	1 cfu/l	100 cfu/l	100,000 cfu/l
Particle Size (on-line) Laser					
0.05-0.1 microns	particles per liter	500	500	na	na
0.1-0.2 microns	particles per liter	300	50	na	na
0.2-0.3 microns	particles per liter	50	na	na	na
0.3-0.5 microns	particles per liter	20	na	na	na
>0.5 microns	particles per liter	4	1	na	na
Reactive Silica	ppt	100	1,000	na	na
Anions	ppt	20-50	1-20	na	na
Cations	ppt	20-50	1-20	na	na
Metals	ppt	20-50	1-20	na	na

Table A. Comparison of biopharmaceutical and microelectronics water quality standards.

small as 150,000 gallons per day, but is typically as large as 2 million gallons per day. A WFI/PW generation system can be as small as 10,000 to 50,000 gallons per day, or as large as 1 million gallons per day (typically for PW only). The type and number of process operations drive this wide variation in WFI/PW system capacities. Biotech facilities consume much of this water in rinsing and washing of tanks and interconnecting piping. Pharmaceutical users require water for compounding, finishing, and washing.

In spite of these size differences, the process of identifying the necessary capacity for a given biopharmaceutical or microelectronics plant is very similar:

- Determine facility average demand based on either tool load projections or based on benchmarking data.
- Size the PW, makeup, and primary systems to support this average facility demand plus reject and maintenance flows within the water treatment system.
- Size the circulated supply loops for the average demand with some peak demand factors plus the minimum circulation flows for turbulent flow. While a microelectronics facility with a consumption of 2 million gallons per day would have a loop circulation of 2,000 gpm, the typical WFI/PW circulation flow would be closer to 200 gpm. There is in general an order of magnitude separation between the sizing scales for the two facility types.

Restrictions on storage of WFI/PW are dependent upon system temperature and hold volumes. Generally, a hot dynamically circulated system is considered to be self sanitizing and hold times are not an issue if in compliance. Recirculated and non-recirculated ambient systems without sanitization should be drained every 24 hours, especially with WFI. This scale difference will drive storage tank sizes for compendial waters of between 1,000 to 5,000 gallons, while UPW storage tanks sizes are limited by transport and shipping considerations: 38,000 gallons with 14-foot diameter are commonly seen. While UPW tanks used to be designed for 2 to 4 hours of storage capacity, as capacities increased, the tank sizes ran into practical size limitations.

Although capital costs of biopharmaceutical and microelectronics high purity water systems are quite disparate, there is some consistency in operating costs on a dollar per 1,000 gallon basis. A typical installed cost for a 100 gpm purified water generation is $1.5 million and with WFI generation by vapor compression the cost rises to $3 million (between 15,000 and 30,000 $/gpm). Conversely, a typical 700 gpm makeup UPW plant installed cost is between $12 million and $18 million (between 17,000 and 25,000 $/gpm). Operating costs for a UPW system are generally between 10 and 15 cents per 1,000 gallons, while WFI and PW water costs vary greatly, between 5 and 14 cents per 1,000 gallons for PW and between 12 and 21 cents for WFI, depending on the distillation technology. As a basis for comparison, potable drinking water generation typically costs 2 cents per 1,000 gallons.

Treatment Processes

Treatment systems are generally designed based on the incoming water quality, the required effluent quality, and the project's reliability, maintenance, and operational criteria. As discussed, there are significant differences in the quality and criteria of water for biopharmaceutical and microelectronics facilities. Both PW and UPW systems are generally fed from a potable water source. A WFI system is usually fed by a PW system with a resistivity of between 1 and 5 Mohm-cm and a TOC of roughly 300 ppb. In contrast, the UPW polish system is fed by a primary loop that typically has a resistivity of between 16 and 18 Mohm-cm and a TOC of 30 ppb or less. This results in more treatment operations in a UPW system than in a WFI/PW system.

In spite of major differences in biopharmaceutical and microelectronics objectives and materials of construction, similarities have resulted.

Biopharmaceutical Treatment System

Compendial water must be generated from potable water. Drinking water standards are usually set nationally, but in the absence of national standards, World Health Organization (WHO) guidelines are generally used. Water purification methods vary widely depending upon water source and municipality. Feed water is pretreated before RO; membranes may become prematurely fouled without adequate pretreatment. As shown in Figure 2, a typical pretreatment and PW process includes:

- Multimedia Filtration
- Softening
- Activated Carbon Adsorption
- Micron Filtration
- Ultraviolet UV Disinfection at 185 nm
- RO Demineralization
- Continuous Electrodeionization (CEDI)
- Submicron Filtration (optional)

The PW source may be utilized to generate WFI by the following methods:

- Distillation (multi-effect or vapor compression) or
- RO Unit (only in US and Japan) or
- Ultrafiltration (UF) Unit (only in Japan)

Although RO is approved for WFI in the US, it is seldom utilized due to problems maintaining high quality water.

Turbulent flow regimes, elevated temperatures (60 to 85° C) and periodic sanitization (either steam or chemicals) are the main tools available for microbial quality control. Distributing water at elevated temperatures is a generally acceptable microbial control measure. This design has economic consequences: increased rouge potential, insulation and personnel protection, more robust elastomers, and energy costs of temperature maintenance. Many users operate with ambient (cold) storage and distribution loops. Such loops are not viewed as self-sanitizing. In fact, they are susceptible to contamination from oligotrophic bacteria; typically *Pseudomonas* types and Gram negative bacteria suited to low levels of nutrients. These organisms are important in the development of biofilm on piping surfaces; however, they may be planktonic; i.e., within water bulk.

Strict adherence to sanitization schedules and methods is required to control microbial contaminants. Ambient or cold loops are most commonly sanitized by heating to the operating temperatures of hot water systems. New methods of sanitizing without costly heating energy and interruptions to loop operation have been adopted. The introduction and use of ozone has increased in the biopharmaceutical industry. Ozone is a toxic substance in the atmosphere and must be removed prior to water takeoff. Moreover, ozone is a very effective sanitant with cell destruction kinetics orders of magnitude higher than chlorine. Ozone will destroy most bacteria in seconds by lysis of the cell wall.

Microelectronics Treatment System

A typical UPW treatment plant is fed potable water; however, some sites will have their own well-water sources. As shown in Figure 3, the makeup and primary system typically includes:

- Filtration for silt reduction using either multimedia or a membrane ultrafiltration or cross flow microfiltration (as low as 0.05 micron)
- Preheat Heat Exchanger
- Micron Filtration
- Serial (two-pass) RO
- Sterilizing and Organic Oxidation with 185 nm UV
- Continuous Electrodeionization (CEDI)
- Mixed Bed Ion-exchange Resins
- Submicron Filtration

The UV/mixed bed deionization/filtration sequence is repeated in a continuously circulating polish loop to ensure reliable supply of 18.2 megaohm-cm water. Depending on the specific specifications, degasifiers (for oxygen removal) are installed upstream of the final mixed beds, 254 nm UVs are used downstream of the final mixed beds and ultrafiltration (6,000 Dalton) is often used as final filters.[11]

The trend in UPW system generation is toward membrane operations, and away from particulate/resin unit operations requiring periodic regeneration or backwash. This trend is due to cost, reliability, and operational advantages afforded by the former. Sanitization is generally performed chemically with either ozone or hydrogen peroxide, or peracetic acid. Hot sanitization is not typically utilized except for final ultrafilter sanitization.

Materials of Construction

To meet facility operational objectives, biopharmaceutical water systems rely heavily on polished and passivated stainless steel as the major construction material with piping and equipment specified for drainability and compatibility with frequent sanitization thermal cycling. In addition, treatment equipment must be selected that minimize introduction of biological load. The water distribution system is a potential contamination source because each point-of-use valve or instrument take-off represents a possible microbial entry site. These sites and the entire storage and distribution system may periodically require batch re-sanitization.

As metal ions can poison a semiconductor, microelectronics water systems rely heavily on fluoropolymers as the major construction material, and minimize metallics in their polish and distribution systems. Piping systems are designed for reliability, pressure control, and avoidance of extractable contaminants. Water treatment equipment for UPW is selected to eliminate all contaminants, and may create a temporary biological load that will be eliminated in subsequent processing. A circulated UPW distribution system incorpo-

rates purification equipment (polish equipment) so the water supply is continuously maintained within specification levels without periodic shutdown.

In spite of major differences in biopharmaceutical and microelectronics objectives and materials of construction, similarities have resulted:

- Valve and component manufacturers for both industries have developed components that eliminate or minimize dead zones and are compatible with various sanitization chemistries and temperatures.
- Piping and component suppliers closely control interior surface finishes to minimize micropores.
- Piping and equipment joining methods have been developed to minimize interior weld beads.
- The same manufacturers supply membranes, filter elements, resins, and other consumables for the common treatment technologies.

Compendial waters for the most part are distributed in sanitary welded 316L stainless steel piping with equivalent grade pumps, heat exchangers, components, and fittings. Silicone, Viton or EPDM elastomers may be used for seals and valve diaphragms. Polyvinylidene fluoride (PVDF) piping is acceptable for exposure to ozone, elevated temperatures, steam, and pressure (75 psi at 80° C), and may present a viable piping construction material for certain applications.

Stainless steel water storage and distribution systems for biopharmaceuticals must be properly cleaned prior to initial passivation to reduce corrosion. Passivation is accomplished with citric acid, or more effectively, a mixture of chelating agents. Periodically, a stainless steel storage and distribution system will require repassivation to replenish the protective oxide layer. Rouge is low-level iron-oxide contamination, which can adversely affect the piping and product. It can be removed by derouging with agents/acids to reduce ferric iron to ferrous, and organic acids to aid in the dissolution of ferrous ion. Repassivation is required after derouging. Typically, a hot WFI system will require derouging every one to two years and a cold/ambient system every three to four years.

Striving for minimal metallics and other extractable constituents in the polish and distribution loops, microelectronic UPW distribution lines are almost universally constructed of PVDF with fluoropolymer coated elastomers and PVDF-lined FRP storage tanks. Stagnant regions at valved branches are minimized with molded PVDF zero-static takeoff valves installed at use points. Many facilities will even require their polish mixed beds and final cartridge filter housings be fluoropolymer lined rather than rubber-lined or electropolished stainless steel.

Instrumentation, Controls, and Analytical Monitoring

Both biopharmaceutical and microelectronics high purity water systems generally include PLC-based control systems with trending capability through a facility management system. Adequate online information is gathered to document critical water quality parameters and to aid in performance troubleshooting. For both systems, the degree of automation varies with size and cost, but typically is based on continuous operation with moderate operator attention.

Conclusion

Because of manufacturing requirements and regulatory conditions, microelectronics and biopharmaceuticals facilities tend to have significantly different capacity and final quality specifications. As a result, the critical treatment technologies vary while pretreatment is similar. Biopharmaceutical high purity water systems tend to be relatively small and more consistent in their design and operation. Through the regulatory process they have integrated treatment technologies and analytical parameters similar to those successfully used in the microelectronics facilities. Microelectronics UPW systems tend to be quite large with minor variations in design and operation. Nevertheless, both capital and operating cost of UPW and WFI, per unit of usage, are quite similar.

Similarities exist in front-end treatment for both industries. Reverse osmosis remains the dominant demineralization process in the generation of high purity waters. Membrane-based CEDI is commonplace in water intermediate treatment. Beyond this point, the system technologies diverge substantially, utilizing different process equipment and operational concepts.

While biological content of water is a significant factor for both industries, the design and operation of WFI systems is highly directed toward this parameter. Less intrusive sanitization processes are required to diminish the costs associated, both directly and indirectly, with operating at elevated temperatures. Membranes with greater tolerance to contaminants, higher temperature resistances, and increased rejection rates are needed to reduce times between failure and sanitization, before they will gain wide acceptance in the biopharmaceutical industry, especially for WFI generation. Other membrane unit operations will gain popularity in the biopharmaceutical arena as users avoid introduction of added ingredients.

The trends toward water and energy conservation and escalating cost will become factors in the development of more efficient unit operations-an area pioneered by the microelectronics industry. The biopharmaceutical industry will be able to leverage these innovations as allowed by the regulatory environment.

References

1. Third Edition, Supplement 2000, European Pharmacopoeia, Council of Europe, Strasbourg. 1999.

2. The Japanese Pharmacopoeia, Thirteenth Edition (JPXIII); ISBN4-8408-0389-7 C3047; Published by the Society of Japanese Pharmacopoeia; Tokyo, Japan 1996.

3. USP 24, United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD, 1999.

4. Concept Paper on the Development of a CPMP/CVMP Note for Guidance on the Quality of Water for Pharmaceutical Use. EMEA/CVMP/510/00 Draft. London, July 27, 2000.

5. Code of Federal Regulations, Food and Drug Administration, current Good Manufacturing Practice for the Manufacturing, Processing, Packaging, and Holding of Drugs; General; Finished Pharmaceuticals Parts 210 and 211 respectively. US Government Printing Office, Washington, DC, 1998.

6. FDA Guide to Inspections of High Purity Water Systems, Revised as of July 1993. US Government Printing Office, Washington DC, 1987.

7. ISPE Baseline® Pharmaceutical Engineering Guide, Volume 4, Water and Steam Systems, First Edition, ISPE, 3816 West Linebaugh Avenue, Suite 412, Tampa, FL, 2000.

8. Klauer, Jörg, PhD, "An Examination of Pipe Self Cleaning in High Purity Water Systems," Ultrapure Water, 2001 March, pp. 56-60.

9. Reidewald, F., "Biofilms in Pharmaceutical Waters," **Pharmaceutical Engineering**, 1997 June, pp. 8-10.

10. Dreyer, C. etal, "Criteria, Tools, and Practices for High Purity Water Distribution Systems," Ultrapure Water, 2000 May/June, pp. 17-28.

11. Payne, J. etal, "Microelectronics Water System Evolution Through 300 MM," **Ultrapure Water**, 1999 May/June, pp. 27-40.

About the Authors

Andrew Baird Msc Eng is a Process Engineer with IDC. The bulk of his work has been in biopharmaceuticals. He obtained a BS, biotechnology in 1988 from University of Reading, United Kingdom and a MSc, biochemical engineering in 1990 from University of Birmingham, United Kingdom. His scope of expertise includes process and equipment design for fermentation and purification of proteins derived by rDNA technologies and utility system design. His experience includes field supervision of an integrated validation team validating a grassroots biotechnology facility.

IDC, 60 Pointe Cr, Suite 200, Greenville, SC 29615, 1-864/235-3533, e-mail: andrew.baird@idc-ch2m.com.

Kirsten Sommer, PE is a Chemical Engineer for IDC, and for the past 14 years has been involved in design, construction, and consulting projects for the semiconductor industry. As a chemical engineer, her areas of expertise include ultrapure water systems, recycle/reclaim systems, wastewater treatment systems, and chemical handling/distribution systems. Sommer also has performed a wide variety of related chemical engineering services for electronics, chemical, printed circuit board, and specialty metals industries.

IDC, 2020 SW 4th Avenue, 3rd Floor, Portland, OR 97201, 1-503/ 244-6040, e-mail: kirsten.sommer@idc-ch2m.com.

Ralph Williams, PE is a Water Technologist for IDC with extensive experience in high purity process systems, water treatment, and in chemical-related code analysis. He has been responsible for management of ultrapure water technology at IDC, and for the last 10 years, played a leading role in the advancement of IDC's technological leadership in the areas of ultrapure water, ultrapure water reclaim, waste treatment, and process piping systems. Williams was previously vice president of Advanced Industrial Designs, Inc. and chief engineer at Balazs Analytical Laboratories.

IDC, 2020 S.W. 4th Avenue, 3rd Floor, Portland, OR 97201, 1-503/244-6040, e-mail: ralph.williams@idc-ch2m.com.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Cutting Energy Costs with Laboratory Workstation Fume Hood Exhaust

This article illustrates how a pharmaceutical research firm reduces costs for heating conditioned makeup air by 30% or more for thousands of dollars in annual savings.

by Paul A. Tetley

Laboratory facilities at pharmaceutical research and manufacturing organizations are burdened with perhaps the most expensive energy costs for heating and cooling per sq. ft. in the country. This is mainly because most laboratories – and some pharmaceutical processing facilities – require conditioned 100% makeup air for their workstation environments. Obviously these demands are responsible for creating substantially higher energy costs since makeup air must be filtered, heated, cooled, humidified, or dehumidified depending upon circumstances.

There is a practical, cost-effective method; however, to lower energy costs for natural gas, oil, or electricity significantly with resultant savings of thousands – or even hundreds of thousands – of dollars annually. This article will discuss how one pharmaceutical research organization[1] handled this problem.

This pharmaceutical research organization was confronted by the prospects of high-energy costs when it recently built a new facility for chemical research activities. The company is involved in research and early stage development of drugs. While the company is independent, it occasionally forms collaborations with pharmaceutical manufacturers, setting up independent joint ventures for both production and marketing of specific drugs it helped to develop.

Even without the need to introduce 100% makeup air into the work environment, laboratory research activities at pharmaceutical firms are major energy consumers. Providing comfortable and safe workplaces for scientists and technicians requires efficient heating and cooling of ambient air. Workstation fume hoods require control and management and other energy intensive equipment and systems associated with the research environment generally consume energy in one form or another. When you add fume hood exhaust systems on the roof – which must operate whenever a workstation

Figure 1. Mixed flow impeller system.

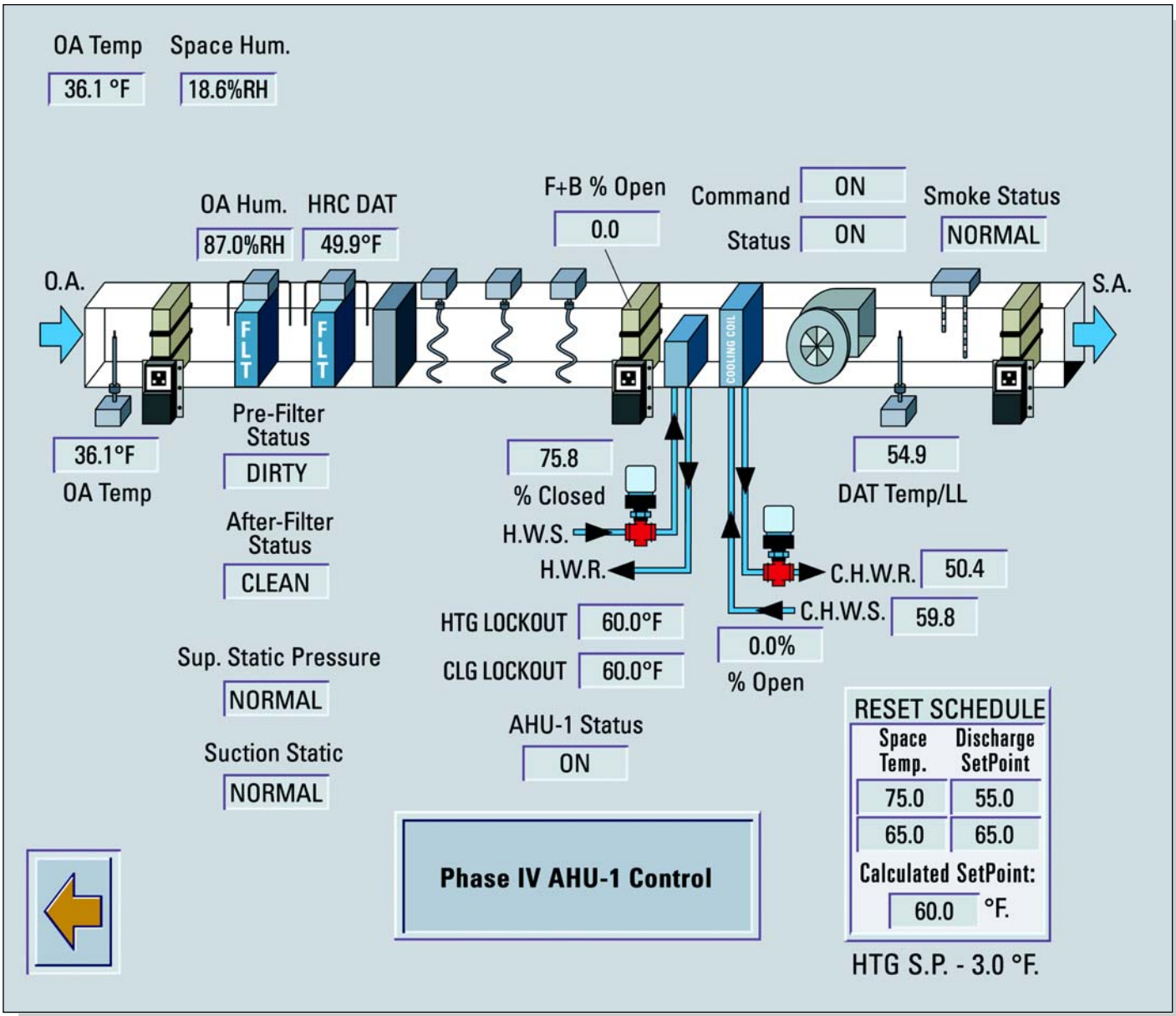


Figure 2. System status monitor – outside air temperature at 36.1°F.

is being used – it's easy to see how energy costs can mount quickly at a large research facility. At this firm, about 30,000 cu.ft. of air per minute has to be moved in and out of its new 20,000 sq.ft. research building which houses 18 laboratory workstations, each with 10' fume hoods.

The facility manager[2] at the company is responsible for the daily operation of the company's physical plant. He is involved in many areas including construction, renovation, energy conservation, and other aspects of managing a complex facility. He benchmarks the average cost to condition makeup air at $3.71 per cu.ft. per year. He said this figure is used by most building engineers. On the other hand, the total energy costs average more than $6 per sq.ft. per year.

Since code prohibits all air in the laboratory workstation environment to be recycled, it must be exhausted. This includes both the ambient air as well as the laboratory workstation fume hood exhaust, and is considered as "100% exhaust, 100% makeup." This facility is a "constant volume building," which means that the volume of air entering and exiting the building is constant. "With the cost of heating or cooling makeup air alone at nearly $4 per cu.ft. per year, clearly this issue had to be studied carefully, and a reasonable solution had to be found," the facility manager commented.

The Solution was on the Roof

The facility manager's approach to the problem was both practical and logical. In fact, most of the solution was already in place, just above his head. That's because the 18 laboratory workstation fume hoods were being exhausted on the building's roof with mixed flow impeller exhaust systems – *Figure 1*. Each system is connected to an exhaust plenum serving the workstations, and is designed to provide high efficiency exhaust and eliminate re-entrainment problems, a particularly critical issue when makeup air is introduced into a building on a constant flow basis.

The systems are designed to accommodate a unique heat recovery system (essentially a heat exchanger containing coils filled with a solution of glycol and water) that extracts ambient

heat from the workstation fume hood exhaust before it is discharged above the roofline – *Figure* 4. This air glycol/water solution is transferred to the supply air handler to preheat the conditioned air entering the building. As a result, the amount of natural gas to preheat the makeup air is reduced substantially.

Reduce Heating Costs 3% for each 1°F Added

The facility manager said that in winter, "there were days when we were putting about 10°F into the makeup air simply by capturing heat from the exhaust stream" – *Figure 3*. He added that 10°F was the temperature difference between the incoming air (at the outside ambient temperature) and the air entering the intake system after it was passed through the glycol loop coils. He stated that "for every degree you add, you reduce your energy costs about 3%. So, a 10°F rise in intake air means that about 30% of energy savings can be realized." As he says, "In addition to saving our company money, we also help contribute to a cleaner environment since less fossil fuel is consumed."

With regard to overall costs – for system hardware as well as energy charges – the facility manager believes that a payback cycle of three years or less has made this solution economically sound for the company (some users have experienced actual payback in two years or less depending upon system configuration, climate, and other variables). With energy costs rising dramatically, it is expected that heating costs alone will rise 30%-50% for the 2000/2001 season over the prior year, and he believes that the company has gone in the right direction with its heat recovery systems on its laboratory fume hood exhaust fans.

Cooling Applications also Use Less Energy

Again, the facility manager cited some specifics. Since the company is located in the Northeast United States, it experiences varying temperatures during the year. Conditioned makeup air is either cooled with fume hood exhaust air during the cooling season or warmed during the heating season. The system is only usable when the outside air temperatures are

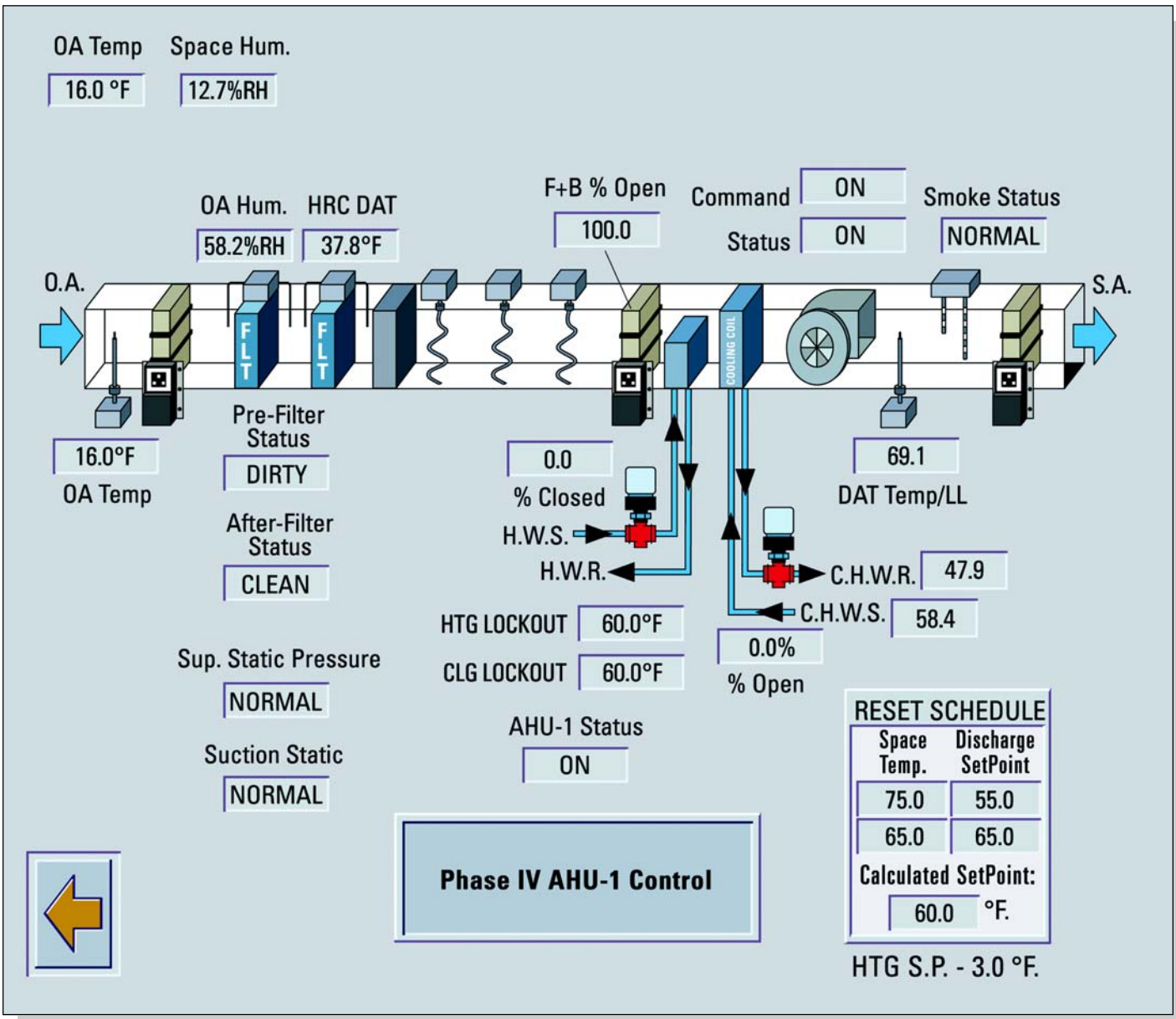


Figure 3. System status monitor – outside air temperature at 16.0°F.

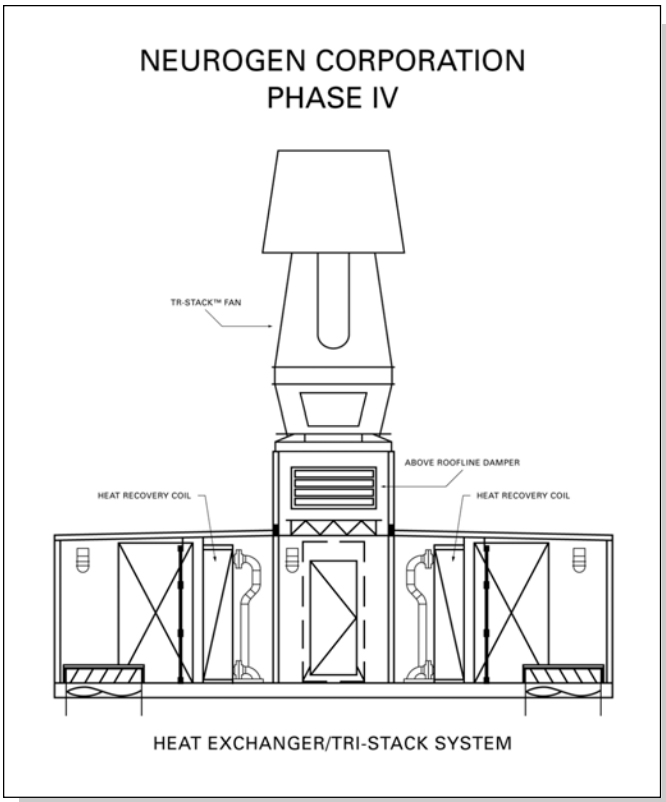


Figure 4. Heat exchanger/mixed flow exhaust system.

below 40°F or above 80°F. "You need a big enough difference between outside and inside air to make it practical," he added – *Figure 4*. With regard to cooling air in warmer temperatures, he pointed out that if outside air, at 90°F is brought back into the building and sent through the heat recovery system, the air temperature drop is typically 4°-5°F. Again, he equates these figures to a 3% drop in energy consumption for each 1°F drop in air temperature.

There are four different pharmaceutical research buildings at the company's complex. At the Phase 1 building, individual dedicated fans are used for exhausting individual laboratory workstation fume hoods. The newly built Phase 4 building incorporates the mixed flow exhaust systems with heat recovery capabilities – *Figure 5*. And, in the Phase 3 building, there are five laboratory workstations with associated fume hoods and dedicated fans for each of them. While he considers the Phase 1 and Phase 3 configurations less efficient by example of his success with heat recovery, he intends to change it with his "list of energy conservation strategies which I have gradually been putting in place."

The Pharmaceutical Industry Experiences "High End" Energy Costs

In fact, he added that one of the influences with regard to committing capital expenses to energy reduction is related to "rebate dollars from the local utilities." He said that, "if you are looking at two projects and one is rebatable and one is not, all other things being equal, you go after the rebate dollars." In light of this, he discussed energy cost averages for the pharmaceutical industry, adding that it is not uncommon to see $6 per sq.ft. per year for energy costs. Since he has an extensive facility management background in other industries, he added that for comparison purposes, public schools run at about $1, and hospitals (also large energy consumers) are still below $5 per sq.ft. per year (these figures are based on Northeast regional facilities where energy costs are slightly higher than the rest of the US). He stressed that the pharmaceutical industry is at the "very high end" of energy costs.

When questioned further, the facility manager said the main reason for this is the 100% conditioned makeup air which is required by code. In a hospital, for example, 80% of the air in an operating room can be recirculated as long as it's filtered through a HEPA system. In the pharmaceutical industry, "we have no opportunity for recirculating air. We just could not bring it back into the building." You can't use it through a heat wheel which is a way of recovering heat from exhaust air since many of them are based on not only getting the sensible heat out of the air, but the latent heat out of the moisture. In a chemical building or a drug research facility, this is not possible.

Heating Energy Costs are Expected to Soar

When discussing energy costs and the future, the facility manager said he expects some "serious increases in natural gas prices in the near future." He added that, for example, he has seen no positive benefits to consumers as a result of electrical power de-regulation policies on the West Coast. "After salaries, energy is the second largest expense item in the pharmaceutical research industry," he said. "It is not unusual in a facility such as ours to use 15% or more of the entire operating budget for energy, and this is not out of line for the industry," he added. Consequently, he believes strongly in selecting an engineering team when designing a new facility or planning a major renovation who has direct experience in the pharmaceutical industry, particularly with regard to the exhaust side as well as the energy reduction/consumption area.

Much of the statistics generated as a result of the energy savings has been logged carefully by the facility manager, and are included here for reference. As he pointed out, "On my screen I can actually see the temperature of the outside air, observe the air going over the heat recovery coil, and then note the air temperature as it passes through." He sees in real time how much heat the system puts back into the makeup air before money has to be spent in heating it; the same is true on the cooling side - *Figures 2 and 3*.

Since he feels very strongly about energy costs, consumption, and savings, the facility manager made it clear that the recent energy de-regulation policies in California have not resulted in reducing costs that were anticipated. "In other words, we are not going to de-regulate ourselves out of these high energy costs," he added. Consequently, he believes that pharmaceutical companies who are holding up energy conservation programs now because they believe de-regulation is "going to do it for them," should perhaps begin looking at other approaches. He commented that "You can tell where the rest of the country is going to be in a year or two by looking at California, and the early results of de-regulation there have not been good – in terms of cost and also in terms of reliability of service." He added that he would not "depend on de-regulation to cut your energy bills; you have to work on the demand side," he concluded.

Mixed Flow Impeller Technology Prevents Re-Entrainment

While roof exhaust re-entrainment can be a serious problem, all of its negative implications may not be widely known. In

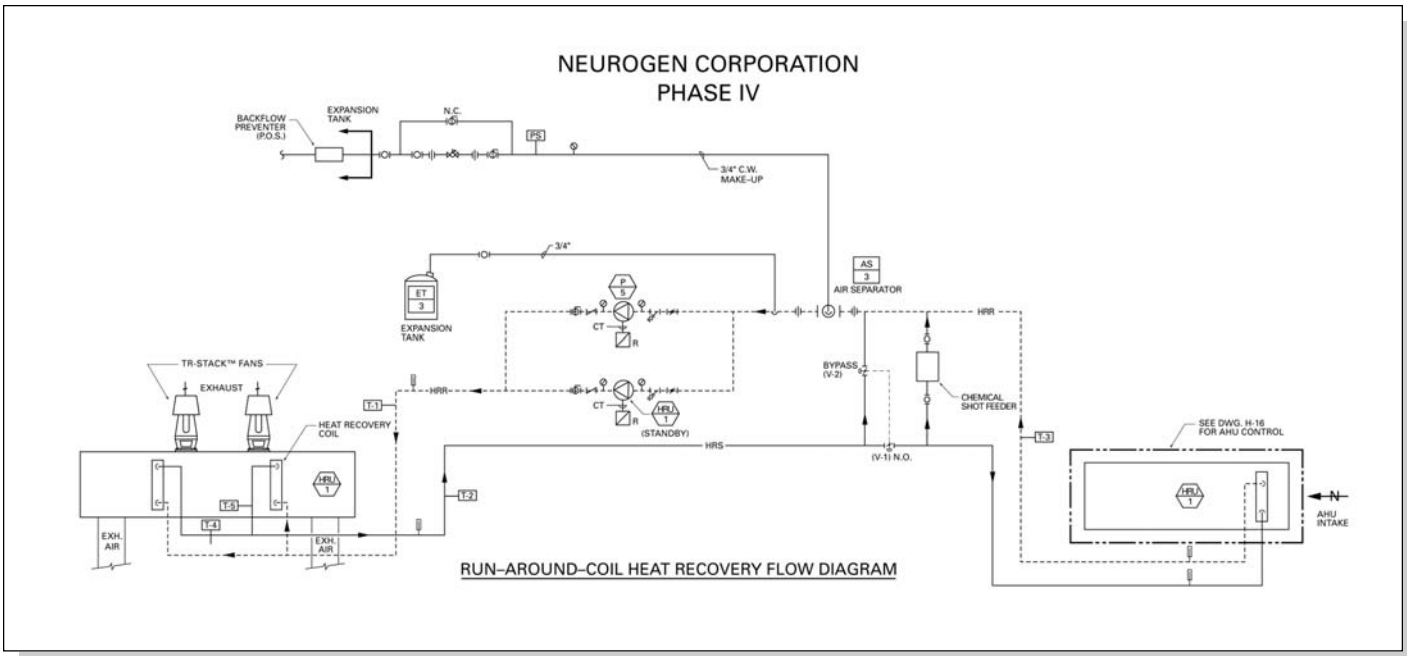


Figure 5. Run-around-coil heat exchanger recovery flow diagram.

fact, not only can the health of building workers be affected by exhaust reentering the building through windows, vents, air intakes, and door openings (among other possibilities), but the legal consequences can extend well beyond their employers. For example, there have been cases where building owners, consulting engineers, Heating, Ventilation, and Air Conditioning (HVAC) contractors, and even architects were named as defendants in major cases associated with employee illness and IAQ. The company's fume hood exhaust fans use mixed flow impeller technology to send the exhaust stream hundreds of feet into the air in a powerful vertical plume, mixing outside air with exhaust gases (dilution) to prevent re-entrainment as well as eliminate odor problems. They also provide other advantages, such as inherently lower energy consumption over comparable centrifugal-type exhaust systems. With the ability to pre-heat and pre-cool makeup air prior to its introduction into the building, the systems offer substantial energy saving benefits to pharmaceutical research and manufacturing organizations.

Mixed Flow Technology Offers Performance and Cost-Savings Advantages

Mixed flow impeller-type roof exhaust systems operate on a unique principle of diluting outside air with plenum exhaust air at high discharge velocities, sending a powerful vertical exhaust plume up to 350' high – *Figure 6.*

Because they introduce up to 170% of free outside air into the exhaust stream, a substantially greater airflow is possible for a given amount of exhaust without additional horsepower, providing excellent dilution capabilities and greater effective stack heights over conventional centrifugal fans.

These systems reduce noise, use less energy, and provide enhanced performance with faster payback over conventional centrifugal laboratory fume hood exhaust systems. With typical energy reduction of $.44 per cfm at $.10/kilowatt-hour, these systems provide an approximate two-year ROI, therefore energy consumption is about 25% lower than with conventional centrifugal fans – with substantially reduced noise levels, particularly in the lower octave bands. They conform to all applicable laboratory ventilation standards of ANSI/AIHI Z9.5 as well as ASHRAE 110 and NFPA 45, and are listed with

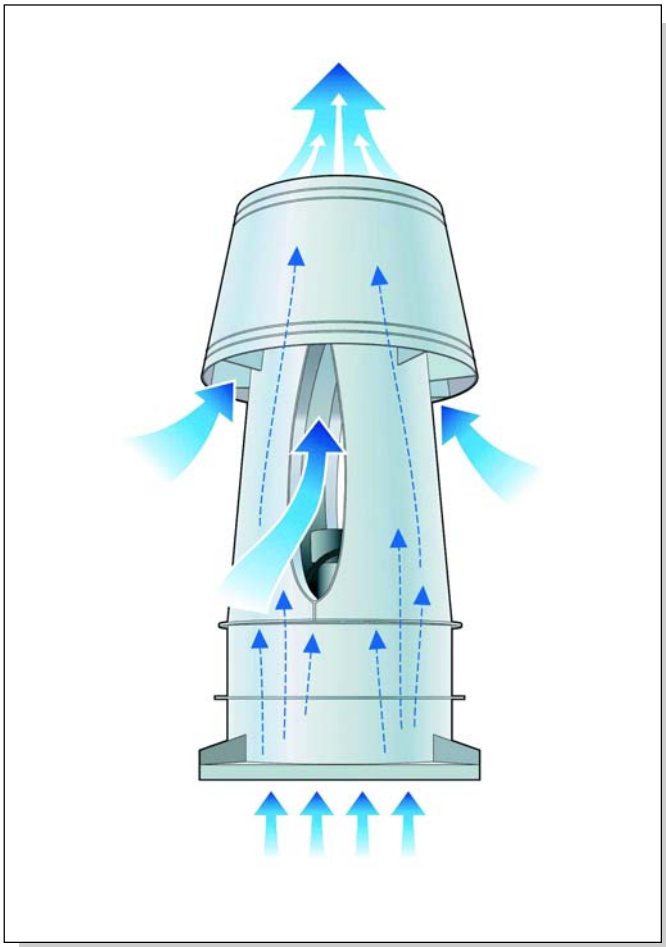


Figure 6. Typical mixed flow impeller system.

Underwriters Laboratory under UL 705.

The systems are designed to operate continuously without maintenance for years under normal conditions - direct drive motors have lifetimes of 200,000-hours. Non-stall characteristics of the system's mixed flow wheels permit variable frequency drives to be used for added Variable Air Volume (VAV) savings, built-in redundancy, and design flexibility.

Virtually maintenance free operation (there are no belts, elbows, flex connectors, or spring vibration isolators to maintain) eliminates the need for expensive penthouses to protect maintenance personnel under adverse conditions. Consequently, additional savings of several hundreds of thousands of dollars are realized in a typical installation.

Mixed flow impeller systems are available with a variety of accessories that add value, reduce noise, or lower energy costs substantially. For example, accessory heat exchanger glycol/water filled coils for use in 100% conditioned makeup air facilities add exhaust heat to intake ventilation air to save thousands (or hundreds of thousands) of dollars in energy.

Conclusion

Recovering ambient heat prior to exhausting it outside the building is generally only cost-effective when 100% conditioned makeup air is required as in the case of this pharmaceutical manufacturer. Because there are so many variables between facilities – including physical layouts, equipment, heating/cooling systems, etc. – it makes sense to look into other methods of heat recovery and/or heat efficiency as well. And, because climate is a key factor in this equation, a full year's outside temperatures should be considered to help make a better determination as to what might be suitable. For laboratory environments, another energy conservation approach would be automated control of laboratory workstation fume hood exhaust rates based upon occupancy sensing.

References

1. Neurogen Corp., Branford, CT.
2. Bill Waldron.

About the Author

Paul A. Tetley is Vice President and General Manager of Strobic Air Corp., a subsidiary of Met-Pro Corp. Since joining the company in 1989 as engineering production manager, he has designed and/or invented many innovative Tri-Stack fan systems, an acoustical silencer nozzle, and a unique multi-fan plenum system.

Strobic Air Corp., 160 Cassel Road, Harleysville, PA 19438, (215) 723-4700, paultetley@strobicair.com.

This article discusses all aspects of modularization in a step-by-step approach. It will list advantages and disadvantages of modularization and provide specific information on what should be a module with a biopharmaceutical (Biopharm) facility.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Modularization in Biopharmaceuticals

by William P. Lefebvre

Introduction

There are many risks and challenges in constructing a Biopharm facility today. One that is of primary concern is the adequate availability of skilled craft labor. This is particularly true in rural areas and areas where there exists an already tremendous demand on skilled construction labor due to a large volume of construction activity. The concern for available skilled craft labor represents significant risk in the areas of cost, schedule, and quality of the facility. One means of mitigating these risk areas is to maximize the use of off site/prefabricated or modular construction in an attempt to move as many craft hours off as is practical. In addition to mitigating the risk of qualified craft labor resources, modular construction offers advantages in safety, schedule, and predictability. This article will provide information regarding one method to select and work with vendors for modularization.

Definition

A module is defined as "a component of the building that can be constructed, tested off-site, and installed into the building as one piece or in sections then reassembled with only a few reconnections to the building services." A module is not a skid. A skid is a component of the building that can be manufactured by numerous vendors with minor modifications to the skid vendor's standard design. Some of the standard skids utilized in biotech facilities are CIP Skids, WFI Skids, Clean Steam Generators, Soft Water Skids, Carbon Filter Skids, RO Skids, and CDI/EDI/DI Skids.

Advantages of Modularization

There are numerous advantages for modularization within the biopharm industry. The below listed advantages are the results in modularization in general and not specific toward any one particular module. The advantages are listed by the area of construction that is affected by the positive effect of modularization.

Schedule

- To move critical craft trade man-hours off of the project at the critical peak man-hour time frame and into an off-site manufacturing facility not near the project site.
- To provide for an early "mechanical completion" date for critical process systems in lieu of stacking these dates in the field.
- Availability of an early start to passivation to again avoid stacking of the activity.
- The successful Factory Acceptance Test (FAT) at the module vendor's shop reduces the start-up and validation effort and schedule on the project.
- The controlled work environment of a module vendor's shop, which eliminates weather/temperature concerns, produce significant schedule benefits over conventional field construction.

Man-hours

- To move 10% to 20% or more of critical trade man-hours from the project site to the module vendor reduces the peak manpower number considerably.
- The reduction in manpower brings a reduction in worker density, which increases work production per man-hour spent in any given area of the project.
- The reduction in onsite manpower of critical labor trades is invaluable where a project would face local manpower shortages of these trades.
- The module vendor's skilled core craft base and proven work processes combine to yield higher work productivity than typical field construction.

Quality

- The ability to work on the module physically from all sides produces a higher quality than typical field construction.

- The use of 3D design with an interference package to develop isometric drawings virtually eliminates any quality issues typically incurred with field construction.

- Module fabrication helps keep the number of blind welds to a minimum.

- An extensive successful FAT ensures a higher quality standard.

- Quality is built in through a module core craft labor force which are experienced in modular fabrication and adheres to the strict module in-house quality plan/procedure.

Cost

- Modules including design engineering, formal design reviews, on-site inspections, FAT, reports, validation documentation, shipping, and field reassembly cost less than most field constructions of the same scope.

- Modules are considered one piece of equipment in most states and therefore subject to minimum tax considerations in lieu of the purchasing all of the components within the minimum tax.

- The additions of headers on feed and drain lines to service the module reduces field construction costs without adding comparatively to the module cost.

- Schedule reductions mentioned above reduce overall project costs.

- With modularization, there is less exposure to delays due to labor unrest and jurisdictional disputes.

- There is a reduced requirement for laydown and marshalling areas on the project site.

Safety

- Module construction at a module vendor's facility is inherently safer due to a controlled work environment and working at grade rather than at heights and virtually eliminating the need for scaffolding.

- The modules arrive at the project site with all of the safety requirements installed thereby eliminating the exposure for fall protection and other such hazards.

- The transfer of numerous hours from the project site to the module vendor reduces the total number of man-hours to be worked on the project and thereby reduces the potential for a safety issue.

Finally, the use of "Lessons Learned" from previous module construction efforts yields benefits in reducing the number of problem issues. This reduction results in a better predictability of cost, schedule, and quality desired.

Disadvantages of Modularization

There are few disadvantages of modularization within the biopharm industry. The disadvantages are listed below:

	Vendor 1	Vendor 2	Vendor 3	Vendor 4	Vendor 5
Module A	3		2	1	
Module B	2	3	1		
Module C		1	2		3
Module D	1			3	2
Module E	3			1	2
Module F		2	3	1	

Table A. Project X module vendor analysis matrix.

- Requires earlier than normal design completion of systems that may not be ready for design completion and may cause several changes in the module design as other contiguous systems complete their design.

- If the module is late, large sections of the building ready to accept the module will have to be left open and thereby cause delay in the construction of that area and surrounding areas.

- There is a risk of a schedule delay if the modules are damaged during shipment or installation.

Module Team

The first step in the modularization process is to establish a Module Team. This team must include Client/Owner, the Architect/Engineer, the Construction Manager, and each of the module vendors. The module vendor member of the Module Team joins the team after the module has been awarded to the module vendor. Based upon the amount/number of modules, there will be several members from these firms.

The Client/Owner member/members must have knowledge of the particular process, design experience, and be able to interface and communicate with all appropriate departments within the Client/Owner organization. One additional person that should be a member of this team is someone from operations, who has extensive experience in maintenance, production procedures, and GMP procedures.

For the Architect/Engineer, a lead module manager is vital. Each individual module or module vendor needs a person to champion the module. This person reports to the lead module manager. Supporting the individual module design lead is a group of designers from utility piping, electrical, process piping, equipment, instrumentation and controls, structural, architectural, and mechanical. How this group of designers is broken up for the modules is dependant upon the number and size of the modules as well as the strength and availability of people.

For the Construction Manager, the lead module person also must be the leader of the Module Team. This person must possess knowledge of biopharm construction, process equipment and instruments, automation control, scheduling, estimating, and rigging. This person should have project management experience with good communication skills, and must be a member of the Construction Manager's on-site building team. This person must work in close harmony with the Construction Manager's on-site building team for coordination and must be able to use the estimating, scheduling, purchasing, and accounting departments to enhance this person's role as leader of the Module Team.

Each of the module vendors must assign a module manager for their particular modules. If the module firm is to produce multiple modules, each one of the modules must have a lead person reporting to the module manager. Supporting the module manager and the module leads are persons from estimating, scheduling, production, management, and design.

Module Selection

The Module Team (minus the module vendor representative) will meet to determine what items within the project that are suggested for modularization. The documents from the Architect/Engineer that are to be reviewed are the latest revision of the: P&IDs, General Arrangement (GA) Drawings, Elevation Diagrams, Orthographic Drawings, and equipment datasheets/drawings. Some of the criteria for selecting modules are as follows:

1. Functionality. Items that function as units to perform a portion of the process are considered as a whole. One such item is to build WPU Generation as a module that would include soft water skid, carbon filter skid, RO skid, CDI, or DI skid along with all interconnecting pipe, electrical, and controls. This module would be started, FAT, and produce proven purified water before it is shipped to the project site.

2. Array. Items that are by design arranged in an array within a platform make perfect module candidates. These array modules would include a platform, all work such as process piping, electrical, instruments, control tubing, etc. The module also would include process equipment such as vessels, pumps, heat exchangers, agitators, control cabinets, etc. Array modules of this type would include Media Prep, Buffer Prep, and Buffer Hold. These modules would have a FAT before it is shipped to the project site.

3. Cluster. Items that are clustered around a frame that could work as a unit or could benefit the project as a unit are to be considered as a module. The modules similar to the array types modules contain all work and equipment within a frame. Cluster type modules are multiple CIP skids combined together with single rinse and final rinse tanks, including all interconnecting work. Another cluster type module could be media filtration and WPU Distribution (including heat exchangers, ultraviolet lights, and pumps).

4. Size. The physical restraints of the building construction, the module fabrication shop, and shipping requirements are other factors in determining modules. The modules can be broken down into sections for shipment and movement into the building. Most likely shipping constraints will determine the size of the module and its sections. The shipping rules vary from state to state, and the best route to take advantage of the most favorable shipping rules, wider roads, and taller bridges or bridges with close "go arounds" will tell the Module Team in what states the module will be traveling. If the Module Team restricts the Module or its sections to 13 feet in height, 15 feet wide, 35 to 45 feet long, and from 36,000 to 40,000 pounds in total ship weight, the team has a good start in determining the size of the module. Note that by protracting legs or handrails down to their lowest configuration will benefit the module design and should be considered on all modules.

The Module Team in deciding the modules will mark up a set of drawings for each module by placing a boundary line around what is to be considered in the module. The Module Team will collect these marked up P&IDs, General Arrangement Drawings, and Orthographic Drawings along with all appropriate equipment data sheets into a packet. The module will then be assigned an equipment number beginning with "MOD," a dash, and the number of the most prominent equipment number, such as MOD-2101. This number is placed within each of the module boundary lines on the drawings. If elevation details or layout details are not available at this time, the Module Team will draft such details. These details will, in addition to providing vital information to the module vendor, establish the overall box size of the module.

The Module Team will collect all of the proposed module packets and list them on a spreadsheet. A copy of each packet and the spreadsheet is distributed to each team member for review. Each team member will share this module information with members within their organizations that can lend a professional review in areas of mechanical, electrical, process instrumentation and control, etc. to ensure completeness of design and intention within the module boundaries. Each team member will collect his or her own comments and those received from their organization review. They will bring all comments to a subsequent Module Team meeting to finalize the module list. At this meeting, the final litmus test as to the feasibility of each module is discussed and challenged. The final product is the Module list for this project with an associated information packet containing all the information documents mentioned above.

In a biotech facility, the following items should be considered for modularization:

- any cluster or array of tanks in a platform to include all heat exchangers, pumps, agitators, control cabinets, etc.

Action Item No.	Date	Action Item Description	Responsibility	Projected Date Completion	Change Estimate No.	Status
2-1	5/7/01	Possible added sampling station at VP-1001	Owner/Client	6/13/01	10	OPEN
1-2	4/30/01	Change size of instrument air line to Fliter FI-1001	Architect/Engineer	6/01/01	8	OPEN
1-1	4/30/01	Reverse slope on clean steam line 23445-01	Architect/Engineer	5/30/01	N/A	CLOSED

Table B. Project X action log.

- purified water system to include soft water, carbon filter, RO unit, and DI unit with all interconnecting piping and controls
- WFI System to include WFI generator with tanks (if not too large), pumps, UV units, heat exchangers, etc.
- waste/biowaste kill system (not in pit) to include the kill unit and all associated tanks and pumps
- buffer and media prep and hold arrays especially in a platform including all pumps, filters, agitators, etc.
- seed bioreactors/fermentors that are arranged parallel to each other and can share common feeds as one whole unit.
- a combined CIP System using multiple CIP Skids and common tankage, pumps, etc.
- filtering or storage systems that can be incorporated into a frame or platform to include pumps, filters, heat exchangers, control cabinets, etc.

Module Bid Documents

The Module Team will develop a module bid package for each module that is to be bid. The Module Team will provide the module bid packages to the purchasing department for procurement. The module bid package is to include the following information. The below list is only a suggestion and can be added to, adjusted, or deleted from in order to better describe the module.

Specific information:

- a written description of the module
- elevation and envelope sketches
- module boundary P&IDs
- component summary list
- module equipment list
- equipment data sheets (pre-purchased equipment)
- module schedule with a copy of the project schedule
- general arrangement drawings with module boundaries
- bill of material (bid form)
- instrument data sheets for the module

General Specifications:

- general module specification
- welding specification for hygienic equipment construction
- general specification for equipment
- pharmaceutical equipment - stainless steel finishes
- specification for vendor data submission
- control systems (with approved vendor/vendors)
- instruments furnished with equipment
- engineered equipment wiring
- building electrical design material and installation
- structural steel with attachments
- structural stainless steel with attachments
- piping material line class specification
- piping supports with attachments
- field painting

Additional Drawings:

- structural details (grating, floor plate, ladders, stairs, rails, platforms, etc.)
- mechanical and electrical details
- loop diagrams

Additional Information:

- building code information enforced at the project site location
- details for three formal design reviews at the architect/engineer's office
- details for the "kick-off" meeting at a location TBD by the Module Team
- shop drawing/submittal information
- FAT information
- information 3D drawings required with bid
- delivery and crating information
- module delivery escort by the module vendor (in addition to truck escort)
- jobsite project rules and regulations
- reconnection information
- start-up information
- validation documentation requirements
- suggested module section breakdown

Module Vendors

Now that the module bid package is being assembled and copies being made, the list of module vendors must be finalized at this time. There are probably numerous vendors who can claim to be module vendors, but only a few have actually produced "modules." To start a vendor list, it is best to start with those vendors that have in fact produced, FAT, shipped, reconnected, and started the modules up on the project site.

To expand this list, a search must be completed of those vendors whom have module experience. Equipment vendors can become module vendors if they have in-house design capabilities, large clean fabrication area, clean equipment fabrication, knowledge of cGMPs, and validation documentation.

A good exercise to perform prior to assigning potential vendors to bid on specific module bid packages involves the entire Module Team (without the module vendor representative) and several others who have a good working knowledge of the vendors and the module bid package scope of work. A Module Vendor Analysis Matrix (Table A) is developed with the module bid packages listed down the left side. All of the potential module vendors are listed across the top of the matrix. Each team member is given a copy of this matrix filled out as described above and that person places a "3 " in the box to the right of the module and under the potential vendor that the team member feels is the best potential vendor to build this module. A "2" is placed under the name of the potential vendor that they feel is next best to build this module and a "1" below the third best. Once the matrix is completed, the Module Team Leader will then total the ranking numbers for each of the vendors per module and the three or four vendors with the highest total rank will be allowed to bid on that particular module. Adjustment may be necessary to balance the bid load and workload. Now the module bid packages can be sent out to the respective module vendors selected from the matrix.

Module Bidding Process

During the bidding period, a "Pre-Bid Meeting" with the Module Team and all of the vendors bidding on that module will meet at a location (usually at the project site) to discuss questions raised and for the dissemination of additional module information.

Any and all questions answered during the bidding time will be transmitted to all the module bidders.

During the bidding period, the estimating team from the Architect/Engineer and the Construction Manager develops a detailed estimate for each module. Before the module bids are

opened, the two estimates are reconciled at a module estimate meeting including the Module Team and the two estimating teams. This reconciled estimate becomes the basis to which the module bids will be evaluated.

Four complete copies of the bid are to be submitted per the bidding instructions (one each for the Owner/Client, Architect/Engineer, Construction Manager, and Purchasing Agent). The Module Team and the Purchasing Agent will meet to analyze the bids and then conduct "Pre-Award" meetings with the low bidders to assure completeness of the bids to make sure that the bids are "Apple to Apple." From these meetings, an award recommendation is sent to the Owner/Client for approval of the recommendation. Upon this approval, the Purchasing Agent will notify the successful vendor and arrange for a "Kick-Off" meeting as quickly as possible. The Purchasing Agent then drafts a contract purchase order to the successful vendor and completes the award process.

Module Design

The Kick-off Meeting starts the design process. The Construction Manager representative to the Module Team runs this meeting. The Agenda is to include the following items: develop contact list for entire module team and support members, finalize information flow, establish schedule including all activities, establish design links between Architect/Engineer and Module Vendor, plus the items described below.

Establishing the design link is the first key activity. The module vendor will establish one or two design stations within the Architect/Engineer's office and begins to download information from the Architect/Engineer into the 3D design program. The design station will remain in place within the Architect/Engineer's office until the main design effort is complete. That could run as long as two to three months.

The Architect/Engineer representative to the Module Team will conduct a teleconference with each module vendor that he or she is responsible for. This person also will be responsible for the "Action Log" that records all items from this teleconference that require action by someone on the module team. Each teleconference session is consecutively numbered, and this number becomes the prefix to each action item from that particular teleconference session. The minimum column headings for the Action Log should be: action item number, item description, Module Team firm responsible for action item, person within firm responsible for action item, date action item must be completed by, change estimate number, status (Open or Closed). This vehicle will keep the team focused and will resolve all problems in a timely manner. When the Module Team is physically together, the Action Item Log needs to be included in the agenda for that week's meeting – *Table B*.

It is recommended that three Formal Design Review (FDR) sessions be held at the Architect/Engineer's Office. The Architect/Engineer representative to the Module Team will orchestrate these sessions. The three sessions are broken down to allow the fabrication to start and continue in an orderly manner in accordance with the schedule. To that extent, the three FDR sessions will focus on different aspects of the design. In the first FDR, the module vendor will present all 3D drawings developed to date, but will submit the structural drawings for approval. The goal of this session is to agree on the structural design and equipment layout to allow the module vendor to begin construction of the structural framework and the setting of equipment while continuing with the balance of the design. The second FDR session concentrates on utility and process piping approval, while the third and last FDR session provides for approval of all of the balance of the design drawings including electrical and control. The module vendor needs to submit the documents for review at the FDR sessions a few days prior to the FDR sessions to allow each and all team members a chance to review and markup the documents to facilitate an efficient FDR session. Team members reviewing these documents for the first time at the session need to be prohibited since this is a tremendous waste of everyone's time.

At the completion of the module design, a matrix of all of the points of connection to and from the module is developed by the module vendor. This matrix will number each of these connections that correspond to the detail design drawings. The matrix also will indicate the service, size of the line, material type, line indicator number, type of connection, and the XYZ coordinates of the point of connection. This matrix along with some of the detail design drawings will be included in the respective field trade contractor's scope of work for connection to the modules.

Shortly after the kick-off meeting, the Module Team leader will meet with the module vendor and the Architect/Engineer representatives to develop a detailed schedule for each module. This schedule should have the following major headings that are scheduled activities on the main project schedule under the module heading: design, fabrication, pre-FAT inspection, FAT, disassemble and crate, ship, set in place, reconnect, and start-up. There is a building activity "module connection to building services" between reconnect and start-up. This is performed on the project schedule by various vendors and the duration also is listed on the module schedule.

Pre-Purchased Items

One thing that all Biopharm Facilities desire besides redundancy is uniformity. To accommodate uniformity, an effort to pre-purchase equipment and instruments must occur.

Once the equipment data sheets are completed for the project (including equipment within the modules), a purchasing effort is to occur to purchase this equipment. For equipment to be included within the modules, the purchase orders to the equipment vendors must indicate what equipment is shipped to the jobsite, which equipment is shipped directly to the module vendor, and more importantly, when the equipment is to be shipped. These ship dates are to be included on the module schedule. The equipment submittal process must include the module vendor. This is especially true with vessels. It is the Module Team leader's responsibility to monitor and ensure timely equipment deliveries to the module vendor.

To provide for uniformity with the instrumentation, it is suggested to pre-price the instruments. One method is to have the Architect/Engineer estimate the quantity of each type of instrument by potential sizes for all instruments (within modules, equipment skids, or in the building itself). The Construction Manager would then solicit unit prices for the instruments based upon the quantity and sizes and issue a zero dollar unit price purchase order to the equipment vendor. The equipment vendor would provide instruments, based upon the purchase order to the module vendors, the equipment skid vendors and the building trade contractors working onsite. If this effort can not occur prior to the award of the modules or equipment skids, then the Construction Manager should use the instrument information provided by the Architect/Engineer and establish an allowance for instrumentation for each module or equipment skid. This allowance is closed out upon

completion of the instrument purchase and installation. Since the module and equipment skid vendors are placing the order for these instruments, they should be responsible for expediting these items. The Construction Manager is usually responsible for the instruments purchased for the field construction.

Spare instruments or spare parts are not purchased at this time. The module vendor or equipment skid vendor shall make a recommendation list for spare instruments and spare parts for each module or equipment skid. This list should be submitted from the Construction Manager to the Owner/Client for approval to purchase these items. Once the Construction Manager has the approval of the Owner/Client, they will issue amendments to the module vendor's contract purchase order. The Construction Manager also should monitor the entire spare instrument and spare parts list for the Owner/Client. These items should be used sparingly into the field construction and replaced as soon as possible.

One item that may not be on many firm's pre-purchasing list is electrical and control cabinets. This is an area that can provide great benefits to the project as a whole. Some of these benefits are: same high quality of fabrication, identical layout and parts simplifies maintenance, eases bottle necks in the electrical shops at the module vendor's shop, allows Owner/Client and Architect/Engineer to determine and manage the control system. The IO is identified and the electrical and control cabinets designed by the Architect/Engineer are then bid and awarded to a control cabinet vendor. This vendor builds the cabinets, tests, and ships them (according to a priority list provided by the Construction Manager) to the module vendors, equipment vendors or the project site. Having purchased sufficient spare parts will allow for smooth start-up and testing.

With the amount of control tubing and wiring in such a tight area, the use of wire ways for wire and air tubing as well as "Festo" type solenoid boxes greatly enhances the design and space available.

Module Fabrication

With the finalization of the first FDR, the module vendor can begin fabrication of the module. The fabrication begins with the structural framing, platforms, and stairs. The pre-purchased equipment is set upon delivery to the module vendor. The process and utility piping begin upon the approval of the second FDR. Receipt of instruments is vital to the installation of the utility and process piping. The fabrication continues with electric work and then finally into the control system after the third and final FDR.

During fabrication, many management and reporting procedures need to occur to assure proper delivery and completion of the modules. At a minimum, the following procedures need to be in place.

Weekly Progress Photos. At the end of each week of fabrication, the module vendor shall take digital and (when appropriate) regular photographs and transmit them to the Module Team Leader. Some of the photos need to be taken from the same vantage point throughout fabrication.

Monthly Reports. At the end of each month, the module vendor is to construct a monthly report. The format and table of contents will vary, but as a minimum, it should include: updated schedule, breakdown of design and shop hours spent versus the estimate, color photos, status of equipment, material and instruments delivery, narrative of fabrication progress, and critical issues that must be addressed.

Weekly Teleconference. As described above, this continues through start-up in the field.

Monthly Inspection. The Module Team Leader will physically visit each module vendor on a monthly basis. The first order of business per this visit is to inspect the module completely and then update the current schedule by marking actual dates of activities and revising information with a red pen. This is called "red lining" the schedule. The module vendor will issue a new schedule based upon this red lining. Other items of business to be reviewed include: any contract/purchasing issues, fabrication issues, action log, and any other issues that could affect the module fabrication and delivery. Color photographs will be taken during this visit for inclusion in the module photo album that the Module Team Leader is creating.

Technical Inspections. At scheduled times per the schedule, the Construction Manager and the Architect/Engineer will send support persons in the mechanical, electrical, instrumentation, structural, and equipment disciplines to the module vendor to inspect the work within their discipline. The schedule times are determined by the fabrication schedule at the point at which decisions may be required.

Telephone. Anyone on the module team may contact any other member to discuss subjects of necessity. Items discussed that need to be added to the action log will be added before the next teleconference.

During fabrication, the module vendor will develop a draft FAT Plan based upon guidelines provided by the Owner/Client and the Architect/Engineer. The entire Module Team and module support members will review the FAT Plan. All comments are sent to the Owner/Client member to the Module Team. This person will coordinate the approval of the FAT Plan and its execution at the module vendor's shop.

The Module Team Leader is to draft a rigging plan for all of the modules individually within one plan. The plan should address the general rigging requirements at the jobsite. The plan for rigging each module should be developed in conjunction with that particular module vendor. It should include the number of sections, their size, and weights. It also should include rigging points, order of shipment, extra bracing and supports, and the time frame for rigging into the building. The rigging plan also should include a procedure to reconnect the module sections and level the module. The rigging plan once reviewed and accepted by the Module Team will be used as a basis to purchase the rigging of the module by a rigging firm. Included in the contract for rigging is the cost for the rigging firm to travel to the module vendors with the Module Team Leader to validate the rigging plan. The module vendors will confirm the rigging plan and weights during the loading of the modules for shipment. The module vendor also will video and photograph the breakdown into section and loading of the module onto trailers for shipment.

Module Pre-FAT and FAT

At the completion of fabrication of the module, the Module Team will send a pre-selected Pre-FAT Team to travel to the

module vendor's shop for a period of time (two to five days) to perform a Pre-FAT inspection. The Pre-FAT Team will consist of members from Owner/Client, the Architect/Engineer, the Construction Manager, and the Module Vendor. The members are selected based upon the skill of the members to perform the Pre-FAT inspection. The leader of the Pre-FAT Team is typically a member from the Owner/Client's team with expertise in walking down equipment/systems, knowledge of the control software, and the basic operation of the module itself. The activities that the Pre-FAT Team must complete are: load the control software, perform IQ type inspection, stroke all valves via the control system, and assure that all instruments, agitators, valves are working properly. The main effort of the Pre-FAT inspection is to assure that the module is properly ready for the FAT.

The FAT will be performed the following day or week depending on the schedule. The FAT Team is comprised of members from the Architect /Engineer and mainly the Owner/Client, but does not include anyone from the Pre-FAT Team. The module vendor is there to assist the FAT Team during the FAT. The leader of the FAT Team is typically a member from the Owner/Client's team with an expertise in the operation of the control software and the operation of the module. The FAT will be performed utilizing the approved FAT Procedures. The FAT per module should take between two to five days depending upon the complexity of the module and the FAT Procedures.

Module Shipment

As mentioned above, the module vendor is to verify the weight of the modules as they load the module onto the trailer for shipment. The module vendor also will verify the pick points during the rigging of the module and its sections. It is suggested that the Module Team Leader meet with the trucking firm during load out to provide specifics concerning the final directions to the project site and any specific project site information regarding security, parking, traffic, etc. Depending upon the size and weight of the module, the trucking firm may be required to escort the load. This escort is to make sure the route per the individual state permits is acceptable for transport by following all of the rules of the permits and verifying bridge information before the truck and the load arrives at the bridge. The module vendor should be required to escort the load to the jobsite. This escort is to monitor and check the module during transit. The module escort should be a member of the reconnection team from the module vendor. This person should drive the tool truck for the module vendor and have a cellular phone with extra batteries and power adapter. The module escort person is to report to the Module Team Leader or a designee periodically on the status and location of the module during the trip to the project site. This allows the Module Team Leader to better coordinate the receipt and offloading of the module.

The module should not be totally covered with poly or tarpaulin. Contact wrap should be placed on any weather or water sensitive items. There should be a deflector of some sort at the front of the trailer to deflect the air, bugs, and other road grime from the module. The module should allow some air passage through it.

Module Completion

The Construction Manager is responsible for all site logistics to get the module close to the crane for pick into the building. The rigging firm has mobilized and has the crane, spreader bars, and all other lifting devices in place. The transfer of ownership of the module happens once the module is lifted off of the trailer. The module is then landed into the building and the rigging firm is responsible to get the module set in place and leveled. The module vendor's on site team supervises this effort and then reconnects the module once level. The module vendor must be given all project rules and regulations prior to mobilization to prepare for the project site work.

Once the module is in place, level, and reconnected structurally, the module vendor begins the mechanical, process, electric, and control reconnection. During this time, the onsite mechanical, electrical, process, and control trade contractors begin their connection to the module. At the completion of both of these activities, the module is passivated along with the connecting piping by the passivation firm and then protected from other construction activities that will be occurring around the module.

The module is then given a complete IQ inspection and is prepared for start-up. The validation manuals that arrived about week after the module are completed with the work that took place on the project site by the module vendor. These manuals are reviewed and turned over to the Owner/Client.

The final step is to conduct a "lessons learned" session with the entire module team and some of the support members. These lessons learned sessions can last all day, must be documented, and should ask the following questions. What we did and must continue to do? What we did and should not do again? What we did not do and should have done? And, what we did not do and should continue to not do?

These lessons learned are to be transmitted to all participants in the session and their management for continual use in an improvement process.

Final Comments

The biggest and most real effect of Modularization is moving critical man-hours off of the project site and thereby reducing the project schedule. The project schedule also is improved by installing a portion of the project as one piece that would have taken months to build in place. Both of these effects have real cost advantages that can be only ascertained with the specific project information regarding schedule and the value of the module work itself.

Modularization must be embraced by the whole project team for there to be success in its implementation. The Module Leads must have the personality and organizational qualities that will allow them to interact with upper management, the module vendors, the project team, and the client.

About the Author

William Lefebvre is Project Executive for Gilbane ATS currently assigned to the Large Scale Manufacturing Facility for Human Genome Sciences (HGS) in Rockville, Maryland. Lefebvre has been working in construction management for more than 23 years with the last 12 years specifically in the construction of biopharm facilities. Lefebvre received his BS in business administration and MBA in finance from Nichols College in Dudley, Massachusetts, and has worked for Gilbane for more than 15 years. Lefebvre has been a member of the Army Corps of Engineer Reserves for 14 years and is a veteran of the Gulf War. He is a member of ISPE, and can be reached at the HGS jobsite at 1-301/309-9309 or e-mail at wlefebvre@gilbaneco.com.

This article reviews engineering methods for scale specifications and theory of calibration requirements in reference to weighing processes procedures, operation methods, and standards for scales tolerances.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Specification and Calibration Requirements for Industrial Scales in Pharmaceutical Applications

by Yefim S. Gudesblat, PE

Introduction

Performance and accuracy of industrial scales in pharmaceutical applications are covered by current Good Manufacturing Practices (cGMPs). Verification of proper operation of process scales is an important factor in finished product Quality Assurance (QA) programs. Incorrect weighing, additions of materials and components in validated processes of formulation, dispensing, and mixing are most likely not recoverable and costly to businesses. Mistakenly released products within an established QA program could be detrimental to patients' health and manufacturers' reputation including legal implications.

This article presents standardized classification of accuracies for weighing systems and describes specifications, methodologies, calibration procedures, routines, and related metrology theories in reference to the current standard. Calibration checks and certification methods are reviewed for illustrations of importance in preservation of weighing integrity.

The Product Master Formula and Batch Records contain information concerning weighing specifications for additions of chemical components. Weighing specifications are scientifically developed to control critical parameters related to scale functional activities. Production recipes include sequential order of chemical component additions, maximum and minimum amounts for each chemical component, mixing time, and feeding rates.

Weighing additions of chemical components will naturally fluctuate from batch to batch. Therefore, cGMPs require that Standard Operating Procedures (SOP) for weighing processes will cover maximum allowed deviations for weights in the process formulas. Products made outside of defined weighing specifications will oblige sanctions of product quarantine for investigation. The almost certain outcome from investigations will lead to destruction or rework of manufactured material.

Permitted variations in component weights need to agree with the scale capabilities. Qualification tests and procedures for scales in validated processes will provide the necessary assurance of accurate weighing execution. Verification of the scale's compliance to the process requirements is an important phase for the system qualification and validation. Selections of calibration procedures, calibration frequencies, and certification methods for weighing systems depend on application, accuracies, and possibilities for in-time accuracy changes.

The manufacturing processes in weighing applications are limited by the scale's calibration accuracy. Scale accuracies are established by scale classes. The product quality compliance requires certification of scales traceable to National Institute of Standards and Technology (NIST) Weighing Standards. Calibration procedures deal with formats of recorded data to establish documentation layout and flow designed to assure traceability of collected data.

Performance verification of weighing measuring devices consists of two parts. One is a calibration certification and the other is a calibration check. The calibration certification summarizes a methodical process defined by a written and approved procedure developed for a range of measurements. A calibration check is a simplified confirmation of the scale performance. Usually calibration checks are represented by one or two test measurements.

Properly established scale tolerances, calibration procedures, and scale functional tests are very important issues for QA programs and production costs. CGMP and metrology requirements issues related to scale capabilities, weighing tolerances, and calibration methodology are addressed in this paper.

The governing document for technical requirements of weighing and measuring devices is Handbook 44. Handbook 44 is the current standard published by NIST for all industrial scales and utilized in engineering practices for determination of weighing tolerances and calibration limits. Handbook 44 was adapted by the 84th National Conference on Weights and Measurements in 1999.

Weighing Process Limits and Scale Tolerances

Weighing requirements for manufacturing processes are represented by upper and lower limits of weight for materials added and mixed at established time intervals. Each process step is intended to be repeatable from batch to batch and executable in accordance with validated formulas.

One of the process characteristics could be defined by the capability of the acceptable fluctuations in weighing additions. Qualified weighing equipment dedicated to the validated processes could be characterized by tolerances and calibration limits of measurements. Capabilities of scales for employed processes represented by tolerances and calibration limits cannot exceed process capabilities characterized by allowable fluctuation in weighing additions.

Aside from possible mistakes initiated by incorrect weighing techniques and applications, there are recognized errors in the actual data produced by any instrument. The instrument inaccuracies are originated from round-off errors as a result of utilizing displays with limited numbers of digits and truncation errors originated from finite approximation of limiting processes. Actual measurements finalized by any instrument display or printout must be rounded-off to the number of decimal places justified by the application.

Understanding the mathematical definition for significant digits is very important in metrology and basic principles of data interpretations. The significant digits in a displayed or printed number included the left-most non-zero digits to right-most digits registered. The established number of significant digits in produced data characterizes accuracy of that data. Table A explains the purpose of significant digits.

Pharmaceutical weighing processes (as well as any weighing processes) are subject to a defined range of chemical additions. For example, the Master Formula of a pharmaceutical process requires an addition of a chemical X. The addition of chemical X is outlined as a minimum amount of 1200.0 Kg and maximum of 1210.0 Kg; which means that the added weight of 1205.7 Kg will be allowable, but 1210.1 Kg or 1199.9 Kg will not be acceptable.

Typically, limits are established by R&D after the process scale-up for production. Limits are presented in a format of an essential significant digit i.e., 1200.0 Kg and 1200 Kg are different values because 1200.0 Kg represent possible measurements between 1199.95 Kg and 1200.04 Kg and 1200 Kg correspond to variation of measurements within 1199.5 Kg and 1200.4 Kg.

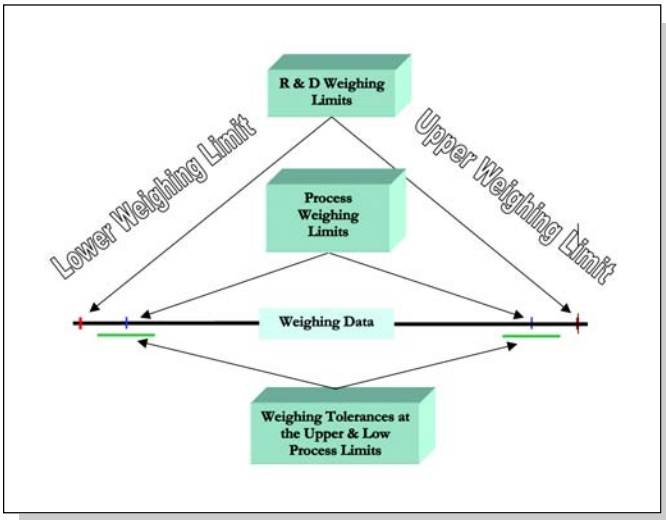


Figure 1. Weighing system tolerance and process limits.

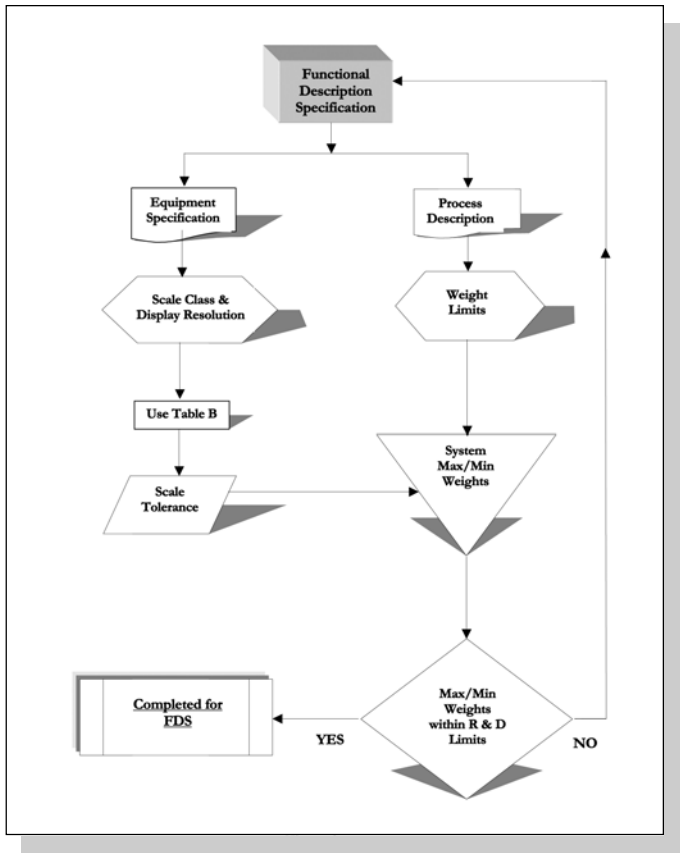


Figure 2. Coordination of weighing system tolerances and calibration limits.

In our example, we like to identify the process scale as Class III with the display resolution of 0.5 Kg and consequent accuracy of ± 1 Kg. The preset process limits (1200 Kg to 1210 Kg) and the scale accuracy are not in conflict with process measurements. Compatibility of scales and requirements for weighing processes are very important for consistency and quality of the final pharmaceutical products. Below is a demonstration that proves this scale will be acceptable for the process.

The manufacturing procedure for the described chemical X addition identifies the target weight as 1205 ± 3.5 Kg. From simple arithmetical calculations, the upper limit of measured weight documented in the manufacturing SOP is 1208.5 Kg and the low limit – 1201.5 Kg. The SOP limits are narrower than actual limits of 1200 Kg and 1210 Kg from R&D findings. The upper and lower weighing limits identified in the SOP are derived from the following calculations:

(a) Upper Limit

For a properly operated scale the registered weight of 1208.5 Kg (SOP upper limit = 1205 +3.5 Kg) could be effectively 1209.9 Kg. The accuracy 1 Kg and display resolution of 0.5 Kg need to be considered in the actual measurements.

The scale display changes in increments of 0.5 Kg. Therefore, scale display may not change before weight change is above 0.4 Kg. The scale accuracy is identified as ±1 Kg, and for the upper weight, 1 Kg and 0.4 Kg should be added to the displayed weight representing 1208.5 Kg.

(b) Lower Limit
For a properly functional scale, the registered weight of 1201.5 Kg (SOP upper limit = 1205 – 3.5 Kg) could be effectively 1200.1 Kg. The same accuracy 1 Kg and display resolution of 0.5 Kg needs to be considered in the actual measurements of the low limit.

The scale display changes in increments of 0.5 Kg. Therefore, the scale display may not change if the weight change is above 0.4 Kg. The scale accuracy is identified as ±1 Kg, and for the lower weight, 1 Kg and 0.4 Kg should be subtracted from the displayed weight representing 1201.5 Kg.

Let's assume that a replacement scale is considered for the chemical X addition. A new scale system is specified for display of 1-Kg resolution, and therefore, accuracy (±2 Kg). The SOP limits for the new scale will require a change to 1205 ± 1 Kg. This change is necessitated by the R&D established limits (1200.0 Kg and 1210.0 Kg) and the new scale specifications.

The replacement scale's upper process limit is 1206 Kg, which effectively can represent 1209.9 Kg. The effective weight of the upper limit considers ±2 Kg scale tolerances and 1 Kg display resolution. The lower process weight limit of 1204 Kg may effectively be 1200.1 Kg. Calculations are the same as previously discussed.

Maintaining the weight additions with an accuracy of ±1 Kg may not be practical, and therefore, this scale shall not be considered for the process. We cannot increase weight tolerances without exceeding the established R&D limits. Changing the process accuracy to ± 2 Kg may take weights outside of the R&D limits.

At ± 2-Kg process accuracy, the displayed weight of 1203 Kg effectively could be below 1200.0 Kg. The scale tolerance ± 3 Kg and resolution of 1 Kg may be representative of 1299.1 Kg. The upper limit of 1207 Kg effectively could correspond to 1200.9 Kg. All calculations are implied from the same algorithm.

The above examples are presented to demonstrate the importance of scale selection for specific processes. The summarized procedure for verification of scales compatibility to the process is shown in Figure 1 and outlined below:

1. Retrieve the R&D limits for weighing application.
2. Verify scale tolerances and display resolution.
3. Check SOP (or new process requirements) for weighing setpoints and limits.
4. Add to the upper weighing limit identified in the SOP the scale tolerance in the represented resolution. The result will represent a possible (effective) weight on the scale at the upper limit.
5. The same procedure can be applied in reverse to the lower weight limit. Subtract from the lowest weight permitted by the SOP the scale tolerance in the represented resolution. The result will represent a possible (effective) weight on the scale at the lower limit.
6. Compare the numbers in steps 4 and 5 to the R&D weighing limits. The upper and lower effective weights cannot exceed the R&D limits.

The weighing process tolerances at upper or lower process limits cannot extend further than R&D weighing limits in the product development protocol. Process operation limits must be set at sufficient levels in relation to weighing process tolerances and R&D limits. Properly established weighing process limits will assure quality, repeatability, and consistency of bulk formulation and compounding processes.

The process operation weighing limits after qualification and validation approvals could be found in a plant SOP for manufacturing sections. Calibration limits will be documented in the SOP for weighing systems calibration. Production and calibration personnel are obliged to comply with the approved SOPs. Properly established limits in the approved SOPs will assure repeatability of the processes and quality of finished product.

The weighing process tolerances, scale classes representing accuracy and sensitivity, and scale display resolution are interrelated. In the following sections of this article, methods and standards by which scale tolerances and weighing capabilities are determined will be discussed.

Determine Weighing Process Tolerances

Performance and accuracies of weighing systems are governed by Handbook 44. Scale tolerances are defined by scale classes and range of measurements. Accuracies for calibration procedures are dictated by established tolerances. The methods described below represent minimum requirements that each scale must confirm.

Scale accuracies and calibration tolerances are interconnected. Calibration tolerances for all industrial scales can be established from data presented – *Table B*.

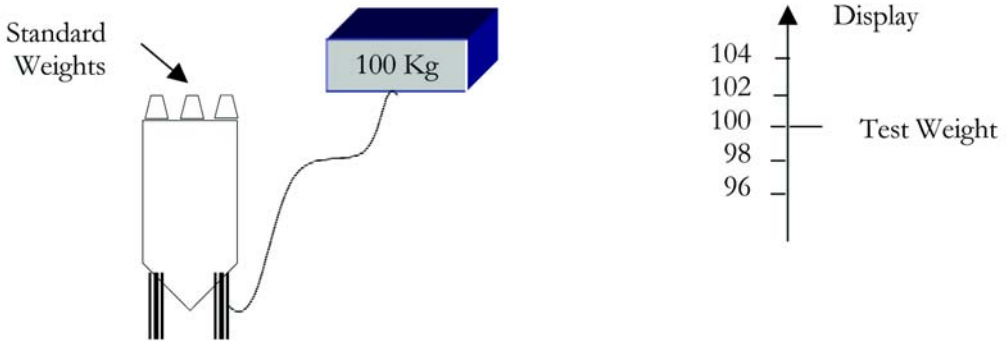
A procedure for defining scale tolerances:

a. Identify Load Cell Class from the nameplate or other documentation. (For example: Class II)
b. From the engineering process documentation and SOPs, identify the scale operating range or ranges. (For example: 0 to 14,000 Kg)
c. Get information of the display resolution. (For example: the display will advance in increments of 2 Kg).
d. In Table B, find the Load Cell Class and follow across to the weighing range. Below the weighing range, find appropriate maximum permitted tolerances presented in the display resolution. (In this case, two numbers will be identified: ± 1 for 0 to 5,000 displayed units and ± 2 for 5,001 to 20,000 divisions)
e. Multiply the tolerance in the display resolution on resolution value. That will be the maximum permitted scale tolerance. (In our example, the scale display resolution is 2 Kg. Therefore, the maximum permitted tolerances for that scale will be ± 2 Kg in the weighing range 0 – 10,000 Kg and ± 4 Kg in the range of 10,001 – 14,000 Kg).

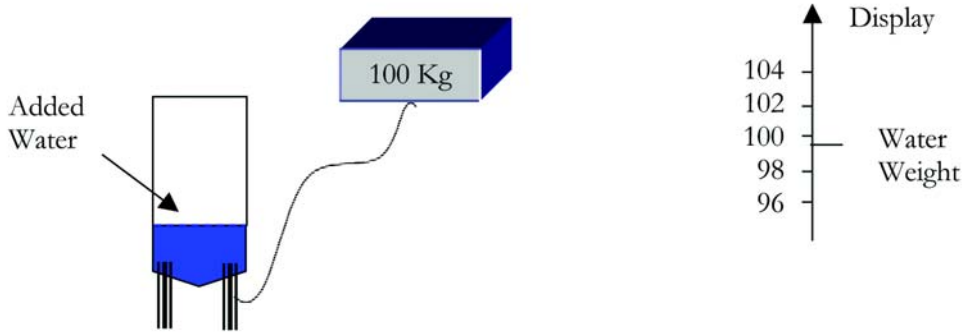
Usually, new and existing process descriptions and equipment specifications are identified in the engineering documentation Functional Description Specification (FDS). Qualification and validation of pharmaceutical processes are based on approved FDS. Qualification and validation protocols are required to verify that selected weighing systems tolerances will not extend over the weighing limits permitted by R&D product development documentation. Dedicated test scripts in the approved protocols are necessitating challenges of engineering calculations in regard to scale tolerances and weighing performances.

In our discussion we explained the imperativeness of interrelation between weighing process limits, scale tolerances, and R&D product development weighing restrictions. An engineering method of identifying weighing system tolerances from load cell classes and display resolutions in relation to weighing process requirements is presented in Figure 2.

Step 1: Load test weights on top of tank scale.



Step 2: Remove Weights and add 100 Kg water. Added water cannot be exactly 100 kg



Step 3: Add Weight on top of tank. The water addition is not an exact weight.
Calibration error is introduced.

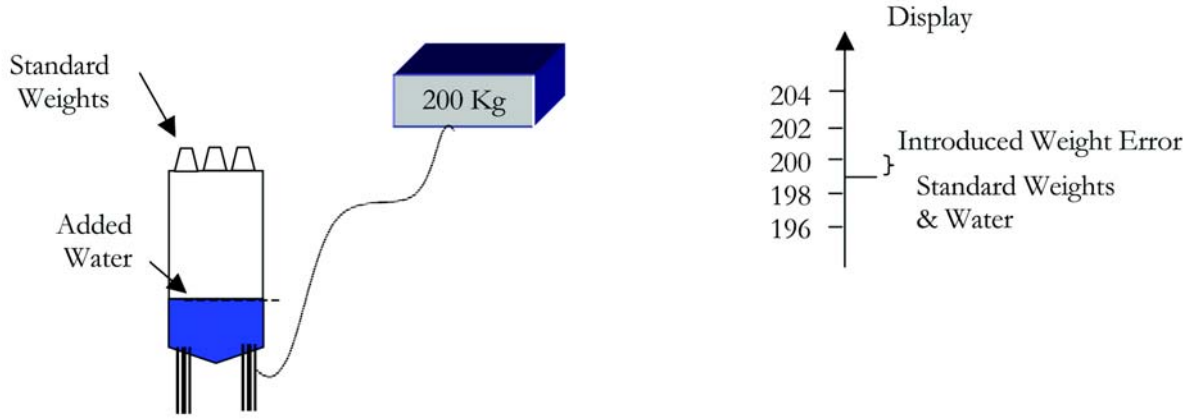


Figure 3. Calibration steps with water additions.

Weighing tolerances and calibration limits of scale systems are interrelated and equally dependable. The identified procedure is important for engineering specifications and identification of weighing tolerances. Calibration limits cannot exceed

Number as Displayed or Printed	Number of Significant Digits	Implied Range
341	3	340.5 to 341.4
00341	3	340.5 to 341.4
0341.0	4	340.95 to 341.04
341 EE7	3	340.5 EE7 to 341.4 EE7
3.41 EE-2	3	3.405 EE-2 to 3.414 EE-2

Table A. Examples of significant digits.

system weighing tolerances. However, in many cases, applied calibration methods require to establish calibration limits narrower than scale tolerances. Properly established calibration limits are a very important factor in cGMP calibration programs. Methods and procedures for defining calibration limits are discussed below.

Scale Calibration Limits

Calibration limits for scales are functions of the scale tolerances, process requirements, and calibration procedures. Calibration scale limits for Acceptance Tests cannot exceed half of maximum permitted tolerances outlined – *Table B*. Process requirements will be represented by tolerances and accuracies transferred to values of calibration limits. Calibration procedures and methods have an impact on calibration limits. Scale calibration procedures may involve the following two methods:

a. Direct placement and removal of standard weights in predetermined fashion.
b. Calibration in steps with loading a tank scale with weights, removal of weights, and addition of water to approximate weight of previously placed standards. Loading standard weight again and repeating this procedure by adding water.

Calibration limits for scales calibrated with direct additions and removal of weights shall comply with process tolerances – *Table B*. Large tank scales calibrated with step loading will concede additional errors by introduction of water additions in the calibration procedure.

Scales calibrated with individual weights and additions of water will have calibration limits as per the Table B minus one. Water additions are inconsistent with standard weights. To satisfy requirements for specified scale process tolerances, it is necessary to reduce the scale calibration limits to one resolution of the weight display.

Graphical representation of the above statement justifies the defined scale calibration limits to satisfy the required process tolerances. The water addition cannot be added at an exact required weight. Graphical representation of calibration steps shown below will explain differences between calibration limits and process weighing tolerances.

Figure 3 shows a calibration procedure with water additions. Such procedures are employed for large tank scales when only direct weights additions are not possible. A tank scale of 15,000 Kg requires calibration of 0 to 15,000 Kg. It is not expected to place 15,000 Kg of standard weights on the top of a tank. Weights of water additions will reduce the amount of standard weights.

A calibration procedure with water additions reduces the expected outcome of scale accuracy. As shown in Step 2 of Figure 3, water addition is not exactly 100 Kg when the display reads 100 Kg. Therefore, Step 3 of Figure 3 will inherit an error. With this and following steps, the scale will accept an additional error of one resolution. This error is additive to the scale calibration accuracy. In order to maintain the specified weighing system tolerances, the calibration limits must be adjusted to compensate for water addition errors.

Standard calibration procedures for large scales include loading and unloading steps. To maintain weighing tolerances as specified in Table B, calibration limits need to be established accordingly. For example, the tank scale process tolerances are identified as ± 2 display divisions. The process tolerance for such scale will be ± 4 Kg. If that tank scale is calibrated with the water additions, then calibration limits should be set to ± 2 Kg. If the tank scale is calibrated with the standard weights only, then calibration limits will be ± 4 Kg.

Engineering process documentation for scale systems needs to consider calibration methods for weighing tolerances. Reductions of calibration limits are not always possible. If the required weight tolerances are equal to one scale resolution then water additions will necessitate zero deviation in calibration tolerances. Absolutely accurate scales are not possible to consider. Therefore, adjustment to weighing processes limits could be contemplated after evaluation of the entire process system and all options.

It is important to remember that weighing process limits and properly calibrated scale tolerances can not permit actual weighing additions to extend above or below the R&D product

WEIGHING SYSTEM TOLERANCES				
Load Cell Class	Weighing Range (All values in this table are in scale divisions)			
I	0 – 50,000	50,001 – 200,000	200,001 +	
II	0 – 5,000	5,001 – 20,000	20,001 +	
III	0 – 500	501 – 2,000	2,001 – 4,000	4,001 +
IIII	0 – 50	51 – 200	201- 400	401 +
III L	0 – 500	501-1,000	(add 1d for each additional 500d or fraction thereof)	
Tolerances: Not to Exceed – in Scale Display Divisions	**±1**	**±2**	**±3**	**±4**

Table B. Weighing systems tolerances.

Test Weights and Load Requirements for Scale Certifications		
Scale Capacity	**Test Weights**	**Minimum Test Load**
0 to 150 Kg	25 Kg weights	@ operation capacity + 25 Kg
151 to 1,500 Kg	25 Kg weights	@ 75% operation capacity + 100 Kg
1,501 to 20,000 Kg	25 Kg weights	@ 50% operation capacity + 200 Kg
20,001 Kg+	25 Kg weights	@ 25% operation capacity + 300 Kg

Table C. Test weights and load requirements for scale certifications.

development limits. If changes within process and calibration limits of scales will not guarantee that weighing additions will be maintained within R&D product development limits, then a new weighing system must be considered.

In the process of scales calibration, the display readings could slightly fluctuate from the weighing standards. Deviations of calibrated readings from standard weights within defined tolerances are acceptable. Requirements for scale adjustments per "as found" data are outside of our discussion. However, in most cases, fluctuations of calibrated data less than 60% of tolerances will not necessitate adjustments.

Calibration Checks

Usually calibration checks are considered as a first step of a batch process to gain an additional assurance in a scale performance. Those checks are accomplished by placing one or two weights on an empty scale and comparing readings of the display to the weights value. With this method, performance of a scale cannot be verified for processes utilizing weighing additions significantly larger than one or two tests.

A simplified calibration check could be performed on the bases of scale capacity and process requirements. Such methods could be named as Functional Certification.

Loads and test weights for Functional Certifications shall be established – *Table C*. Table C could be utilized for setup of weighing systems calibration ranges. Non-critical scales utilized for measurements of raw product storage, inventories, etc. may not be required for calibration at the full range. That issue must be carefully examined to make sure that a range that is not calibrated will have no impact on the finished product.

Conclusion

This article is written to explain methods and procedures for identification of process weighing tolerances and corresponding calibration limits for process scales. The described methods and procedures could provide simple tools for setting up new weighing process specifications and verification of existing scale capacities in regard to process requirements.

The actual calibration methods and calibration procedures are subject to the established metrology standards and are not covered in this article. Standard weight selections and standard weight classifications are subjected to NIST standards. The sources for metrology procedures are identified in the bibliography.

Specified process weighing tolerances and calibration limits must guarantee that properly functional calibrated systems will keep weighing additions for compounding or formulation processes within the established R&D product development weighing limits. Specification for process weighing tolerances and calibration limits should consider safety factors of small fluctuations in the scale's calibration and performance. "As found" calibration data outside of permitted weighing tolerances shall trigger an investigation of all products produced between the date of the last calibration and current date of detected calibration out-of-limits.

Reliability of weighing systems is critical for finished product quality and manufacturing QA program. Proper selection of equipment with matching tolerances and calibration limits will minimize possibilities of incorrect weighing additions in compounding and formulation processes. Incorrect weighing additions produced by the system will generate unrecoverable cost of rejects and rework. Improperly setup weighing systems could lead to poor product quality and mistakes in product releases. Pharmaceutical products made outside of approved specifications could be harmful to patients and will set off grave implications to a firm if released on the market by mistake.

References

1. Handbook 44, 2000 Edition.
2. Specific Technical Guidelines from NVLAP Calibration Laboratories Technical Guide, http://ts.nist.gov/ts/htdocs/230/235/h143/intro.htm.
3. Specifications and Test for Strain Gage Pressure Transducers. ISA=37.3-1982(R1995).

Glossary of Terms and Definitions

Calibration of Weighing Device - Applying known weights to the scale for verification of accuracy and tolerances over portion of the weighing range.
Capacity - The scale rating defined by the maximum load for which the system is designed.
cGMP - current Good Manufacturing Practice
FDS - *Functional Description Specification.*
Load Cell - A device (electronic, hydraulic, and pneumatic) that produces a signal proportional to the applied load.
Scale Divisions - The smallest indication of the difference between two consecutive weighings.
Scale Sensitivity - The value of test load that produces a specific minimum change in the position of rest on the indicating display.
Specifications of Scale Class - A requirement usually dealing with the design, construction, and making of a weighing device.
Tolerance - A value fixing the limit of allowable error or departure from true performance or value.

About the Author

Yefim S. Gudesblat, PE is presently employed by Engineering Solutions, Inc. He is responsible for all activities in the electrical and instrumentation department. In 1971, Gudesblat completed his studies in physics and electrical engineering technology in Odessa, Ukraine (Formally USSR). He is a registered Professional Engineer in Pennsylvania, North Carolina, and New Jersey. Gudesblat has 20 years of experience in the pharmaceutical industry and several articles in leading technical magazines, including **Pharmaceutical Engineering**. He was employed by Wyeth-Ayerst Laboratories and Johnson & Johnson – Merck. Presently, Gudesblat works on projects for many pharmaceutical and biological companies.

Gudesblat can be reached at 1-856/489-2585 or gudesby@labs.wyeth.com.

This article describes stainless steel types and their chemistry, tubing/piping fabrication standards, and fabrication procedures. It also addresses compliance with biotechnology and pharmaceutical standards, codes, and guides, as well as surface characterization, electropolishing, joining techniques, passivation, measurement, and inspection for Cr/Fe ratios, corrosion types, and guidelines for hygienic systems.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
September/October 2001, Vol. 21 No. 5

Stainless Steel Tubing in the Biotechnology Industry

by Michelle Gonzalez

Introduction

Chemical services of any kind may require special alloys for corrosion resistance, freedom from metal ion contamination, or both. Bioprocessing applications can have even more stringent requirements due to the high degree of cleanliness required to convey sterile and non-sterile products or solutions. Tubing and/or piping systems must, therefore, meet these requirements in their fabrication, particularly when it applies to their product or solution contact surfaces.

Stainless steels are uniquely qualified not only because of their long service life, availability, and fabricability, but also because they are non-corroding, non-contaminant, they can be polished to very smooth finishes, they are strong and rigid, they can withstand heat and chemical sterilization treatments, and they are easily welded.

Stainless Steel Types

There are more than 70 standard types of stainless steel and many special alloys. These steels are produced in the wrought form [AISI (American Iron and Steel Institute) types] and as cast alloys [ACI (Alloy Casting Institute) – types]. Generally, all are iron based with 12% to 30% Chromium, 0% to 22% Nickel, and minor amounts of Carbon, Columbium, Copper, Molybdenum, Selenium, Tantalum, and Titanium. Following are descriptions of the most widely used stainless steels in the Chemical Processing Industry (CPI):

Wrought Stainless Steels

***Martensitic*:** characteristically magnetic and hardenable by heat treatment; are oxidation resistant. Type 410 is the most notable example. These alloys contain 12% to 20% Chromium with controlled amounts of Carbon and other additives. Their corrosion resistance is inferior to that of austenitic stainless steels and are generally used in mildly corrosive environments. Used rarely in process applications, martensitic grades are primarily used in cutlery, turbine blades, and high-temperature parts.

***Ferritic*:** characteristically magnetic (because of the ferrite structure), but not hardenable by heat treatment. Ferritic contains 15% to as much as 30% Chromium with low Carbon content (0.1%). Its corrosion resistance rating is good due to the higher chromium content. Type 430 is widely used in nitric acid plants.

***Austenitic*:** widely used in bioprocessing, are characteristically non-magnetic, not hardenable by heat treatment, and are the most corrosion resistant of the three groups. The many types of austenitic steels include the highly alloyed, the lower alloys in which Manganese has been substituted by Nickel (the 200 series), and the **18-8** group which includes types **304** and **316** and all their variations. Types **304L** and **316L** are the workhorse materials of the bioprocessing industry. They have their Carbon content lowered from about 0.08% to a maximum of 0.030% which minimizes the chromium carbide precipitation. These steels do not rust *(see Rouge)*, are easily weldable and machinable, and are not reactive, additive, or absorptive to any extent where strength, quality, or purity of the feed is compromised. Table A presents their basic chemical composition.

Cast Stainless Alloys

Widely used in pumps, valves, and fittings. All corrosion resistant alloys have the letter C plus a second letter (A to N) denoting increasing nickel content. Numerals indicate maximum carbon. Typical members of this group are CF-8, similar to 304 stainless; CF-8M, similar to 316; CF3M, similar to 316L and CD4M Cu, which has improved resistance to nitric, sulfuric, and phosphoric acids.

High Performance Alloys

Because the weaknesses sometimes encountered in the ferritic and 18-8 austenitic grades 304, 316, and variations thereof, new and better "super" stainless steels have been developed. These are **superferritic grades**, **duplex grades**, and **superaustenitic grades**. Of these three, the high-performance austenitic grades have all the weldability and fabricability of

conventional 18-8 varieties, coupled with nitrogen induced strength comparable to the duplex grades, and a very high resistance to chloride pitting and stress corrosion cracking.

The most notable low carbon, high purity *superaustenitic* stainless steel (nickel-based alloy technology) is the 6 Mo (6% Molybdenum) known by its trade name **AL-6XN** (UNS N08367) or "6 Moly" stainless steel. This alloy is the material of choice for many modern high performance piping systems, and it is available in standard pipe sizes and all commercial sizes of tubing. AL-6XN appears in ASTM A240 (Plate, Sheet, and Strip), and will soon appear in ASTM A 312 (Pipe), ASTM A 249 (Heat Exchanger Tubing), and ASTM A 270 (Sanitary Tubing). Its basic chemical composition is presented in Table A.

Duplex (two-phase microstructure) *alloys* were originally developed to combat corrosion problems caused by chloride-bearing cooling waters and other aggressive chemical process fluids. Their composition and microstructure also enables them, by several orders of magnitude, to resist corrosion in organic-acid solutions better than the austenitic stainless steels. In many environments, duplex stainless steels offer general corrosion resistance equal to or better than that of high-cost, nickel-based alloys.

Having a ferrite microstructure, *superferritic grades* are highly resistant to chloride pitting and crevice corrosion. They have found extensive applications as tubing for power-plant condensers and heat exchangers handling chloride solutions such as seawater.

Nickel-Based Alloys

The most widely recognized are:

- 200 series, International Nickel Co. (**Inco**) series, such as commercially pure nickels Nickel 200 and 201 which are widely used in the chemical process industries.
- 300 series are precipitation and dispersion strengthened low-alloyed grades.
- 400 series are Nickel-Copper alloys (non-ferrous alloys), well known as **Monel** alloys.
- 500 series are the precipitation-hardened 400 alloys such as **Monel** K500.
- 600 series also known as **Inconel** alloys are Nickel-Chromium alloys such as Alloy 625.
- 700 series also known as **Inconel** alloys are precipitation-hardened Nickel-Chromium alloys.
- 800 series are Nickel-Iron-Chromium alloys also known as **Incoloy** alloys.
- 900 series are precipitation-hardened Nickel-Iron-Chromium alloys.
- 1000 series are also known as **Hastelloy B** – 61% Nickel, 28% Molybdenum, 5.5% Iron, 1% Chromium (available as wrought and cast, resistant to all concentrations of hydrochloric acid at all temperatures), and **Hastelloy C** – 54% Nickel, 16% Molybdenum, 5.5% Iron, 15.5% Chromium (resistant to all concentrations of hydrochloric acid at room temperature, wet and dry chlorine, hypochlorite, and chloride solutions).

Refractory Metals

The pharmaceutical industry, confronted with increasing pressures to speed new products to market, keep plants running at top efficiency, and more stringent cGMP protocols, has expanded its horizons to find new materials that can enhance their facilities' flexibility, allow for rapid process changeover, and reduce maintenance and shut downs. These materials are the members of the refractory metals family, and are characterized by their high melting point.

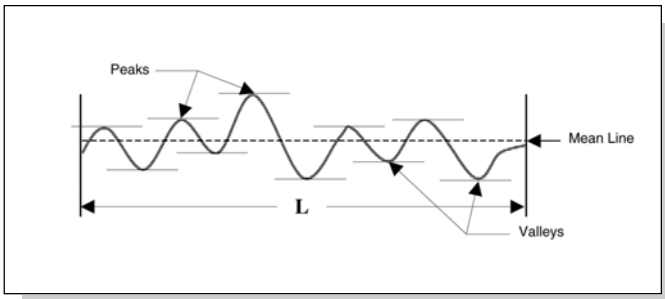


Figure 1. Pictorial display of surface texture.

Tantalum and **Niobium** are ductile, silvery gray in color, have excellent formability, are resistant to chemical attack, and possess good thermal conductivity values which makes them reliable materials for heat transfer applications. Their major limitation is reactivity with oxygen and nitrogen in the air at temperatures above 300°C to 400°C. The primary tantalum alloy of choice for the pharmaceutical industry is Tantalum NRC® 76 alloy (2.5%W). This alloy contains 2.0% - 3.5% Tungsten that improves the overall strength of the pure metal without affecting its corrosion resistance. Some of the major applications for tantalum and niobium in the pharmaceutical industry are reactor vessels, columns, bayonet heaters, shell and tube heat exchangers, lined piping, valves, spargers, rupture disks, and orifice plates.

Stainless Steel Selection

As noted in the previous descriptions, corrosion resistance is the paramount concern when it applies to the proper selection of materials applying to the chemical processing industry at large. This same basic principle applies to the biotech and/or pharmaceutical industries, except that only until recently, this selection process has been broadened to include more sophisticated alloys in an almost continuous progression of small steps. This progressive scale relating to corrosion resistance for metals used in the biotechnology and/or pharmaceutical industries is as follows:

1. Austenitic Stainless Steels 304 (S30400), 316 (S31600), and their L (S30403, S31603) grades, both in cast and wrought forms.
2. High Performance Austenitic Stainless steels such as the Duplex Stainless Steels group that are several orders of magnitude better than the austenitic stainless steels in corrosion resistance to organic-acid solutions. Representative of this alloy class are the 2205 (S31803), 2507 (S32750), 255 (S32550), and 7MoPlus (S32950).
3. High Performance Austenitic Stainless steels such as the Superaustenitics, in particular "6Mo" with its best-known alloy AL-6XN (N08367). The 6Mo grades nicely fill many of the gaps between the corrosion performance of Types 316 and 317 stainless steels and some of the nickel-based alloys.
4. Nickel-Based Alloys commonly called the "Alloy C family" are the highest order of corrosion resistance under oxidizing conditions. Among the best known are, Alloy C276 (N10276), Alloy 22 (N06022), and the newest, Alloy 59 (N06059) also called Alloy 5923 hMo, which refers to its Nickel (59%) and Chromium (23%) content.
5. Refractory Metals such as Tantalum and Niobium have excellent corrosion resistance properties; however, they are used mostly in heat transfer applications.

Chemistry

Tubing/Piping Fabrication Standards

Austenitic stainless steel tubing and/or piping used in bioprocessing are produced following various specific industry standards:

ASTM A249/ASME SA249 *Standard Specification for Welded Austenitic Stainless Steel Boiler, Superheater, Heat-Exchanger, and Condenser Tubes* – (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades). Scope covers pressure tubes made from austenitic stainless steels.

ASTM A269 *Standard Specification for Seamless and Welded Austenitic Stainless Steel Tubing for General Service* – (Types 304, 304L, 316, 316L, 321, and other austenitic grades). Scope covers grades of nominal wall thickness, stainless steel tubing for general corrosion resisting, and low or high temperature service. Tubing sizes and thicknesses usually furnished to this specification are ¼ inch in inside diameter and larger and 0.020 in nominal wall thickness and heavier.

ASTM A270 *Standard Specification for Seamless and Welded Austenitic Stainless Steel Sanitary Tubing* - (Types 304, 304L, 316, 316L). This specification covers grades of seamless and welded austenitic stainless steel sanitary tubing intended for use in the dairy and food industry and having special surface finishes. Tolerances are much tighter than those specified in ASTM A269 and ASTM A312 allowing a closer alignment of tube to tube to fittings which is necessary for compatibility with automatic orbital welding. Pharmaceutical quality may be requested as a supplementary requirement. This specification covers tubes in sizes up to and including 6 inches.

ASTM A312/ASME SA312 *Standard Specification for Seamless and Welded Austenitic Stainless Steel Pipe* – (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades). Scope covers stainless steel pipe intended for high temperature and general corrosive service. In contrast to sanitary tubing, industrial piping and components are not compatible for sterile service due to their basic design and manufacturing techniques. However, due to the size limitations of sanitary tubing, industrial piping Nominal Pipe Size (NPS) must be used in large-scale biotechnology or pharmaceutical facilities. When industrial piping and components are selected, high quality standards must be met, particularly where their internal finishes and fit-up is concerned, to assure that piping systems have a minimum of places for product entrapment and that the systems are sanitizable and sterilizable.

ASTM A358/ASME SA358 *Standard Specification for Electric Fusion-Welded Austenitic Chromium-Nickel Alloy Steel Pipe for High Temperature Service* – (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades). Scope covers pipe used for corrosion and high temperature service, normally not less than 8-inch nominal diameter.

ASTM A409/ASME SA409 *Standard Specification for Welded Large Outside Diameter Light-Wall Austenitic Chromium-Nickel Alloy Steel Pipe for Corrosive or High Temperature Service* – (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades). Scope covers pipe with nominal diameter 14-30 inches in schedules 5S and 10S.

Tubing Fabrication Procedures

There are two categories of tubular products (welded and seamless) and each has its advantages, disadvantages, and share of advocates.

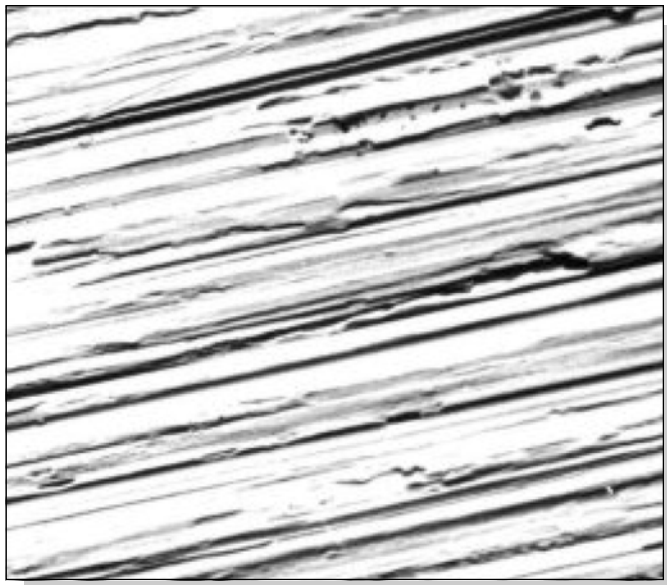


Figure 2. Before electropolishing, the mechanically polished surface of stainless steel appears rough as viewed under 1000x magnification on Scanning Electron Microscope.

Welded Tubing

Starts at the melting operation where special requirements on the alloy are placed to facilitate welding. The strip from which the tube is made may be supplied as either a hot or cold rolled coil. Cold rolled strip has the advantage of extremely close tolerances, smooth surface finish (ASTM A480/A480M-00 "Standard Specification for General Requirements for Flat-Rolled Stainless and Heat Resisting Steel Plate, Sheet, and Strip"), and excellent mechanical properties. Coils are slit into precise widths and then put through a sequence of procedures that will yield a close tolerance tube. These procedures are:

Forming - this includes the use of an entry guide, breakdown rolls, fin rolls, closure rolls.
Welding - this includes the use of rolls to close the seam, rolls to squeeze during the weld, and rolls to restrain the solidifying weld to prevent tearing.
Weld bead conditioning - may be one of two types, 1) *weld rolldown*, usually for thicker wall tubes, and 2) *weld forging* for thinner wall tubes.
Sizing - reduces the oversized tube to the proper diameter, roundness, and straightness.
Cutoff - uses two types of cutting to establish the final length: *abrasive cutting*, which is the most popular since it does not require a die change with each size of tubing, and *shear cutting* which generally requires a die to contain the tube to prevent deformation during the operation.

Seamless Tubing

Made by piercing, extrusion, and gun drilling of a metal bar. *Piercing* is a controlled tearing of a hole in a hot metal bar then ironing the sides to produce a smooth walled tube. Piercing is not a viable method for alloy tubing above 12% Cr.

Extrusion is simply changing a billet or bar of metal into a tube by pushing it through a die over a mandrel. Since extru-

sion is not generally limited by alloy content, it is very widely used to produce high alloy tube hollows. Prior to extrusion, billets are soaked at a temperature above 1100°C (2000°F), glass is added to the inside diameter, and the billet rolled in a glass blanket and shoved into the extrusion container. The ram with an attached mandrel is pushed into the billet and the extrusion begins. Then, the tube hollow is quenched in water to break the glass off the surface. Extruded tubes have several problems, namely high eccentricity and surface imperfections on both the inside diameter and outside diameter.

Gun drilling produces the best quality tube hollow, both dimensionally and freedom from surface flaws. The gun drilling process starts with a rotating round bar or billet that is fed over a stationary straight flute drill, chips are flushed out of the cavity, and by using intermediate inspection for concentricity, it is possible to maintain the straightness of the hole. Although expensive, the quality of the tube hollow cannot be rivaled.

Secondary Fabrication

Occasionally it is necessary to cold reduce the tube hollow for dimensional or metallurgical reasons. Two methods are used: cold drawing and cold pilgering.

Cold drawing is a tensile operation in which a tube is pulled through a die to reduce its diameter or to change its shape. There are three types of drawing: *sinking* (tube is pulled through a die without a mandrel), *mandrel or bar drawing* (uses a solid bar as a mandrel), *and plug drawing* (tube is pulled over a plug inserted into the die) the most accurate of the three.

Cold Pilgering is a compressive method for simultaneously reducing the OD, ID, and the wall thickness of tubing. It uses two opposing dies into whose faces are cut a tapered groove, half in each die. The dies rotate either 180° (more ductile alloys) or 360° (less ductile alloys) depending on the type of machine. Because it uses compression to shape the tube, very high reductions are possible, up to 90%, although the normal reductions are in the range of 65%.

Standards, Codes, and Guides Criteria

As mentioned in the introduction, tubing and/or piping fabrication must meet a high degree of cleanliness to convey sterile and non-sterile products or solutions, particularly when it applies to their product or solution contact surfaces. Following are the definitions of these surfaces and an overview of some of the most important Standards, Codes, and Guides used in bioprocessing.

Contact surfaces are *"all surfaces exposed to the product or from which liquids may drain, drop, or be drawn into the product,"* and solution contact surfaces are *"the interior surfaces of the circuit used exclusively for supply and recirculation of cleaning and/or sanitizing solutions."*

Standards

ASME Bioprocessing Equipment (BPE-1997/BPEa-2000)

American National Standard that covers, either directly or by reference, requirements for materials, design, fabrication, examination, inspection, testing, certification (for pressure systems), and pressure relief (for pressure systems) of vessels and piping for bioprocessing systems, including sterility and cleanability (Part **SD**), dimensions and tolerances (Part **DT**), surface finish requirements (Part **SF**), material joining (Part **MJ**), and seals (Part **SG**) for the bioprocessing systems in which the pressure vessels and associated piping are involved. This Bioprocessing Equipment Standard does not address all aspects of these activities and those aspects that are not specifically addressed should not be considered prohibited.

Requirements of this Standard apply to:

1. all parts that contact the product, raw materials, and/or product intermediates during manufacturing, process development, or scale-up
2. all equipment or systems that are a critical part of product manufacture, such as Water For Injection (WFI), clean steam, ultrafiltration, intermediate product storage, and centrifuges

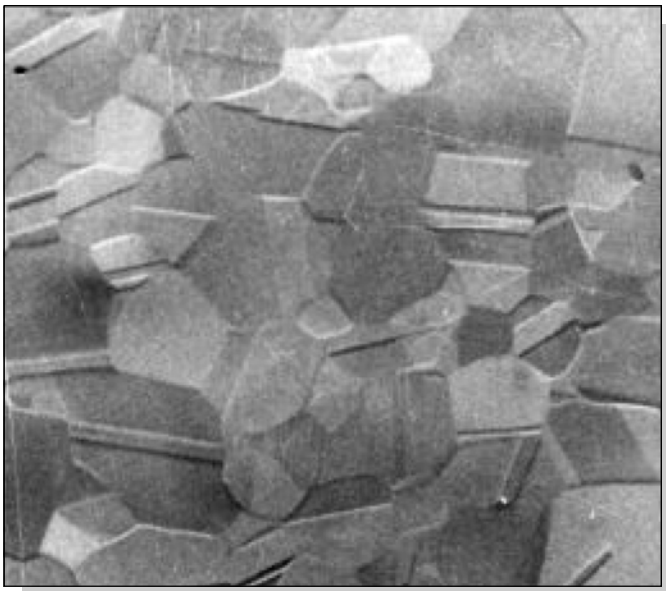


Figure 3. After electropolishing, the same surface appears smooth as viewed under 100x magnification on Scanning Electron Microscope.

3-A Sanitary Standards

3-A Sanitary Standards for Polished Metal Tubing for Dairy Products, Number 33-00

Published by the International Association for Food Protection (IAFP) formerly known as the International Association of Milk, Food, and Environmental Sanitarians (IAMFES). These standards cover the sanitary aspects of polished metal tubing used to conduct dairy products in processing lines or systems that also may include sanitary fittings. These standards do not apply to tubing used in pneumatic conveying systems for dry milk and dry milk products. For tubing, these standards refer to the use of AISI 300 series stainless steel, and compliance with ASTM A270.

3-A Accepted Practices for Permanently Installed Product and Solution Pipelines and Cleaning Systems Used in Milk and Milk Product Processing Plants, Number 605-04

These standards apply to the cleaning of rigid solution lines and for the mechanical cleaning (CIP) unit which circulates the pre-rinse, rinse, cleaning solutions, and post-rinse liquids used for cleaning and sanitizing the product pipelines and process equipment.

ASME B31.3 Process Piping

American National Standard that covers piping typically found in petroleum refineries, chemical, pharmaceutical, textile, paper, semiconductor, and cryogenic plants, and related processing plants and terminals. Certain piping within a facility may be subject to other codes and standards, including, but not limited to: (a) **NFPA Fire Protection Standards:** fire protection systems using water, carbon dioxide, halon, foam, dry chemicals, and wet chemicals. (b) **NFPA 99 Health Care Facilities:** medical and laboratory gas systems. (c) **Building and Plumbing Codes**, as applicable, for potable hot and cold water, and for sewer and drain systems.

It must be noted that B31.3 does not address hygienic tubing and/or piping; it applies mostly to inspection, examination, and testing of systems.

Codes

cGMPs - Code of Federal Regulations (CFR), Title 21 - Foods and Drugs

Chapter I – Food and Drug Administration (FDA), Department of Health and Human Services

Subchapter C - Drugs – General (Part 200)

Part 210	*cGMPs for Finished Pharmaceuticals* (Human and Animal)
Part 211	*cGMPs for Finished Pharmaceuticals* (Human and Animal)
Part 225	*cGMPs for Medicated Feeds* (Animal)
Part 226	*cGMPs for type A Medicated Articles* (Animal)

Subchapter F - Biological Products (Part 600)

Part 600	*Biological Products: General* (Human and Animal)
Part 610	*General Biological Products Standards* (Human and Animal)
Part 680	*Additional Standards for Miscellaneous Products* (Human and Animal)

NOTE: These parts are the substantive current Good Manufacturing Practices as contained in Appendix 4 of the Pharmaceutical GMP Annex, US FDA.

Guides

ISPE Baseline® Pharmaceutical Engineering Guides

A series of industry publications developed in partnership with the US FDA. Each volume in the series is a collaborative effort of industry leaders representing a broad cross-section of manufacturers and other industry experts. The Guides document current industry practice for facilities and systems used for production of pharmaceutical products. They are intended to:

- establish a baseline approach to new and renovated facility design, construction, commissioning, and qualification that is based upon clear understanding of the type of product and its manufacturing process
- prioritize facility design features based upon the impact on product and process
- avoid unnecessary spending on facility features that do not contribute to consistent production of quality products

The Guides include six product manufacturing operation based guides (vertical guides), and three support system/function based guides (horizontal guides):

Vertical Guides

1. Volume I - Bulk Pharmaceutical Chemicals (Published 1996)
2. Volume II - Oral Solid Dosage Forms (Published 1998)
3. Volume III - Sterile Manufacturing Facilities (Published 1999)
4. Volume VI - Biopharmaceuticals (under development)
5. Oral Liquids and Aerosols
6. R&D Laboratories

Horizontal Guides

1. Volume IV - Water and Steam Systems (Published 2001)
2. Volume V - Commissioning and Qualification (Published 2001)
3. Volume VII - Packaging and Warehousing (under development)

Surface Characterization

"Surface finishes are all interior surface finishes accessible and inaccessible, that directly or indirectly come in contact with the designated product in bioprocessing equipment and distribution system components." Reference should be made to ASME BPE-1997 Standard, Part **SF**, "Stainless Steel and Higher Alloy Interior Surface Finishes."

Part SF comprises: Scope (SF-1), Objective (SF-2), Applications (SF-3), Material (SF-4), Typical Stainless Steel Interior Surface Anomaly Characteristics (SF-5), Classification of Interior Surface Finishes on Weldments for Process Equipment and Components (SF-6), Inspection and Techniques Employed in the Classification of Interior Surface Finishes (SF-7), and Description of Various Surfaces Available on Stainless Steel and Higher Alloys (SF-8).

Surface finishes have been quantified utilizing different names and measurement units, such as Grit Numbers, USA Finish Numbers, Common Name, Ra (Microinch), Ra (Micron), Rmax (microinch), Rmax (Micron), RMS, ISO number, Japanese Standard, etc. Each of these roughness parameters has a specific use, but this variety of systems also has provided a broad and sometimes overlapping range and a high degree of confusion – *Table B*.

To be complete and unambiguous, a universally recognized and accepted surface roughness specification and measurement standard must be considered, and final criteria shall be determined by that standard (**Ra** values) rather than by polishing methods. Following the definition of the standard:

Arithmetic Average Roughness (Ra). The arithmetic average height of roughness component irregularities from the mean line measured within the sample length (L). This measurement conforms to ANSI/ASME B46.1 "Surface Texture – Surface Roughness, Waviness and Lay;" the surface is measured and normally described using the arithmetic derivation **Ra** (formerly known as AA or Arithmetic Average in the US, and CLA Centerline Average in the UK) usually expressed in microinches (***µin***) and measured with profilometers and/or borescopes – *Figure 1*.

Refer to Tables SF-1 through SF-8 of ASME BPE-1997 for acceptance criteria of interior surface finishes for tubing, fittings, valve bodies, and vessels.

Cr Chromium	18.0 – 20.0	18.0 – 20.0	16.0 – 18.0	16.0 – 18.0	20.0 – 22.0
Ni Nickel	8.0 – 11.0	8.0 – 13.0	10.0 – 14.0*	10.0 – 15.0	23.5 –25.5
C Carbon	0.08 max	0.035 max	0.08 max	0.035 max	0.03 max
Fe Iron	Balance	Balance	Balance	Balance	Balance
Mo Molybdenum	—	2.0 – 3.0	—	2.0 – 3.0	6.0 –7.0
Mn Manganese	2.0 max	2.0 max	2.0 max	2.0 max	2.0 max
Si Silicon	0.75 max	0.75 max	0.75 max **	0.75 max**	1.0 max
P Phosphorus	0.040 max	0.040 max	0.040 max	0.040 max	0.040 max
S Sulphur	0.030 max	0.030 max	0.030 max	0.005–0.017***	0.030 max
N Nitrogen	—	—	—	—	0.18 – 0.25
Cu Copper	—	—	—	—	0.75 max

***** 11.0 – 14.0 (A269)

****** 0.030 (A269)

******* Sulfur has greatest effect on weld quality. Controlling sulfur facilitates orbital field welds by minimizing stabilization problems. To comply with ASME BPE Standard, ASTM added A 270-98a "Supplementary Requirements", S2. Pharmaceutical Quality Tubing - S2.1.1

Table A. Chemistry comparison.

Electropolishing

In addition to purely mechanical finishes, sanitary tubing also is available in a number of highly polished surfaces. These surfaces are accomplished by an electrochemical process also known as "chemical machining" and/or "reverse plating" that is far superior to any available mechanical process for the **removal** (as metallic salts) of surface imperfections in stainless steel. Electropolishing levels and brightens the material surface by anodic dissolution in an electrolyte flowing solution with an imposed electrical current. When the proper combination of electrolyte current temperature is attained, the high points of surface irregularities, or high current density areas, are selectively removed at a greater rate than the remainder of the surface resulting in improved surface measurements – *Figures 2 and 3*.

Electropolishing typically uses mixed acid solutions sometimes with organic additives (electrolyte) and a cathode that is pulled through the inside of the tube. The tube becomes the anode so it preferentially dissolves, removing metal from the peaks and not from the valleys. Normally, the cathode would be plated if the solution chemistry did not cause the metals to dissolve as fast as they are plated.

In addition to appearance, electropolished tubing has five primary advantages:

1. extremely smooth surface which minimizes adherence of debris on the electropolished surface
2. an increased chromium to iron ratio on the electropolished surface to improve corrosion resistance
3. creation of a passive layer that is free from iron contamination
4. improved ability to visually detect surface defects
5. improved mechanical property performance through minimization of stress risers

Economic Considerations

In general, the largest portion of the cost associated with stainless steel is derived from the Chromium, Nickel, and Molybdenum content. When comparing economic factors in the most widely used classes of stainless steel, 304, 304L, 316, 316L, and AL-6XN, there are no exact parameters regarding pricing, size, and/or finishes demand. However, if as an example we consider a very broad selection of base alloy, 1 inch to 1 ½ inch diameter of 304 stainless steel welded tubing with 0.065 wall thickness, provided in 20 feet lengths, and conforming to ASTM A 269 or ASTM A 270, and assign it the number **1,** we will see the following:

a) 316 would be equal to **1.15**
b) AL-6XN would be equal to **3.4**

Considering finishes, a different ratio develops when it comes to cost differences. If we use as an example, a typical 20 feet length of 2 inch diameter 304L stainless steel welded tubing conforming to ASTM A 270, with 0.065 wall thickness, bright annealed inside diameter (no polish), and assign it the number **1**, we will see the following:

a) 316L, bright annealed inside diameter (no polish) will be equal to **1.42**
b) 304L, mechanically polished inside diameter to 20 R*a* will be equal to **1.02**
c) 316L, mechanically polished inside diameter to 20 R*a* will be equal to **1.44**
d) 316L, mechanically polished plus electropolished to 15 R*a* will be equal to **2.14**
e) 316L, mechanically polished plus electropolished to 10 R*a* will be equal to **2.54**
f) AL-6XN, bright annealed (no polish) will be equal to **4.62**
g) AL-6XN, polished inside diameter to 20 R*a* will be equal to **4.92**

h) AL-6XN, mechanically polished plus electropolished to 15 R*a* will be equal to **6.12**
i) AL-6XN, mechanically polished plus electropolished to 10 R*a* will be equal to **6.93**

It is important to understand that the ratios mentioned above do not apply across the size ranges defined in ASTM A 269 or A 270, and that they are not based on deep scientific research, but rather in a general view of present circumstances and/or common applications. The ratios should be used only as a general approach to estimating.

Joining Techniques

Connections between tube-to-tube or tube-to-fitting, and even tube/fitting to equipment during system fabrication and/or erection can be accomplished by diverse means. However, it is paramount to understand the requirements for hygienic system cleanliness integrity. ASME BPE-1997 defines hygienic as "of or pertaining to equipment and piping systems that by design, materials of construction, and operation provide for the maintenance of cleanliness so that products produced by these systems will not adversely affect human or animal health." It becomes clear that in order to achieve the required cleanliness levels, a system, shall as much as possible reduce the use of joints where impurities entrainment may occur, such as flanges and threaded joints (must be avoided), or even hygienic clamps. Thus, systems shall preferentially be joined using butt-welding practices only.

Automatic Orbital Welding

Welding technologies have improved significantly to meet the increasing requirements of pharmaceutical and microelectronics industries. Tubing and/or piping welding for the biotechnology and pharmaceutical industries used to be simply qualified to ASME Section IX of the Boiler and Pressure Vessel Code with reference to ASME B31.3. However, in response to specific quality requirements imposed by higher levels of complexity in bioprocesses, ASME has developed guidelines that do not necessarily replace the present code, but rather reference existing standards applicable to the industry for equipment design and fabrication. These guidelines are contained in ASME BPE-1997 Part **MJ**, Material Joining. This Part comprises: Scope (MJ-1), Materials (MJ-2), Joining Processes and Procedures (MJ-3), Weld Joint Design and Preparation (MJ-4), Filler Material (MJ-5), Weld Acceptance Criteria (MJ-6), Inspection, Examination, and Testing (MJ-7), Procedure Qualification (MJ-8), Performance Qualification (MJ-9), Documentation Requirements (MJ-10), and Passivation (MJ-11).

Hand executed Gas Tungsten Arc Welding (GTAW), commonly referred as Tungsten Inert Gas (TIG), has lost much

RMS (Microinch)	RMS (Micron)	R*a* (Microinch)	R*a* (Micron)	Grit Size
80	2.03	71	1.80	80
58	1.47	52	1.32	120
47	1.20	42	1.06	150
34	0.86	30	0.76	180
17	0.43	15	0.38	240
14	0.36	12	0.30	320
		4-8		320 EP
		10		400

Table B. Surface measurements comparison.

Table C. The Galvanic Series.

popularity as an acceptable technique for bonding sanitary piping systems. Since the advent of automatic orbital welding equipment, the use of 316L grade stainless steel with highly polished interior surface has become mandatory if overall results of this precision welding process are to be achieved.

The automatic orbital welder is used to fusion weld thin wall tubes and fittings together in a totally inert environment without the use of filler materials or special weld preparation, pieces, or machining. Essentially, an arc established between a tungsten electrode (installed in a rotor within the weld head) and the tubing, accomplish the fusion weld. It consists of a series of spot welds in which the main welding current penetrates the material and the background current chills the puddle.

The quality of the fusion joint that is made by this equipment is predicated on the use of two pieces of material of the same thickness and grade or type. Therefore, great care must be exercised in material and component selection.

In operation, the two pieces of material tube-to-tube or tube-to-fitting are placed in the welding head – *Figure 4*. This head, which contains the tungsten electrode, is provided with clamping jaws which securely hold the parts to be welded in position and in alignment with the tungsten (because weld heads are not typically strong enough to clamp and maintain proper alignment between long lengths of tubing, most manu-

facturers of welding equipment recommend "tracking" to avoid separation during welding). At the same time, the entire area to be welded is enclosed in the welding head, forming a purge chamber which is filled with shield gas, usually argon, during the entire weld sequence to prevent oxidation of the welded material. Meanwhile, the inside of the tube can be purged free of oxygen and allow the entire area to be completely covered with argon gas. The weld cycle is preprogrammed and set in the machine; therefore, the entire operation is *automatic*. The tungsten rotates around the weld seam on an internal gear, while the head remains stationary. When complete, the head can be opened and immediately removed from the welded section.

Passivation

A final treatment/cleaning process used to restore (by introduction of oxygen) the disturbed, chemically inert surface, or passive layer of stainless steel piping, tubing and/or equipment by removing/dissolving free iron or other anodic contaminants from the surfaces of corrosion-resistant parts and leaving chromium and iron oxides as the primary metal components.

Welding of the piping systems as well as process conditions affect the thin chromium oxide film with some oxides of iron and nickel that forms on stainless steel naturally and almost instantaneously in contact with air, making it "passive" and resistant to corrosion. Because welding disturbs that passive layer by reducing the chromium and increasing the iron, thus altering the chromium/iron ratio (measure of corrosion resistance), upon completion and approval of the weld, the weld surface and adjacent boundary area must be brought back to a passive state. Additionally, normal operating conditions in typical Water For Injection, Reverse Osmosis, Deionized Water, Clean Steam, some process systems, and in some rare cases CIP piping, often lead to formation of the most prevalent form of self catalyzing corrosion called "rouge" *(see Rouge)* which is a colloidal form of iron oxide containing, chromium and nickel in various forms. This problem is accentuated by the use of high temperature, aggressive process chemicals, and ultra pure water, and can be overcome only by restoring the surface to its passive state.

Methods and tests for cleaning and passivation of critical water, product, and process piping systems are described in ASTM A380 "Standard Practice for Cleaning and Descaling Stainless Steel Parts, Equipment, and Systems."

Passivation can be accomplished by one of two methods:

Chemical Oxidation

Chemical Oxidation is the most common method of passivation and usually the most cost effective. It can be performed by many techniques including the use of mineral acids or citric-based chelant systems. Warm dilute nitric acid and other mineral acids are effective on removal of iron; however, they will not remove many of the inclusions or other surface metal contaminants. Citric acid and Ammonium Citrate (Ammoniated Citric Acid) together with other chelants dissolves surface contaminants and iron compounds. They also allow the dissolved ions attached to the chelant to be flushed from the system with rinse waters.

A number of events can trigger the need for repassivation. Generally, any change to the system, including additions and deletions, rewelding, or exposure to a highly corrosive agent, may be cause for system repassivation followed by revalidation.

"In Situ" Electropolishing

Electropolishing of small assemblies welded on the workbench can be accomplished with relative ease by the same techniques used to electropolish lengths of tubing. Electropolishing in place for complex systems may become more difficult. As with tubing, irregularities on weld surfaces will be leveled and a protective surface oxide layer will be formed by electropolishing the weld surface.

Measurement and Inspection for Cr/Fe Ratios

Chemical cleaning and passivation procedures on stainless steel tubing systems and equipment are very important steps in the preparation of surfaces to be used in corrosive environments. However, to ensure that a passive layer has been established through a selective dissolution of iron and the subsequent enrichment of chromium and other alloys in the passive film and metal phase of the surface, test procedures to detect, measure, and quantitate the chrome/iron ratio are of critical importance. These tests are:

Ferroxyl Test for Free Iron

A highly sensitive test used to detect iron contamination (iron-tool marks, residual iron salts from pickling solutions, iron dust, iron deposits on welds, embedded iron or iron oxide, etc.). This test checks the effectiveness of the passivation procedure and is described in ASTM A 380 – 99 "Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems" Section 7.3.4. The testing solution is applied to the surface being tested; and if there is evidence of surface iron contamination, a blue stain will appear within 15 seconds of application. Ferroxyl test offers no quantitative information as to the amount of chromium oxide or iron at the surface.

With better passivation techniques (primarily citric and other chelant materials), new measurement techniques have been developed. Test methods now at the forefront are:

Auger Electron Spectroscopy (AES)

Direct testing method which measures the elemental chromium/iron ratio on the metal surface and sub-surface with depth profiling, before and after a passivation treatment. This technique bombards the metal surface with electrons and the difference between the elements binding energy and the electron bombardment is a unique number identifying the element. The common reporting convention is the ratio at the surface and at the maximum peak point (concentration of the element is related to the intensity of the peak) which results in the higher the ratio, the higher the degree of passivity.

This type of analysis also can detect all elements with an atomic number greater than that of helium with the additional ability to analyze sub micron-diameter features. It is not as quantitative as Electron Spectroscopy for Chemical Analysis (ESCA) and cannot determine the chemical state of an element. The primary advantage of Auger is that when combined with etching, a chemical depth profile can be measured rapidly, and it can image the distribution on the surface of spatial limitation resolution of 100 to 1,000 angstroms (depending on the equipment capability).

X-Ray Photoelectron Spectroscopy (XPS) or Electron Spectroscopy for Chemical Analysis (ESCA)

XPS or ESCA is a direct testing method and its primary advantage is the ability to detect and measure the chromium/iron ratio on the metal surface and the oxidation states of

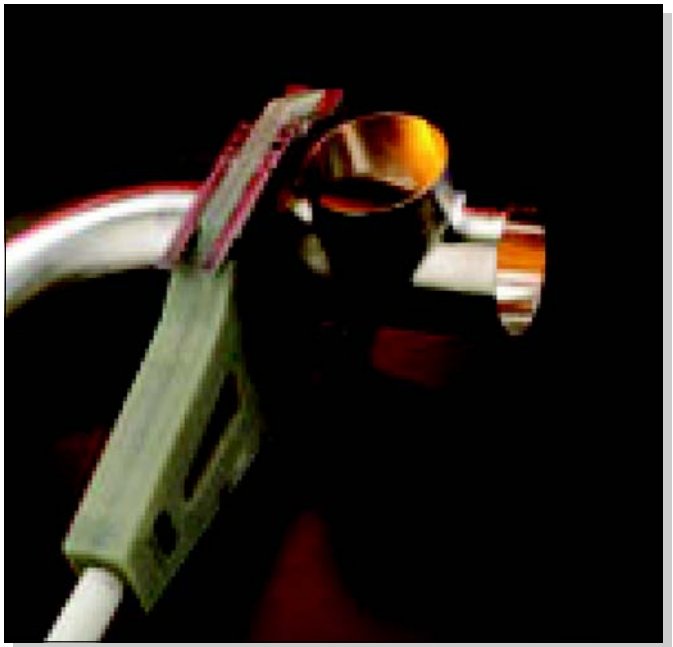


Figure 4. Automatic orbital welder in the process of joining two long tangent stainless steel fittings.

elements found on that surface. A surface-sensitive technique that uses X-Rays to bombard the metal surface and is capable of detecting all elements with an atomic number greater than that of helium, ESCA provides data on the outermost several atomic layers of a material, and has a sensitivity in the order of 0.5 atomic percent.

Cyclic Potentiodynamic Polarization (PP)

An electrochemical test (ASTM G61 "Cyclic Potentiodynamic Polarization Standard Practice") that measures the point at which pitting corrosion begins. PP uses an electrolytic cell to directly measure the corrosion rate. By using the test piece as the working electrode, initiation of localized corrosion is shown by the potential at which the current density increases rapidly. This point is called the "pitting potential." The lower the current density at this point, the more resistance to pitting corrosion. The current density is measured in micro-amps per square centimeter.

Rouge

The phenomenon known as "rouge" in stainless steel tubing and/or piping systems is the formation of an iron oxide on the metal surface. Rouge material is colloidal iron oxide together with smaller traces of heavy metals such as nickel and chromium and may contain other contaminants such as aluminum. Rouge is commonly associated with the production of highly purified water and its scavenging nature, WFI stills, and clean-steam generators and their high operating temperatures, and it may originate at one or more areas within a water system. It is migrational, tenacious, and destructive, and is characterized by the initial appearance of a light red or brown color, progressing to a dark red, dark brown, or a brownish-gray, and in the extreme stages, a dark gray and/or black.

By composition, this element is slightly different than plain "rust" and based on studies by a major tube manufacturer, it appears that there are three different classes of rouge depending on their origin:

a) Rouge from external sources. Particles generated by cavitation, external erosion, or oxides from foreign sources i.e., carbon steel bolts, nuts, etc.
b) Rouge from in-situ oxidation of the stainless steel. Low chromium/iron ratio resulting from mechanical polishing, and non-chemically passivated surfaces.
c) Black oxide rouge. Originates from high temperature steam service.

Corrosion Types

Corrosion can be divided into two basic types:

1. *General Corrosion*. The dissolution of the metal at a uniform rate over the entire surface exposed to a corrodent. It is caused by the loss of the protective passive film that forms on the surface in environments where the steel is resistant. General corrosion is usually expressed in corrosion rates as "mils" (thousandths of an inch) or millimeters per year (mpy or mm/y).

2. *Localized Corrosion*. The dissolution of the metal in which only a small area is affected, but the rate is relatively high. Stainless steel in the passive state appears in a relatively noble position in the galvanic series and is usually cathodic, therefore, not subject to attack – *Table C*. However, under certain conditions all or portions of a piece of stainless steel may become active. This active surface becomes anodic to the more noble mass and in the presence of an electrolyte, a galvanic cell is set up and attack will occur. The rate of attack will vary with different electrolytes and the area relationship of the anode and cathode.

Intergranular Corrosion

This type of localized corrosion is rarely a problem if the stainless steel is used in the "mill annealed" condition. Austenitic stainless steel becomes susceptible to intergranular corrosion in some environments after they are heated for short times in the range of about 900°F /1500°F. This susceptibility can be avoided by either using only stainless steel in the annealed condition, using alloys that have low carbon, or using "stabilized" alloys by adding carbides such as titanium or columbium.

Pitting Corrosion

A type of localized corrosion can occur for several reasons, and probably the most common reason is the lack of cleanliness. If scale, dust, etc., are allowed to deposit on a stainless steel surface, the metal underneath these deposits will not have ready access to oxygen which is required to maintain the corrosion-resistance film that gives stainless steel its high corrosion resistance. This corrosion may be accelerated by chemical changes in the corrodent beneath the deposit. Other common causes of pitting corrosion are the presence of chlorides and stagnant conditions where deposits may become lodged on the metal surface thus permitting the concentration of damaging elements.

Contact or Crevice Corrosion

Contact or crevice corrosion is the most common cause of pitting of stainless steels. Whenever a solid or semi-solid material adheres or lies against a stainless steel surface in contact with an electrolyte, pitting may occur. The relative anode and cathode areas and the type of electrolyte will influence the rate of attack. This type of corrosion will spread as products of corrosion deposit on other areas of the metal

form new cells which cause further pitting. Regular, efficient cleaning with correct cleaning agents will minimize these types of attack.

Galvanic Corrosion
Galvanic corrosion or Bi-metal attack is a type of localized corrosion that occurs when two different metals come in contact in the presence of an electrolyte. The least noble metal in the galvanic series becomes sacrificial to the more noble. In general, the corrosion resistance of stainless steel is reduced when in contact with lead, nickel, copper, copper alloys, or graphite. On the other hand, it is improved at the expense of the other metal when in contact with iron, steel, aluminum, zinc, or cadmium. The solution to this problem is to use metals of the same composition for complete system assemblies or to use flange gasket sets and/or dielectric unions to form a separation of the two metals at the point of contact.

Stress Corrosion and Corrosion Fatigue
This type of localized corrosion is the result of combined residual or applied stresses a corrosive environment and temperatures above 120°F. Metal under stress is slightly anodic in relation to the unstressed metal of the same analysis. Austenitic steels under stress are subject to attack when exposed to certain corrosive agents. The Halogen salts are probably the most serious offenders. It is important to design installations that eliminate sources of stress such as applied loads, vibration, flexing, and excessive expansion and contraction due to temperature changes.

Electrolytic or Stray Current Corrosion
Stray electric currents may produce pitting attack on stainless steel. The rate of attack with an AC current is considerably less than DC and in most cases insufficient to be considered.

Chemical Corrosion
Austenitic stainless steels are resistant to most chemicals; however, there are compounds such as Halogen and Sulfur that are notorious for attack on stainless steel. In general, acidic solutions will cause more severe attacks than basic solutions of the same elements. The use of inhibitors may render these solutions less harmful.

Erosion Corrosion
Certain liquids or gases moving at high speeds may cause erosion corrosion; however, if these same materials remain motionless, they would not affect the stainless steel. It is believed that the attack is due in part to the destruction of the passive layer on the surfaces. The action of fluids in rapid motion is not always destructive, and in some cases, the scouring effect keeps the stainless steel free of deposits and sludge that may cause other types of corrosion.

Factors Affecting Corrosion

Other than the metal composition and corrodents, some of the factors that influence corrosion are:

a) the presence of even minor percentages of impurities in the corrosive medium
b) the temperature of the corrodent (generally, corrosion increases as temperatures increases)
c) the degree of aeration to which a corrodent is exposed
d) velocity of the corrodent

Guidelines for Hygienic Systems

Hygienic as defined in ASME BPE-1997 "of or pertaining to equipment and piping systems that by design, materials of construction, and operation provide for the maintenance of cleanliness so that products produced by these systems will not adversely affect human or animal health."

General Considerations
All hygienic/sterile designs involving the use of stainless steel tubing or piping should conform to the applicable requirements of ASME BPE-1997, ANSI B31.3, E-3-A, and FDA regulations, latest editions. Some of these considerations are:

- Direct connections between sterile and non-sterile parts are not permitted.
- Positive pressure should be maintained within the systems to prevent contaminants from entering. This does not apply to pathogen containing systems due to the danger of leakage to the environment. Alternate methods of preventing contaminates from entering a pathogen system must be investigated.
- Consideration of a steam seal should be given to vessel connections which are not in use. For example, sample valves should have live steam entering on the exit side.
- Where the media or product is heat sensitive such as in the case of antibiotics, sterilization can be accomplished by using a 0.2 micrometer sterile filter to remove organisms.
- In cleanrooms, filling lines, or other post purification processes, exposed piping should be minimized. Such piping should be routed in encased chases with exposed branches as short as possible.

Guidelines
General Design Guidelines for sterility and cleanability applicable to all bioprocessing equipment, components, assemblies, and systems are detailed in ASME BPE-1997 Part **SD**. This standard addresses Cleanability (SD-3.1), Sterility (SD-3.2), Surface Finishes (SD-3.3), Materials of Construction (SD-3.4), Fabrication (SD-3.5), Static O-Rings, Seals, and Gaskets (SD-3.6), Connections and Fittings (SD-3.7), Exterior Design (SD-3.8), Containment (SD-3.9), Miscellaneous Design Details (SD-3.10), System Design (SD-3.11), and Drainability (SD-3.12).

Specific Guidelines for sterility and cleanability applicable to all bioprocessing equipment, components, assemblies, and systems are detailed in ASME BPE-1997 Part **SD**. This standard addresses Instrumentation (SD-4.1), Specialty Fittings and Hoses (SD-4.2), Centrifuges (SD-4.3), Filtration Equipment (SD-4.4), Pumps (SD-4.5), Process (Hygienic) Valves (SD-4.6), Vessel Design (SD-4.7), Agitators and Mixers (SD-4.8), Heat Exchange Equipment (SD-4.9), Cell Disrupters (SD-4.10), High Purity Water and Steam Systems (SD-4.11), WFI Generators and Clean/Pure Steam Generators (SD-4.12), Micro/Ultrafiltration and Chromatography Systems (SD-4.13), Sterilizers/Autoclaves (SD-4.14), and CIP Systems and Design (SD-4.15).

Dead Legs

"Dead legs" are areas of entrapment in a vessel or piping run that could lead to contamination of the product. Generally, liquid collects in dead legs and is not removed, even after cleaning, because cleaning fluid will not flow within the leg. Therefore, dead legs must be minimized by keeping them as short as is technically possible. ASME BPE-1997 "Bioprocessing

Equipment" Section SD-3.11.1 defines dead leg in a piping system as *"a pocket, tee, or extension from a primary piping run that exceeds a defined number of pipe diameters from the ID of the primary pipe." "It will be denoted by the term L/D or L/A, where L is equal to the leg extension perpendicular to the normal flow pattern or direction, A is the annular gap width, and D is equal to the ID (or inside dimension) of the extension or leg. In some existing standards, the dimension L is measured from the centerline of the primary pipe." "For bioprocessing systems, and L/D of 2:1 is achievable with today's design technology for most valving and piping configurations."* To understand the 2:1 ratio, imagine a soda pop can which has approximately a 2:1 ratio, and the cardboard tube of an aluminum foil roll which has an approximate ratio of 6:1; which one would have the better chance of having its contents swept out with a crossflow across one end?

In practice, vertical dead legs that drain downward are preferable to horizontal dead legs. Conversely, horizontal dead legs are preferable to vertical dead legs that collect fluids via downward flow. Dead legs can result from design features such as instrument taps and pressure relief devices. These are considered *permanent* while *configured* dead legs are the result from closing a valve.

References

1. Kilkeary, John J., Roll, Daryl L., and Sowell, Tim, New Developments in Passivation Technology, Update 2000, Interphex, March 22, 2000.

2. Whitcraft, Paul K., High-Tech Steels to the Rescue, **Chemical Engineering**, January 1992.

3. Nicolio, Curtis, Curb Organic-Acid Corrosion with Duplex Stainless Steel, **Chemical Engineering**, November 2000.

4. Dillon, C. P., Rahoi, D.W., and Tuthill, A.H., Stainless Steels for Bioprocessing, **BioPharm**, April 1992.

5. Pollock, Warren, What's Hot in Metal Alloys, **Chemical Engineering**, October 1992.

6. Stretar, Dennis W., Manufacturing Methods for High Purity Grade Stainless Steel Tubing, ASME Winter Annual Meeting, November 1990.

7. Tverberg, John C., Ledden, James A.., Rouging of Stainless Steel in WFI and High Purity Water Systems, 1998.

8. Tuthill, Arthur H., Stainless Steel: Surface Cleanliness, **Pharmaceutical Engineering**, November/December 1994.

9. Electropolishing: A User's Guide to Applications, Quality Standards, and Specifications Delstar Electropolish, Houston, June 1992.

10. Grant, Arnie, Henon, PhD, Barbara K., and Mansfeld, Florian, Effects of Purge Gas Purity and Chelant Passivation on the Corrosion Resistance of Orbitally Welded 316L Stainless Steel, **Pharmaceutical Engineering**, March/April 1997.

11. Evans, Robert W., and Coleman, Drew C., Corrosion Products in Pharmaceutical/Biotech Sanitary Water Systems, 1999.

12. Banes, Patrick H., Passivation: Understanding and Performing Procedures on Austenitic Stainless Steel Systems, **Pharmaceutical Engineering**, November/December 1990.

13. ASME BPE , The American Society of Mechanical Engineers, Bioprocessing Equipment, An American National Standard.

14. ASME B31.3, The American Society of Mechanical Engineers, Process Piping, An American National Standard.

15. Coscia, Michael, Tantalum and Niobium Materials for the Pharmaceutical Industry, **Pharmaceutical Engineering**, March/April 1994.

Conclusion

It is very clear that the biotechnology industry demands special care and attention in the selection of materials for product contact surfaces as well as solution contact surfaces. Emphasis has been placed primarily on the cleanliness and corrosion resistance issues. For these purposes, a whole segment of the industry dedicates considerable time and effort in R&D for new materials applications, better application of existing procedures, new and more reliable testing for various parameters, such as passivation and its measurement, surface characterization, standardization of dimensional parameters, and general fabrication procedures.

The intention of this article is to provide a general update of what is involved in the use of the industry workhorse, stainless steel tubing and fittings, not only from the AEs point of view, but also the users, contractors, fabricators, and any other group that may derive their success in the involvement with this dynamic and continuously evolving industry. For this purpose, the National Standard ASME BPE-1997 has intentionally been quoted repeatedly, a cost comparison guideline has been included, and a very generic scale for materials corrosion resistance from standard to high has been described.

Awareness and adherence to present Codes and Regulations as well as knowledge of new and advanced technologies are the key to successful completion of design and engineering of systems utilizing this very valuable resource.

About the Author

Michelle M. Gonzalez is the Engineering/Quality Manager at Fluor Daniel, South San Francisco, California. She has nearly 35 years of experience in facilities design and engineering. Since relocating to the United States in 1965, she has held positions of increasing responsibility in mechanical engineering with firms such as Shell Oil, Kaiser Engineers, Bechtel Corporation, and Fluor Daniel. For the last 17 years, she has focused her professional expertise in the pharmaceutical and biopharmaceutical industries. Gonzalez holds an MS in architecture from the Pontificia Universidad Javeriana in Bogotá, Colombia. She is a lecturer at the Stanford School of Engineering, member of the ISPE Baseline® Biopharmaceutical Guide Task Team, and ASME BPE subcommittees on dimensions and tolerances, and surface finishes. She is also an active member of ISPE as a speaker, writer, and chapter committee member.

Fluor Daniel, 395 Oyster Point Blvd., Suite 321, South San Francisco, CA 94080.