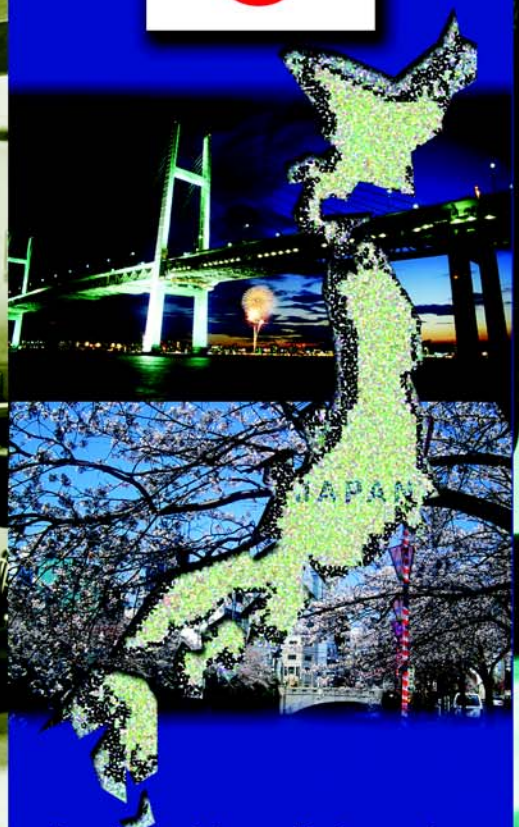
Country Profile

A look at the Pharmaceutical Industry in

JAPAN



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THE SOCIETY FOR LIFE SCIENCE PROFESSIONALS

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2nd Annual ISPE Japan Affiliate Conference

June 12-13, 2003
Tokyo, Japan

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This new feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on the Nordics in the May/June issue of *Pharmaceutical Engineering.*

Photographs courtesy of Takayuki Hayashida, ISPE Member.

ISPE
THE SOCIETY FOR LIFE SCIENCE PROFESSIONALS

Dear ISPE Member:

The origins of Japan's pharmaceutical history go back over one thousand years with its notable period of growth occurring in the Edo Period (1603-1868). Developing in several distinct regions of the country, pharmaceuticals were soon to become a leading industry.

Now, with its graying population, there is an increasing need in Japan for new pharmaceutical products. This will further drive the requirement for development of quality R&D as well as production sites in Japan.

As local manufacturers set their sights on supplying domestic and export markets, and as the major global firms invest in a long-term presence in Japan, regulatory harmonization and compliance will be of critical importance.

Meanwhile, the matter of optimal sharing of information is being addressed. As an example, seminars presented by visiting Life Science professionals hosted by the Japan Affiliate are simultaneously interpreted, while the translation of ISPE publications into the Japanese language is being energetically promoted.

We trust that our Japan Country Profile will be of interest to you and contribute to an understanding of the background against which the Affiliate very recently emerged.

Yours truly,

Tomiyasu Hirachi

Tomiyasu Hirachi
Chairman, ISPE Japan Affiliate

Japan - the World's Second Largest Pharmaceutical Market

For more than 10 years, Japan has been one of the world's largest pharmaceutical markets with sales totaling about $56 billion in fiscal year 2000. Figure 1 shows the changes in sales of pharmaceuticals and ethical drugs from 1990 to 2000; the growth rate for this 10-year period was 11.2%.

Moreover, the size of the market for ethical drugs alone was about $49 billion, representing some 13% of the world total market (Figure 2) and putting Japan in second place after the United States. For comparison, pharmaceutical sales in Japan comprise about 54% of sales in all of Europe.

Table A shows the growth forecast by IMS Health—the Japanese market is expected to see growth of about 2.3% and the nation is expected to remain the world's second largest market overall with some 15.1% of the total world market share.

Recognizing this important status and with the need for further stimulus in mind, the Japanese government has published its vision of the future of the Japanese pharmaceutical manufacturing industry, outlining three major themes:

- Create a good environment for the development of effective new drugs. In particular, aim to establish systems for developing, testing, and licensing new drugs based on genome R&D to bring better ethical products to market more quickly than at present.
- Plan to revise the Pharmaceuticals Affairs Law.
- Plan for growth in the generic and OTC drug markets.

Japan's rapidly aging society is expected to see large increases in medical expenses. Also, planned growth of Japan's pharmaceutical industry, based on the government's future vision, suggests that the industry has substantial potential.

Status of Japan's Pharmaceutical Manufacturing Industry

Japan's pharmaceutical manufacturing industry is characterized by a very large number of small

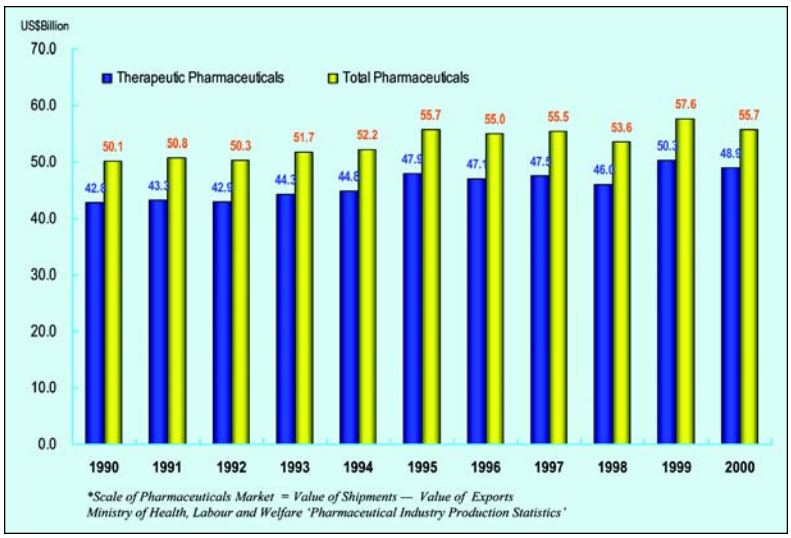


Figure 1. Japan's pharmaceutical market.

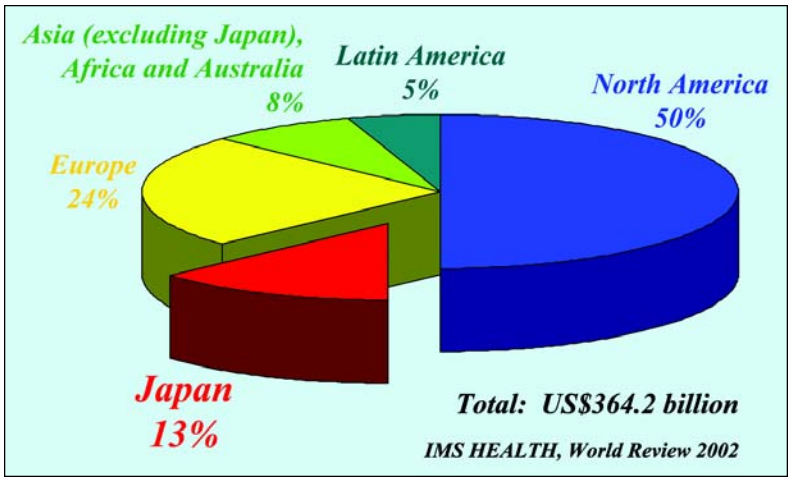


Figure 2. Share of world pharmaceutical market (2001).

	Total Sales 2000 (US$ Billion)	Forecast Sales 2005 (US$ Billion)	Forecast Annual Growth 2000-05 (%)	Market Share (%)
USA	150	263	11.8	60.5
Japan	58	66	2.3	15.1
Germany	17	24	7.5	5.6
France	16	22	6.0	5.0
UK	11	16	8.3	3.7
Italy	11	16	8.2	3.7
Canada	6	10	10.7	2.3
Spain	6	10	9.9	2.3
Australia	3	5	9.3	1.1
Belgium	2	3	5.6	0.7
Total	**280**	**435**	**9.1**	**100.0**

Table A. Growth forecast for top 10 world markets (2000).

manufacturers. In addition, there has been a recent increase in foreign investment after the market-opening measures. Moreover, companies in other business fields are entering pharmaceuticals by developing their own technologies. Although the market is large, the framework of the National Health Insurance (NHI) system makes future expansion likely to see more competitors scrambling for a share of the pie. New drugs are being developed to compete with the overseas pharmaceutical giants and Mergers and Acquisitions (M&As) are being examined as a means of surviving in an increasingly competitive market place, but positive activity seems more probable in the future.

Size and Structure of the Pharmaceutical Manufacturing Industry

In 1997, Japan's pharmaceutical manufacturers produced about $51 billion of products, accounting for about 1.02% of Gross Domestic Product (GDP) and 1.9% of all manufactured products. The proportion rises to 3.4% of all manufactured products in terms of value added through payments of salaries to employees and taxes to government, demonstrating the large role of the industry in Japan's economy.

Employee numbers increased until 1985, but have stabilized at around 2,000,000 since then, comprising about 0.3% of Japan's total labor force and 1.4% of the manufacturing industry. The workforce is relatively small in comparison to the impact of the production value on the Japanese economy.

Looking at the market shares of the world's top 31 companies with total sales exceeding $20 billion, 12 US companies account for more than 50% of total sales, followed by two UK companies with 15.4%, and two companies each in Switzerland and France with 9% and 8%, respectively. The top seven Japanese manufacturers had an 8.4% share—these seven businesses are all of similar size and jostle for position in the crowded domestic marketplace. However, there are big differences between the top seven and the other lower-ranked companies.

About 80% of some 1400 pharmaceutical manufacturers in Japan are capitalized at under $2.5 million and 60% are medium or small companies with total annual sales of less than $2.5 million. In addition, about half have fewer than 50 employees, 22% have fewer than 10 employees, and only 8% have more than 1000 employees. On the other hand, the top 50 companies account for about 87% of annual pharmaceutical sales.

The 18 foreign-capitalized companies have about a 25% share of sales; the number of these companies and the size of their market share are both expected to increase in the future.

Special Features of Japan

A unique feature of the Japanese pharmaceutical business is the traditional practice of salesmen visiting private households once

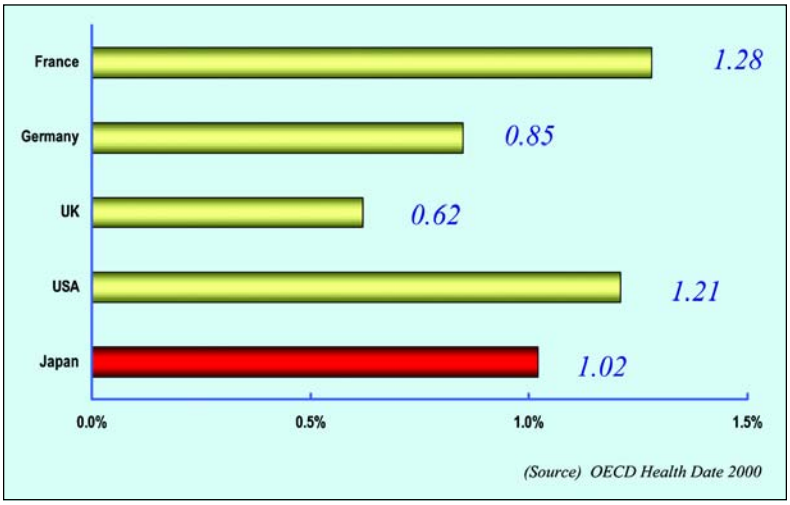


Figure 3. Contribution of pharmaceutical to GDP (1997).

	Amount (US$ Billion)	Proportion of GDP	Proportion Industry
Market Size (1997)	61.9	1.5%	-----
Value (1997)	51.2	1.2%	1.9%
Value Added Pharmaceuticals (1997)	33.8	0.8%	3.4%

(Sources)
OECD Health Data
"Value": Ministry of Health, Labour and Welfare 'Pharmaceutical Industry Production Statistics'
"Value Added Pharmaceuticals": MITI Table of Industry Statistics

Table B. Role of pharmaceutical industry in Japanese economy.

	Value of Shipments (US$ million)	Value Added (US$ million)
Pharmaceuticals	51,128	33,809
Soft Drinks	18,940	8,311
Oil Refining	67,528	4,949
Steel Manufacturing	38,256	16,633
Household Appliances	34,488	13,712
Computers	83,861	18,128
ICs	60,669	20,581
Automobiles	177,491	43,306

(Source)
MITI 1998 Table of Industry Statistics

Table C. Comparison of pharmaceutical and other industries.

a year to leave a medicine box and charging only for medicines that have been used in the previous year when replacing them at the next annual visit. This unusual sales technique is a remnant of business practices from the middle Edo period 200 or 300 years ago, and is typically found in Toyama Prefecture. Businesses making and selling OTC drugs comprise the largest number of Japanese pharmaceutical companies, but account for less than 12% of production value.

In Japan, the government controls the prices of ethical drugs. Unlike the United States and Germany where businesses can choose high- or low-price strategies, Japanese manufacturers do not have freedom to set the prices of controlled products. In addition, ethical drug prices are continually forced down. This is clearly different from the United Sates and Germany where prices for the same products either increase or remain stable. Furthermore, the impact of generic drugs is relatively limited in Japan unlike the United States and Germany where the arrival of generics on the market has a large impact on branded drugs.

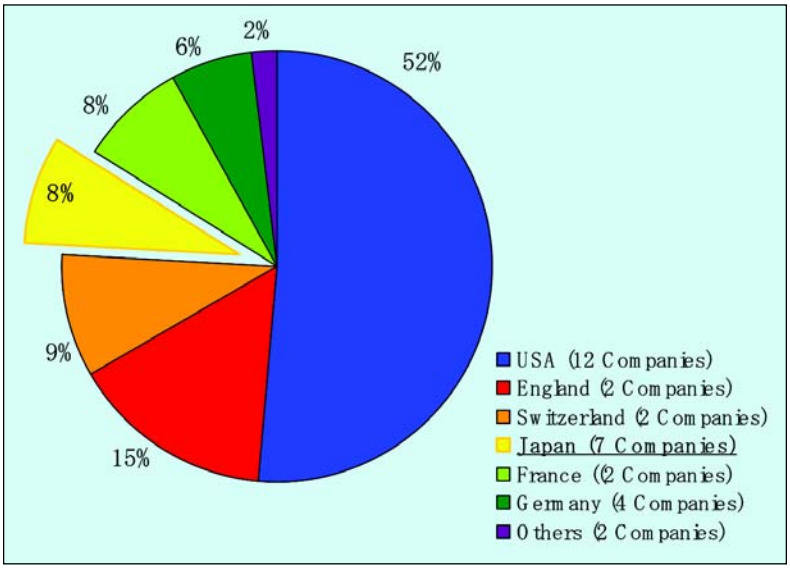


Figure 4. Market share of world's top 31 pharmaceutical companies.

Meeting Future Challenges

The ballooning development costs for new ethical drugs cannot be recovered from domestic sales alone, and a major issue is whether or not to enter overseas markets. Success or failure of the business is clearly dependent on the sales growth of new drugs for overseas markets. On the other hand, foreign-capitalized businesses are becoming more active in the domestic market and there will undoubtedly be more dependence on foreign capital in the future. This process is leading the pharmaceutical industry toward adoption of various global unified rules and standards, meaning that there will be no room in the future for just domestically focused management policies. Some are of the opinion that it will be difficult even for large manufacturers to follow an independent path considering the conditions of the global market, but it might be possible to survive independently by choosing the right strategy. One possibility is reorganization, and many Japanese pharmaceutical manufacturers are taking steps in this direction. This competitive weeding-out is likely to lead to better industrial productivity and an efficient business structure.

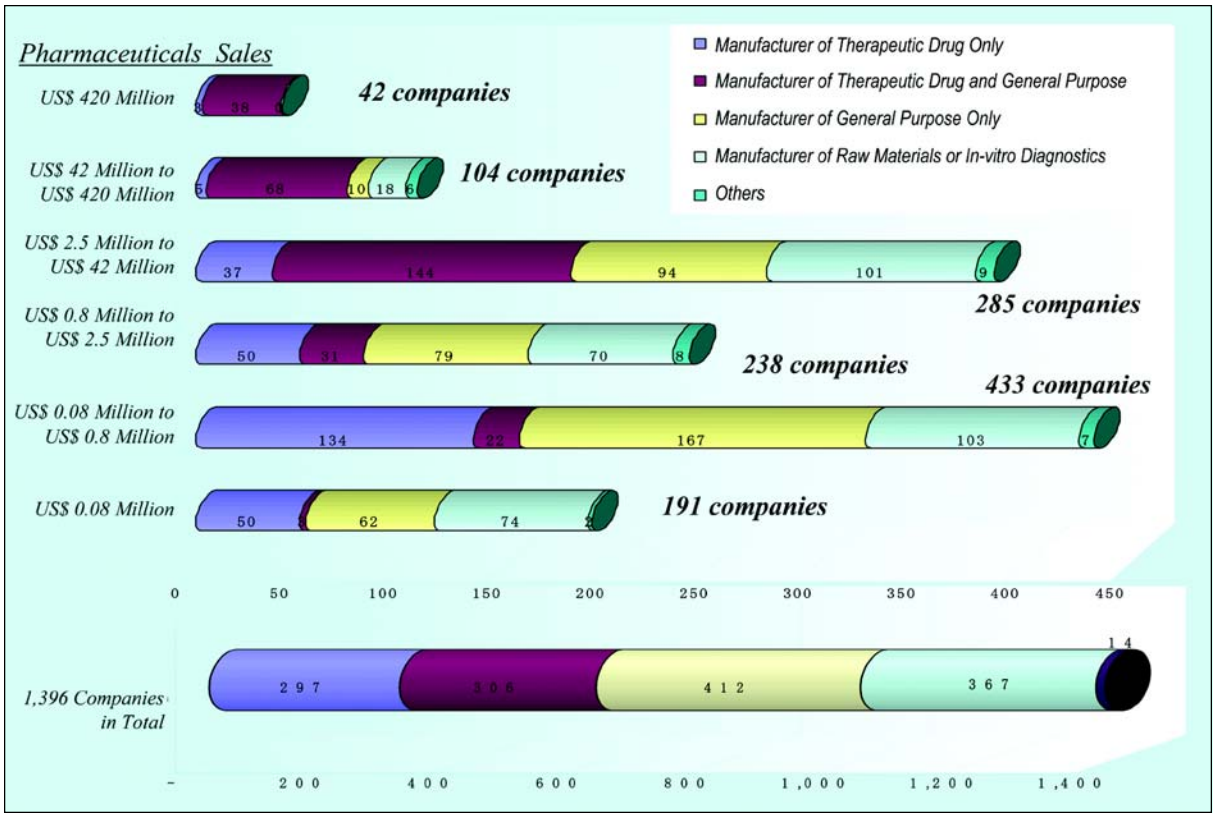


Figure 5. Structure of Japan's pharmaceutical industry.

As a result, we can expect to see the appearance of manufacturing giants who can bear the burdens of massive R&D costs by offering revolutionary new drugs to the world's markets. On the other hand, we will probably see an increase in the growth of generic drug companies responding to the increasing need for low-cost, good-quality ethical drugs.

Moreover, since R&D results can be shared in the pharmaceutical industry, relatively small-scale businesses also have an opportunity to achieve major results. There are also many instances where medium-level businesses can use these opportunities to achieve growth in their specialist fields.

Pharmaceutical Development in Japan

Many New Ethical Drugs Discovered in Japan

Development of the Japanese pharmaceutical industry started in earnest after the postwar recovery. Japanese society changed greatly with economic growth and the NHI system was introduced in 1961 creating a surge in demand for pharmaceuticals. In line with these changes, there was a need for new and more effective drugs. As a result, Japanese pharmaceutical manufacturers focused their attention in the short term on introducing and marketing products from the US and Europe while establishing their own R&D systems and improving their technical abilities in new drug development.

Japan								*(Unit:%)*
Fiscal Year	**10 employees or less**	**11 ~ 50 employees**	**51 ~ 100 employees**	**101 ~ 300 employees**	**301 ~ 1,000 employees**	**1,001 ~ 3,000 employees**	**Over 3,000 employees**	**Total**
1980	24.9	40.2	9.7	12.0	7.0	3.5	2.7	100.0
1985	27.4	33.4	12.0	13.6	7.2	3.6	2.8	100.0
1990	29.4	32.4	10.7	13.7	6.7	5.0	2.2	100.0
1995	25.6	30.3	11.2	16.4	8.0	5.1	3.4	100.0
1999	22.3	32.7	11.5	16.8	8.7	4.8	3.2	100.0
2000 JPMA (84 Members)	-----	-----	1.2	4.8	27.4	41.7	25.0	100.0

(Sources)
"Pharmaceutical Survey" by Ministry of Health and Welfare. UP to FY 1998.
"Pharmaceutical and Medical Device Industry Survey" by Ministry of Health, Labour and Welfare FY 1999.

Table D. Pharmaceutical manufacturers by number of employees.

Figure 8 shows the national shares of new international ethical drugs in the last 20 years.

Table E lists new ethical drugs discovered in Japan.

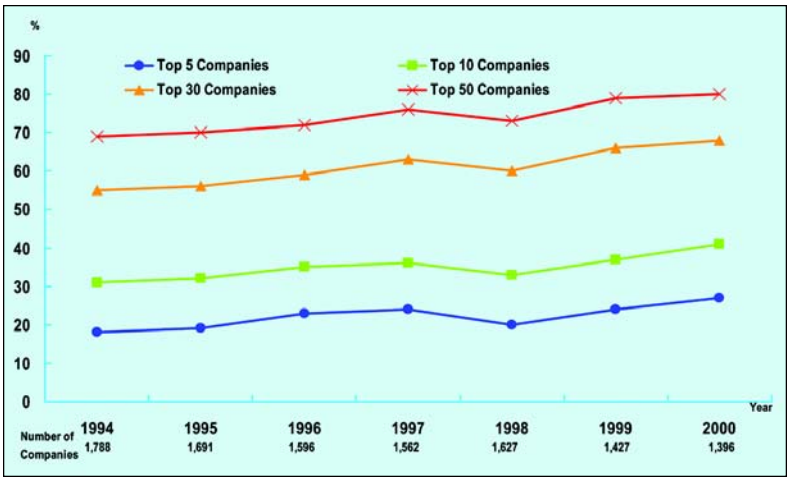


Figure 6. Japan's pharmaceutical manufacturers based on sales.

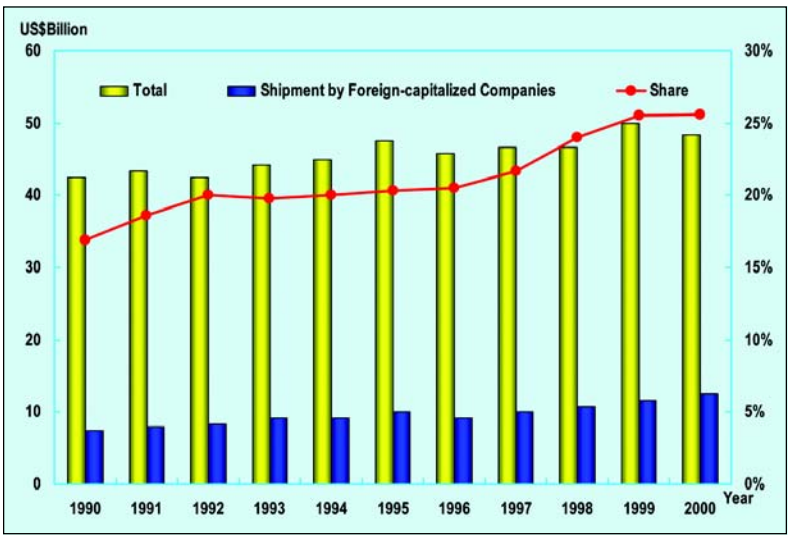


Figure 7. Pharmaceutical shipments by foreign-capitalized companies.

This data indicates that Japan's pharmaceutical industry has discovered a large number of new ethical drugs, and that, clearly, the ability to develop original drugs has increased greatly since the 1980s.

For the present and in the near future, we can expect attention to be focused on the development of new drugs based on data from the human genome project. R&D activities in new ethical drugs are being revolutionized by integration and improvement of a wide range of leading-edge technologies and knowledge including genome research, protein research, bioinformatics fusing IT, and biotechnology—as well as optimizing and screening of compounds, technologies, etc. Development of new ethical drugs requires increasingly large investments, driving worldwide M&As leading to the birth of pharmaceutical giants with the requisite financial and human resources.

Japan has lagged slightly behind the leaders in genome analysis—investment by the Japanese pharmaceutical industry compares unfavorably with the major international pharmaceutical companies. If this trend continues, there are worries that the Japanese pharmaceutical industry will

be weakened in the future. The Japanese government has therefore established a national project based on further improvements in drug safety to create a favorable environment for developing original ethical drugs for international markets and to strengthen the competitive power of the nation's pharmaceutical manufacturers. Clearly, the 21st century will be the age of IT and biotechnology; Japan's pharmaceutical industry is being nurtured to become one of its leading industries and is increasingly important in the overall development of the Japanese economy.

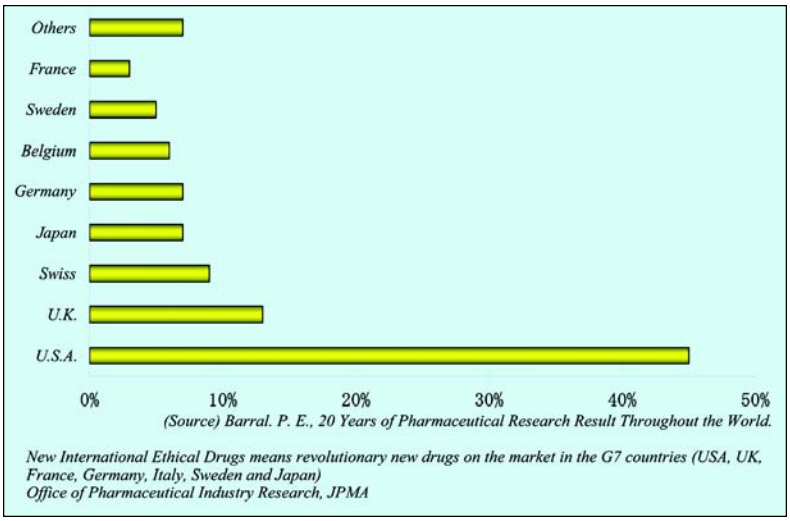


Figure 8. Share of new international ethical drugs.

R&D Investment- More than 12% of Sales

Development of useful new ethical drugs is a key factor in growth of the pharmaceutical industry. Japan's principal pharmaceutical manufacturers invest almost 13% of total sales revenues in R&D and there are indications that the ratio is rising.

Figure 9 compares the change in R&D investment between Japan and the US since 1990. The ratio to sales has remained at a relatively high level.

Bringing a New Ethical Drug to the Market Takes More than a Decade

Data from the Japan Pharmaceutical Manufacturers Association (JPMA) shows that 15 to 17 years are required from the start of R&D to final approval, and bringing the new drug to the market. Furthermore, the chance of a candidate compound obtaining approval is one in 11,300 or 0.009%. As shown in Figure 10, the success rate from the start of pre-clinical testing until a product comes on the market rises to 0.13% with a minimum R&D investment

Company	Nonproprietary Name	Indication	Launch (Year)	Sale (Country)
Eisai	Rabeprazole Na Donepezil hydrochloride	Peptic ulcer Alzheimer	1998 1997	3 36
Ono	Alprostadil Gemeprost	Obstructed peripheral artery Prostglandines	1985 1984	17 15
Sankyo	Troglitazone Cefpodoxime Pravastatin	Diabetes Infection Hyperlipemia	1997 1991 1990	7 58 72
Shionogi	Ceftibuten	Infection	1992	46
Takeda	Candesartan Lansoprazole Leuprorelin Cefotiam Citicoline	Hypertension Peptic ulcer Prostate cancer Infection Disturbance of consciousness	1997 1991 1989 1981 1970	> 10 > 80 > 60 > 10 > 20
Tanabe	Imidapril hydrochloride Diltiazem hydrochloride	Hypertension Hypertension	1995 1977	5 > 100
Daiichi	Lavoflxacin Ofloxacin Tranexamic acid	Infection Infection Allergy	1997 1985 1965	25 140 100
Dainippon	Sparfloxacin Enoxacin	Infection Infection	1994 1987	18 17
Chugai	Lenograstim Nicorandil Sucralfate	Leukocytopenia Angina pectoris Peptic ulcer	1993 1993 1971	55 11 < 100
Fujisawa	Tacrolimus Cefdinir Nilvadipipine Cefixime Ceftizoxime Zotepine Cefazolin	Graft rejection Infection Hypertension Infection Infection Schizophrenia Infection	1993 1991 1989 1987 1982 1982 1971	26 5 5 77 43 3 60
Yamanouchi	Famotidine Nicardipine hydrochloride Josamycin Cefotetan sodium Tamulosin hydrochloride Formoterol fumarate	Peptic ulcer Hypertension Infection Infection Dysuria Bronchial asthma	1986 1984 1980 1984 1995 1988	112 56 67 11 40 53

Table E. New ethical drugs discovered in Japan.

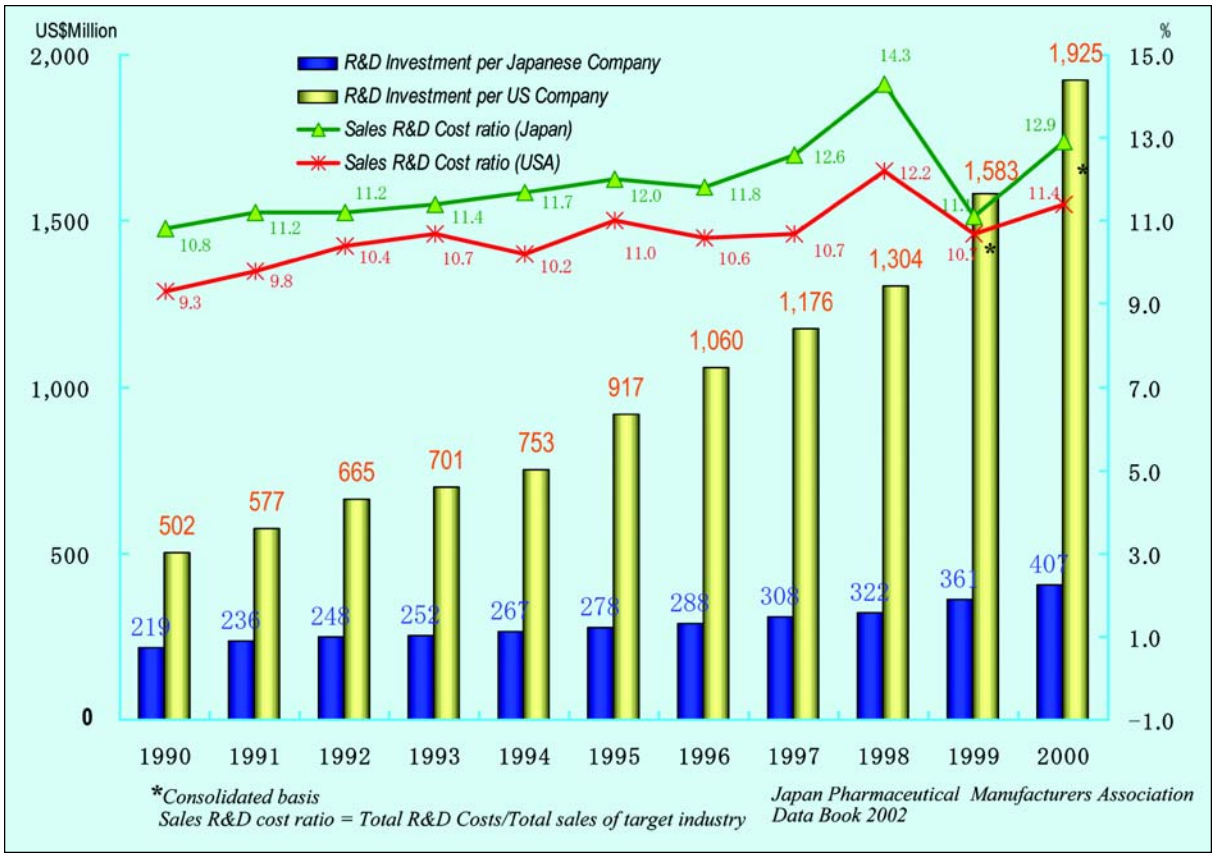


Figure 9. R&D investment in Japan and US.

of $220 to 300 million and a time investment of 11 to 12 years.

Hollowing-out of Clinical Trials?

Clinical trials are an indispensable stage in the development of new ethical drugs and the costs of clinical trials comprise about 40% of the total R&D investment in any new drug.

Looking at the situation in Japan, although R&D investment is increasing, the number of applications to conduct clinical trials in Japan is decreasing. This is due to the impact of trial-related changes to regulations, such as new drug pricing evaluation, new Good Clinical Practice (GCP) enforcement, and expanded acceptance of data from overseas clinical trials—Japanese pharmaceutical manufacturers are focusing on development of new international ethical drugs to come on the market first in the United States and Europe and are changing the trial environment by placing greater priority on trials in these countries. In other words, there is a hollowing-out of clinical trials in Japan.

This hollowing-out of clinical trials is having a certain level of impact on Japan's public healthcare and the international competitiveness of its pharmaceutical industry. The government has therefore included changes to the clinical-trial envi-

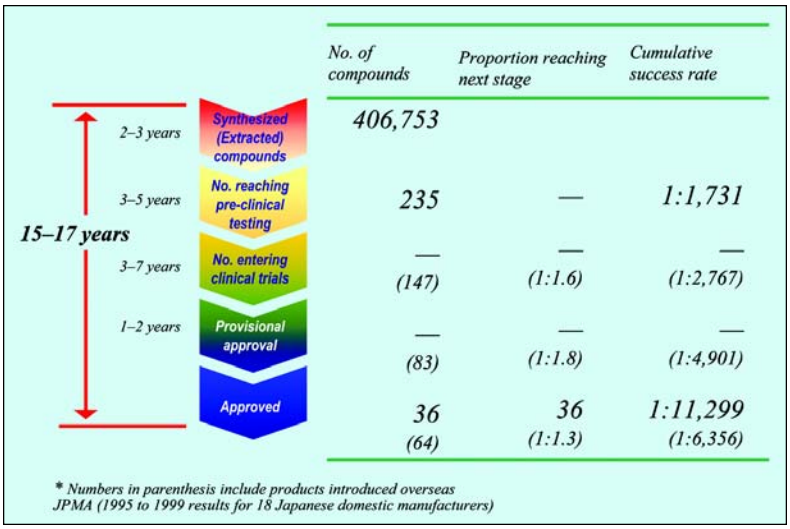


Figure 10. Success rate and time required to develop branded drugs.

ronment as one item in the national action plan.

Foreign Products Make Up 44% of Japan's Pharmaceutical Market

Currently, about 44% of pharmaceuticals sold in Japan are foreign products—no other market in Japan is as open as this.

The trade balance of pharmaceuticals in Japan is showing a slightly decreasing trend, but there is still an excess of imports.

Conversely, the trade in pharmaceutical-related technology has been overwhelmingly export led since the mid-1990s, demonstrating the high technological level of Japan's pharmaceutical industry.

Hopes and Fears - Focusing on Japan's Pharmaceutical Manufacturing Environment and Industry

In the short term, Japan's pharmaceutical industry is endeavoring to ensure its ability to develop new ethical drugs. Developing new effective drugs that contribute to healthcare while simultaneously having an impact on Japan's economic growth presents a number of issues. Against this background, the government canvassed opinions from various medical-related bodies, manufacturers' associations and learned persons. In August 2002, it finally incorporated a *Vision for the Pharmaceutical Industry* in a national action plan aimed at developing a future image for the industry and promoting growth.

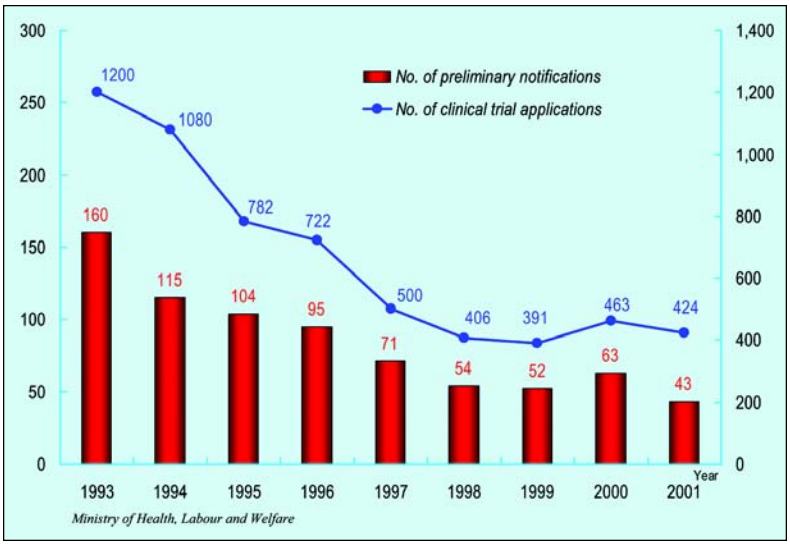


Figure 11. Clinical trial applications.

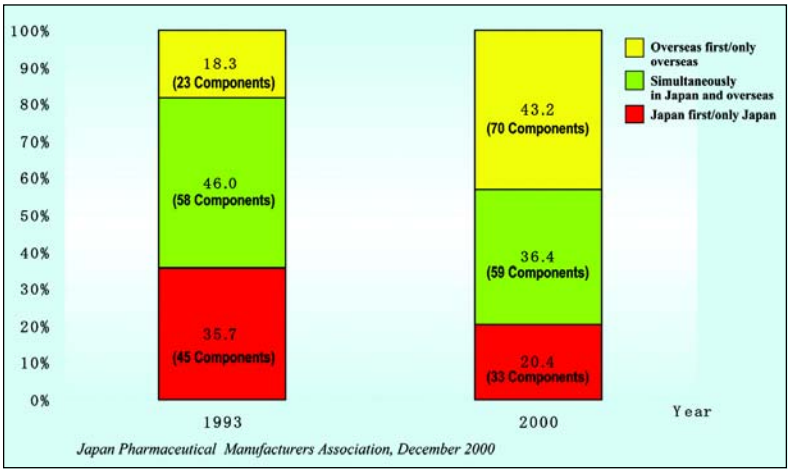


Figure 12. Ethical drugs under development in Japan.

The items related to new drug development are listed below.

1. Strengthen systems for supporting fundamental research with the intention of discovering new ethical drugs and acquiring excellent technologies.

2. Strengthen systems for transferring results and technologies from national research organizations to private companies and for assisting long-term cooperation between industry, government, and academia.

3. Make changes to regulatory environment controlling clinical trials.

4. Create a responsive body for approving new ethical drugs.

5. Establish a NHI drug price system that encourages innovation.

Attention should be given to the future Japanese pharmaceutical manufacturing environment and industry.

Japan's Medical and Public Welfare Systems

Overview

If Japan's medical and public welfare system could be summed up in one phrase, it would be NHI. This uniquely Japanese system was set up in 1961; it is a public medical health insurance system for ensuring that everybody in Japan has fair and equal

access to medical treatment. An advantage of the system is not that everybody who has joined the system receives the very best medical care, but that anybody can access average care at any time. Japanese now have the longest average life expectancy in the world, possibly reflecting the success of the NHI system. On the other hand, Japan's rapidly aging society means that the nation faces rising medical costs and worsening NHI financial resources that will require drastic solutions.

National Medical Costs

The facts of healthcare in Japan can be examined based on data from the NHI system.

As shown in Figure 16, due to the rising life expectancy and improvements in medical technology, annual national medical costs are increasing steadily and have already passed $250 billion—a nearly 50% increase in 10 years. A unique characteristic of the data is that about 35% of the total costs is medical care for people aged 70 or older. The Ministry of Health, Labor, and Welfare (MHLW) estimates that the proportion of the elderly population will increase from 11.8% at present to 21.7% by 2025 when the nation's medical costs will exceed $670 billion—56% of this amount will be for geriatric care. In these circumstances, there will be tremendous pressure to force medical costs down, meaning a reversal in the proportion of costs for pharmaceuticals. There has already been a 10% drop in the proportion over the last 10 years - *Figure 16*. In comparison to the runaway total medical costs, the total for pharmaceuticals has remained broadly similar for the same 10-year period.

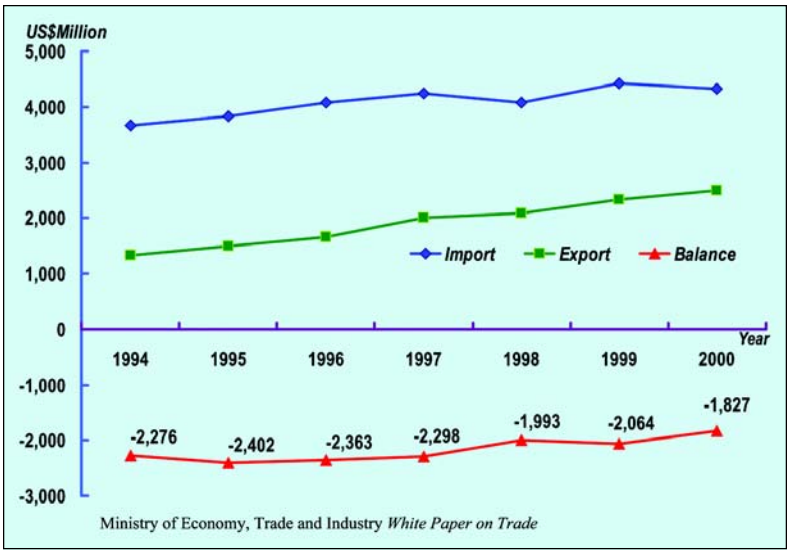


Figure 13. Pharmaceuticals trade balance.

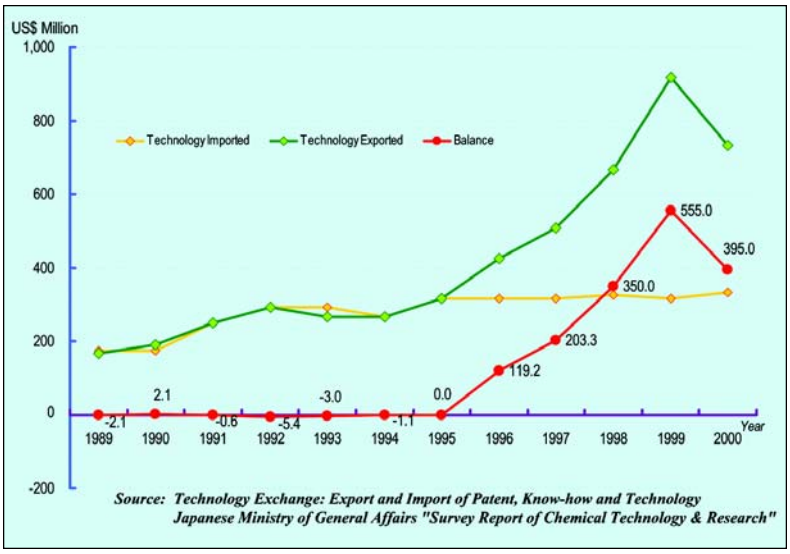


Figure 14. Pharmaceutical technology exchange.

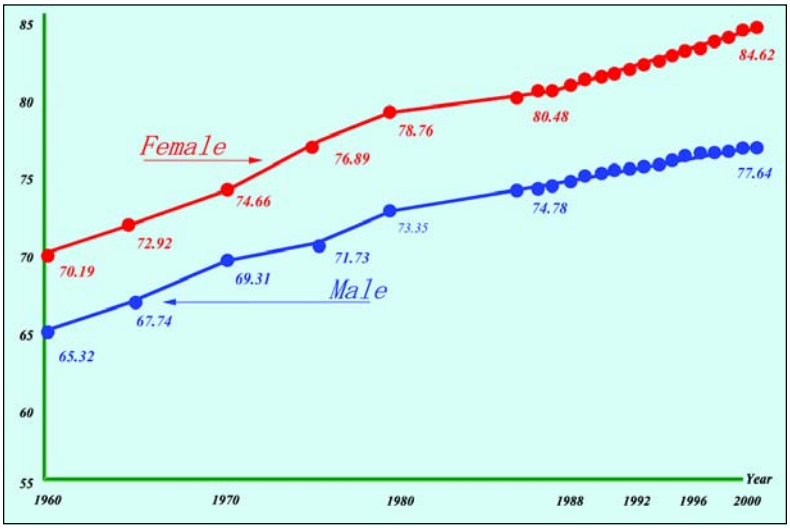


Figure 15. Average Japanese life expectancy.

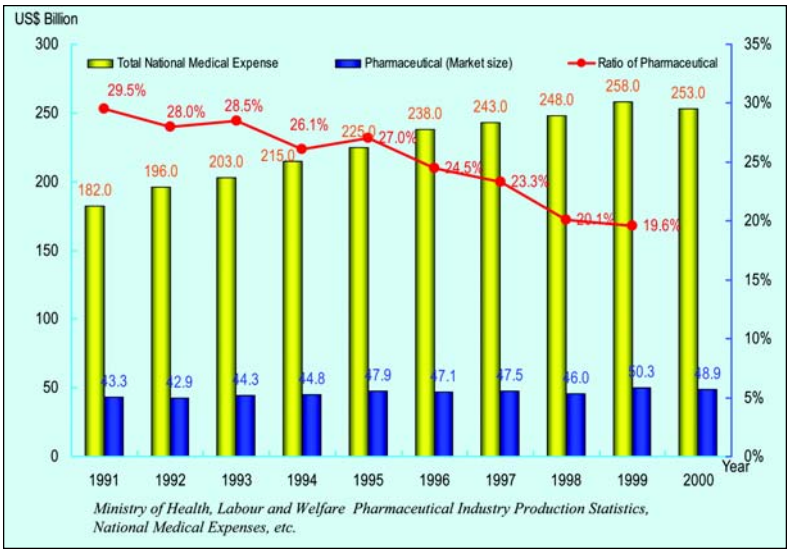


Figure 16. National medical costs and proportion of pharmaceuticals.

Price of Pharmaceuticals

As described above, the market conditions for ethical drugs are extremely severe. One reason is that unlike the US and Germany, Japanese pharmaceutical manufacturers are limited in their power to set prices freely. In Japan, the government sets the prices of new drugs coming on the market based on the NHI drug price system while the actual price set by the manufacturers is always higher than the government price.

The data in Figure 17 demonstrate this situation very well—only Japan has seen a drop in the pharmaceutical price index.

Reforming Medical Systems

Japan is an aging society and statistics for 2000 show that Japanese women are only having 1.36 children on average. In addition, figures published in 1996 for the 29 Organization for Economic Cooperation and Development (OECD) nations show that in Japan, the average hospital stay is 33.5 days. These circumstances are putting a very severe strain on the financial resources of the health insurance associations supporting the NHI system. Although the private health insurance organizations have been said to have a relatively good surplus of resources, some 78% actually had business deficits in fiscal 2001.

In these circumstances, the government is starting to make concrete proposals for drastic reforms of the Japanese healthcare system. Such reforms are bound to have a major impact on the market for ethical drugs in Japan and the

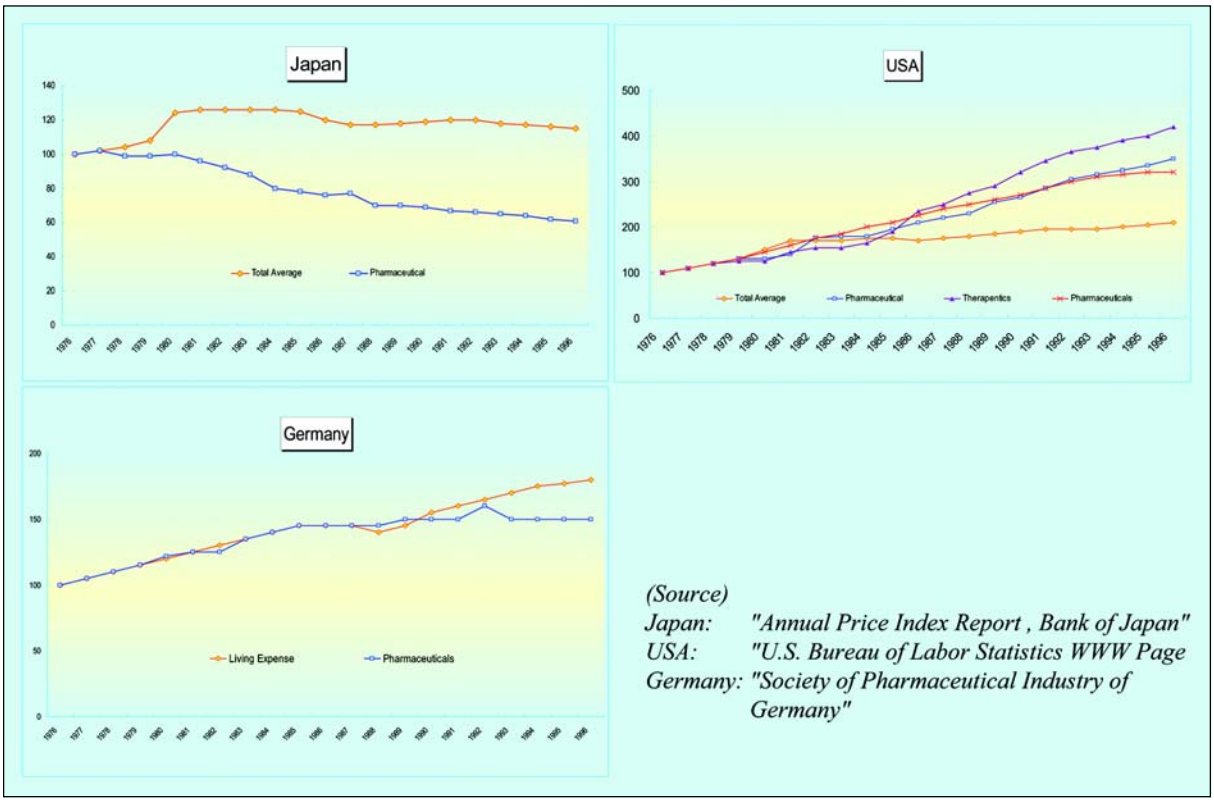


Figure 17. Pharmaceutical price Indices in Japan, US, and Germany.

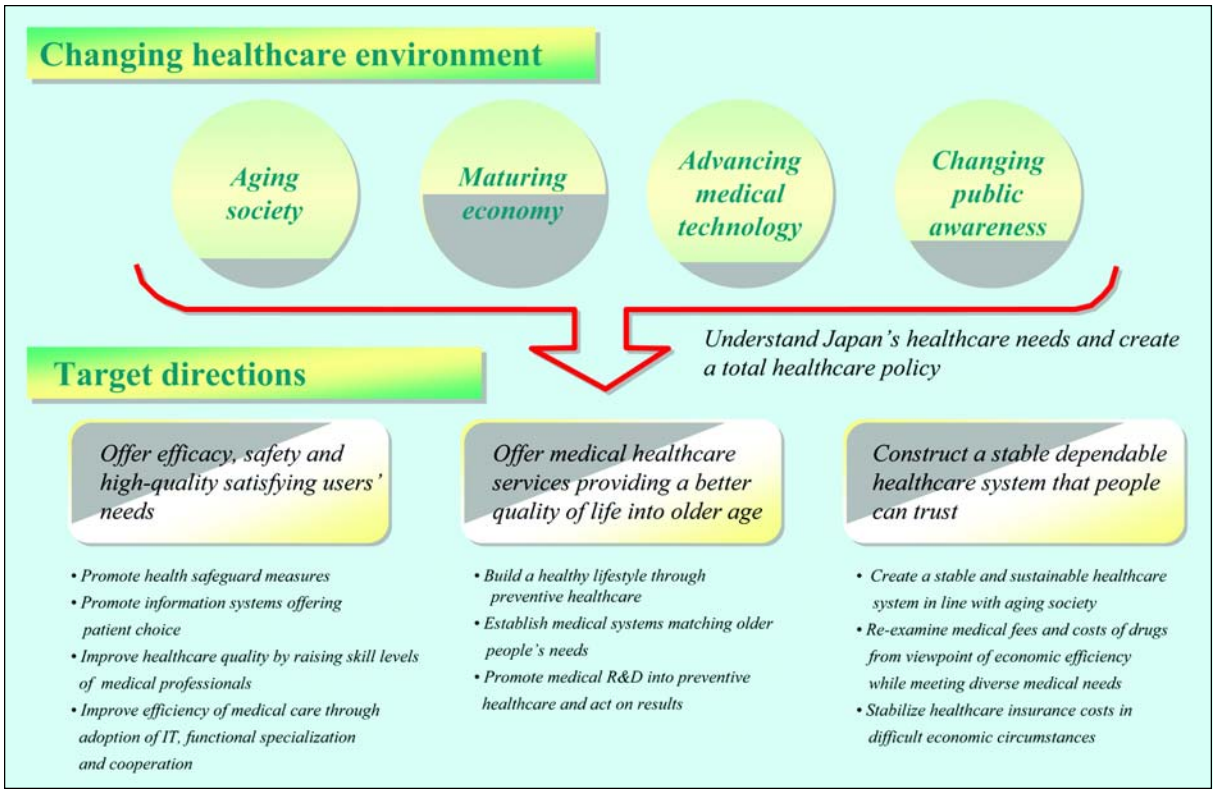


Figure 18. Healthcare system reforms.

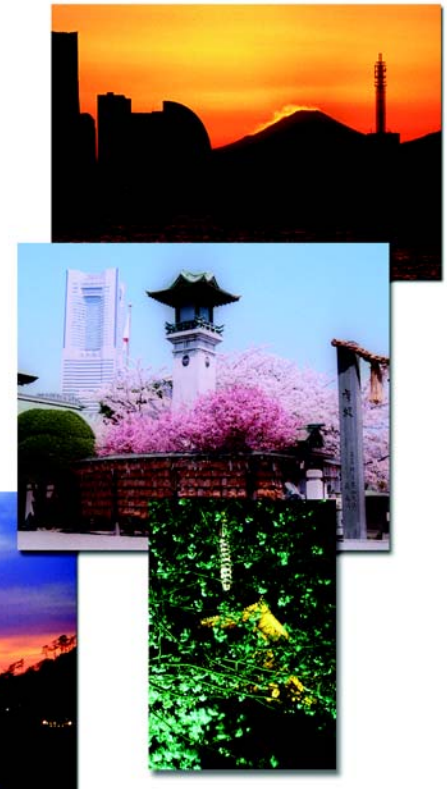
business plans of Japanese pharmaceutical manufacturers.

Conclusion

The quality of pharmaceuticals produced by Japanese manufacturing plants is second to none and a great many resources are invested in quality assurance. On the other hand, the pharmaceutical industry is rapidly becoming globalized and we have entered the age when internationally recognized quality standards are required.

Furthermore, drastic reforms will be required to sustain healthcare systems like Japan's NHI system based on medical insurance.

In this type of business environment, Japanese pharmaceutical manufacturers are gradually expanding their international business presence while doing their best to offer patients in Japan and around the world even safer and more effective new drugs in the shortest possible development timeframes.



Representative Japanese Organizations Active in the Pharmaceutical Field

JPMA

Japan Pharmaceutical Manufacturers Association

日本製薬工業協会

The Japan Pharmaceutical Manufacturers Association is a voluntary organization of research-based pharmaceutical manufacturers that contribute to society by developing new pharmaceuticals.

As of October 2002, the JPMA had 80 members (including 22 foreign affiliates) and 11 committees. The JPMA works in close cooperation with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

http://www.jpma.or.jp

JSPME

Japan Society of Pharmaceutical Machinery and Engineering

日本製剤機械技術研究会

The Japan Society of Pharmaceutical Machinery and Engineering is a not-for-profit volunteer society founded in 1991 in order to advance pharmaceutical technology through exchange of knowledge and experience in a wide range of industries that are devoted to pharmaceutical production.

Members are scientists from academia, government, and companies involved in pharmaceuticals, machinery, construction, electronics, and computers who are dedicated to obtaining the highest level of quality and efficiency.

Merino Bld. 5F 1-28
Kandasuda-cho Chiyoda-ku
Tokyo 101-0041, Japan

Tel: +81-3-3252-3048
Fax: +81-3-3252-3049

E-mail:info@seikiken.or.jp

http://www.seikiken.or.jp

MHLW

Ministry of Health, Labour, and Welfare

厚生労働省

1-2-2 Kasumigaseki Chiyoda-ku
Tokyo 100-8916 Japan

Tel: +81-3-5253-1111

E-mail: www-admin@mhlw.go.jp

http://www.mhlw.go.jp

OPSR/Kiko

The Organization for Pharmaceutical Safety and Research

医薬品機構

Establishment: October 15, 1979

Japanese semi-governmental organization authorized by the Minister of Health, Labour, and Welfare (MHLW).

Shin-Kasumigaseki Building, 9th Floor
3-3-2 Kasumigaseki, Chiyoda-ku
Tokyo 100-0013 Japan

http://www.kiko.go.jp

The following Executive Summary represents the draft of the ISPE Biopharmaceuticals Baseline® Guide that has been available to FDA and ISPE members for comment, with comments due to ISPE by March 2003.

It is likely that parts of this summary will change to reflect these comments, and therefore the summary should be considered only a general indicator of the topics covered in the Baseline® Guide.

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ISPE Baseline® Pharmaceutical Engineering Guide For New and Renovated Facilities Volume 6: Biopharmaceuticals - *Executive Summary*

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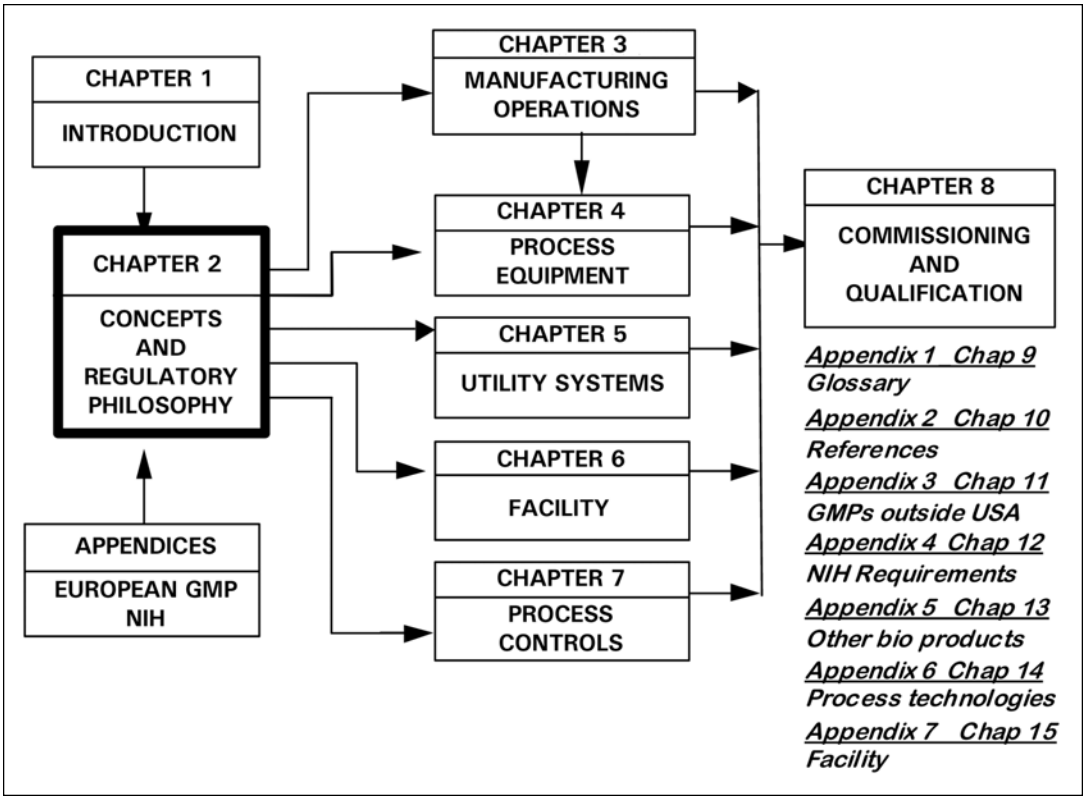

Figure 1. Proposed structure of the final ISPE Baseline® Guide for Biopharmaceuticals.

1. Introduction

1.1 Background

The design, construction, commissioning, and qualification of biopharmaceutical facilities will challenge manufacturers, engineering professionals, and equipment suppliers. These facilities must not only meet cGMP regulations, but must comply with local codes, laws, and regulations.

The current situation is one of confusion and sometimes little science:

- Solutions are applied out of context (one product's approaches inappropriately applied to a different type of product)
- Product and process are not considered in decisions. A common reason is "Company X did it, so we should, too."

Capital concerns:

- Capital funds may be limited, so wise use of funds is important
- The need to get quick facility approval at all costs has led to overspending to remove potential snags during inspections

Money is not going toward product protection as much as to "fluff:"

- Money that could have been used for protecting the product is diverted to features with no product impact:
  - Mirror finishes, "stainless steel" facilities
  - Confusion regarding required process water quality, often overspecified without economic or scientific justification
  - Classified spaces (cleanrooms) where they are not needed, as for closed processes

1.2 Scope of the Guide

This Guide may be used by industry for the design, construction, commissioning, and qualification of new and renovated biopharmaceutical facilities. It is neither a standard nor a GMP, nor is it a detailed design guide. It is not intended to replace governing laws or regulations that apply to facilities of this type. The application of this document for new or existing facilities is at the discretion of the facility owner or operator. Approaches to meeting GMP provided in this Guide need not be retroactively applied to currently licensed facilities.

This Guide applies to large molecule biotech products, cell-cultured, or fermented:

- It does not apply to blood, vaccines, etc. However, most concepts in this Guide may be applied to these products.
- It applies to biopharmaceutical Active Pharmaceutical Ingredient (API) products licensed by both the Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER).

US GMPs:

- Not much is specifically stated in the US GMPs, but best practices are covered here. It is ultimately the owner's responsibility to justify decisions and approaches to regulators.

Other GMPs are covered in the Appendix. National Institute of Health (NIH) and other safety issues are mentioned in the Guide where they affect GMPs or design.

The audience for this Guide is professionals involved in the design, construction, validation, and operation of licensed biopharmaceutical manufacturing facilities.

- The mission of the Baseline®Guides is to help operating companies satisfy the GMPs and produce product in a manner that allows the manufacturer to stay in business.
- This Guide is not a GMP, but instead it focuses on the use of resources to meet GMP. This Guide is but one approach to satisfying the intent of the GMPs. Other methods of protecting the product may exist now or evolve in the future. If an issue is not covered in this Guide, or if alternatives appear feasible, the reader is advised to discuss them with the appropriate regulatory agencies before significant financial commitments are made.
- It is intended that this Guide will be used by regulators and quality control personnel to understand the technical issues regarding the facility or process. This Guide does not attempt to cover the basics of the engineering sciences, nor does it attempt to cover biopharmaceutical GMPs that do not address the facility or the manufacturing process technology.

1.3 Key Concepts of the Guide

1.3.1 Does the Process Equal Product?

There is a continuum of process and facility approaches **based on the product** and processes used to make the product. The best engineering solution makes optimal use of people, materials, and capital while protecting the product. There is not one "right" or "perfect"

way to design and operate the facility. However, the design of a facility has a profound impact on process design and on how the facility is operated.

Due to limitations in analytical methodologies and only superficial understandings of the relationships between process variables and final product quality, biopharmaceutical processes have historically been viewed as "black boxes." Thus, there also has been a prevailing view that the "process equals the product." This view has led to reluctance to alter biophar-maceutical processes, a reluctance that has been reinforced by conservative regulatory approaches. How could manufacturers assure the identity of the final product in the case of process variations? How could manufacturers assure the final product with changes in scale or changes in the facilities of manufacture?

As the industry has developed a better understanding of biopharmaceutical processes and as analytical methods have improved, we have developed a better understanding of the "cause and effect" relationship between process variables and products. This evolution has caused a change in focus to those issues that are critical to the consistent manufacture of high quality products. Products and processes have been proven to be transportable between facilities and can be operated on different scales.

1.3.2 Process Design is Tied to Facility Design

This Guide covers the variables that most directly affect the process and facility:

- Open versus closed processing:
  - Closed processing places more emphasis on protecting the product INSIDE the process.
  - Open processing places more emphasis on the facility and its people.
- What works best for one product, facility, or process scale may not work best for another product, facility, or process scale.
- Features that work well in a single product facility may be inadequate for a multiple product facility.
- Chapter 3 discusses these issues as well as viral clearance and clinical materials manufacture.

Process controls:

- Automation is not a GMP requirement, but if automation is used, then there are GMP implications. Chapter 7 provides more insight regarding automation.

For subjects generic to all pharmaceutical facilities, the reader is directed to other sources for more in-depth information.

- Qualification basics are covered in the ISPE Baseline® Guide for Commissioning and Qualification.
  - Commission everything in accordance with Good Engineering Practice, but qualify only direct impact systems and critical components of those systems.
  - Design Qualification or Enhanced Design Review will help comply with ICH Q7A.
  - Qualification considerations specific to Biopharmaceutical systems are covered in Chapter 8 with reference to topic-specific qualification activities in Chapters 3 through 7.
- Water and steam systems are covered in the ISPE Baseline® Guide for Water and Steam Systems.

The Guide user is encouraged to work with the regulators to iron out "unique" issues before they become significant issues.

1.3.3 Controlled Processing

The product must be protected by controlling the process and often its surroundings. This requires knowledge of the product and process and protection utilizing segregation and flow patterns. Chapter 3 discusses controlled processing in more detail.

1.3.3.1 Know the Product (and its Process)

Intimate knowledge of the product, its critical parameters, the processes involved, and processing parameters is essential. Evaluation of potential contamination routes is needed. Data that demonstrate control of the process and to justify processing decisions will be key to a successful facility.

1.3.3.2 The Process Cannot Add Contamination

The process's contamination profile must be known and the process controlled to specifications.

- Process Water should reflect the product purity profile.
- Chapter 3 discusses recovery from upsets and prevention of contamination in manufacturing operations.

1.3.3.3 Contamination Control Strategy

As discussed in Chapter 3, bulk biopharmaceutical manufacturing is low "bioburden" production. Aseptic-like processing steps or "sterile" processing operations utilizing sterilized process equipment are usually operated **closed**.

Chapter 3 also discusses housekeeping, cleaning, and fumigation. Chapter 4 discusses equipment cleanability, and closure.

1.3.4 Segregation and Flow

Segregation protects the product from contamination in its surroundings (i.e., from the facility and other products). Segregation may be accomplished via procedures, timing, or by physical means. Flow patterns in the facility influence segregation, especially if more than one product is manufactured there. Chapter 6 provides more detail to help decision-making regarding segregation and flow.

Primary and secondary segregation: As discussed in Chapters 2, 3, and 6, protection of product may be accomplished through primary and secondary segregation.

Primary Segregation - used to mitigate a known risk of product contamination, usually supported by a strong GMP driver and process data. It is the foundation of the basic organization and operation of the facility and identifies process steps at risk.

Secondary Segregation - used when there is little demonstrated risk to product, but segregation is desirable to minimize the risk of human error and mix-ups. There is no direct impact on product quality, but it helps define the facility and its operation although more from a management standpoint than

intrinsic process protection. Secondary segregation is open to interpretation as to applications and methodology.

1.3.4.2 Flow and Traffic Patterns in the Facility

Implementation of the segregation strategies results in "flow."

- Flow patterns should address scale, volume, and duration of expected traffic.
- Flow patterns also should address upset conditions (such as maintenance and change out of large equipment) and future construction.
- A mature materials handling philosophy must be in place before establishing flow patterns.

Philosophies of primary and secondary segregation affect flow patterns:

- Raw Materials Flow
- Product Flow, including intermediates and hold points
- Personnel Flow
- Glass and Equipment Flow (through cleaning protocols)
- Waste Flow

Flow patterns may force issues with the cleanliness of the facility:

- Materials of construction and architectural details
- Building layout and potential contamination routes (via air, people, equipment)
- Issues with cleaning of equipment and piping:
  - CIP/SIP
  - Wash Facilities

1.3.5 Open versus Closed Processing

If a unit operation is demonstrated closed, it may operate in Controlled Non-Classified (CNC) space.

- Closed - segregation by physical means (hardware) to protect the product and process from contamination by the surrounding environment (outside the process)
- "Closure" and its measures must be defined by the Owner, and demonstrated to prevent contamination of the product.
- Various operating systems have varying degrees of closure, some may be absolute, while others also provide segregation, but to a lesser degree. The use of a "hard" definition may limit the understanding of "closed."
- The surrounding room environment is not part of the equation for a closed process, but it should be "controlled."

1.3.5.2 If a unit operation is open, the product must be protected by other means.

- Open = not "closed"
- Product = process + facility
- Surrounding environment is a factor in the process.

Either a classified space or a controlled non-classified environment will likely be needed, but the need for area monitoring is driven by the open process.

The choice between closed processing in Controlled Non-Classified (CNC) space and open processing in classified space is often driven by scale of the process, cost of operations, and value of product at risk.

Chapter 4 provides information to help in selecting process equipment to meet open or closed requirements. Chapter 6 discusses the effects of process closure on the facility.

1.3.6 Scale Affects Decisions

Chapters 3, 4, and 5 deal with process design and support utility design issues connected with process scale, and Chapter 6 covers facility layout options.

One size does not fit all. As scale of the process increases, there is a shift toward:

- Vertical layouts with gravity flow of materials
- More closed operations
- More Primary segregation
- Equipment fixed in place (often dedicated)
- More automation
- Controlled non-classified space instead of classified space (due to closed processing)

Small process scales tend to include:

- Horizontal process flow with pumps
- Open operations
- Segregation by time (campaigning)
- Manual operations (mixing, etc.)
- Less automation
- More portable equipment, often shared with other products
- More need for classified spaces
- Single product vs. multiple products manufacture

As discussed in Chapter 3, when more than one product is manufactured in a facility, ensuring the products' safety and quality becomes more difficult, but no less important. Multi-product manufacturing facilities may segregate products by campaigning (one product at a time) or may process multiple products concurrently.

- Campaigning depends heavily on validated cleaning and changeover procedures (Chapter 3).

Concurrent manufacturing must avoid cross-contamination through physical segregation and operating procedures. (Chapters 3 and 6)

1.4 Using the Guide

1.4.1 Organization of the Guide

An overview of the Guide's structure is shown in Figure 1.

1.4.2 Application of the Guide

As shown in Figure 1, it is necessary to begin by understanding the GMP requirements (Chapter 2) and then addressing the product and operational requirements (Chapter 3). From there, once operational concepts have been established, User Requirements defined, and perhaps even a Functional Design created, the discipline designers may begin detail design.

Users of this Guide are advised to refer to other ISPE Baseline® Guides for more detailed or complementary information. For example, water and steam systems are thoroughly discussed in the ISPE Baseline® Guide for Water and Steam Systems, and the design of classified pharmaceutical manufacturing space is discussed at length in the ISPE Baseline® Guide for Sterile Manufacturing Facilities.

Users of this Guide are also encouraged to understand GMP and specific product requirements thoroughly before attempting facility design. Where there is conflict or a lack of understanding, manufacturers and engineers are encouraged to discuss concepts with the appropriate regulatory agency.

Such early discussion opens dialogue and helps to settle potentially thorny issues.

2. The Regulatory Basis for Facility Requirements

During the design of new facilities, every manufacturer faces numerous issues that may significantly affect the facility cost. These include process definition, process equipment requirements, the definition of a suitable manufacturing environmental quality to support manufacturing, water requirements, and facility layout. While some of the issues faced may affect the quality of the Active Pharmaceutical Ingredient (API or bulk drug substance), others may have no impact.

The primary element to be considered in a biopharmaceutical facility is the ability of the facility and the process to protect, i.e., prevent contamination of, the API. Product protection issues may be addressed in a voluntary Product Protection Control Strategy.

The evolution of facilities for manufacturing biopharmaceutical products has led to many extremes in size, complexity, and capital/resources. Processing approaches and designs suitable for a small-scale process are often inadequate or inappropriate for a large-scale facility. The multi-product facility will differ in certain key areas from either of these dedicated facilities.

Specifically, each company should determine the appropriate requirements to provide adequate protection for its product(s), and thereby, the requirements for the completed facility. No single solution or design fits all drug substances or products since the decisions made and incorporated in the facility will depend upon:

- Nature of the process and product (i.e., contamination-sensitive processes to less sensitive processes, open versus closed processing, etc.)
- Scale and complexity of the process
- Number and types of the products in the facility

This Chapter addresses some of the significant process-related concepts and facility attributes with regulatory implications to be considered when designing a facility. Key points developed include:

- There is not one universal "GMP" standard or approach to biopharmaceutical facility and process design. The nature of the product and its processes greatly influences these decisions. Systems and their components will have varying effect on each product.
- Biotech manufacturing operations are not usually intended to produce a sterile drug substance, but rather one of low bioburden. Although the voluntary adoption of aseptic manufacturing techniques and facility standards have occurred in the industry, such standards are not required. The production process and facility should include the appropriate controls to prevent, limit, and detect API contamination.
- Processes may be closed or open. Closed processing presents less risk to product and presents fewer demands on the facility design. Local controls may be used with open processes to provide protection of the product.
- Multiple products segregated by appropriate procedural or physical means may be produced within a single facility.
- Water used in manufacture should be appropriate to the process; WFI may not be scientifically necessary throughout the entire process for most products.

3. Manufacturing Operations and Activities

This Chapter involves the operational aspects of a biopharmaceutical facility, as opposed to the physical design of the facility itself, and addresses key regulatory issues and concepts defined in Chapter 2. The Chapter addresses the impact of facility and equipment design decisions on manufacturing operations. Conversely, the Chapter also describes how operability and maintainability considerations should influence the design of a biopharmaceutical facility. Concerns and issues of production management, process operators, and other plant support personnel are included. Important concepts addressed in this Chapter are as follows:

- **Operational and Procedural Controls** can play an important role in protecting the product, and must be factored into the "open versus closed" design decision. Application of these types of controls with a well trained manufacturing staff can often be a better solution than over-engineering a system.
- **"Bioburden-Controlled Processing" and "Pyrogen (Endotoxin)-Controlled Processing"** are key operational concepts that have a significant impact on process and facility design, and both are distinctly different from sterile processing. Some features of traditional sterile design and operation may be employed, but are typically not required to establish the appropriate level of control.
- **Viral Clearance (Reduction and Inactivation)** – Biopharmaceutical processes commonly use raw materials from biological sources, starting with the cell line and often extending to supplements added during the cell culture and purification stages. Cell lines used in the biotechnology industry are extensively characterized for identity and purity, and are tested for the presence of infectious agents. Nevertheless, it is still a regulatory requirement for manufacturers using mammalian cell culture-based processes to demonstrate adequate viral clearance during the manufacturing process. In addition, increasing concern over the transmission of prions from animal-sourced raw materials has required manufacturers to take additional measures to minimize the risk of such contamination. The decision on how/where to accomplish viral clearance can have an impact on the equipment design, and may affect the design and layout of the facility.
- **Segregation** is critical in any biopharmaceutical operation to ensure product protection. Traditional applications include:
  - Between organisms, products, or technologies
  - Between processing steps (e.g.,

upstream and downstream operations)
- Between raw materials or products at various stages of quality control or process step
- Between components or equipment at different stages of cleanliness

Segregation can be accomplished by procedure, by spatial separation (physical), by time (temporal), by environmental control, or by process design (system closure).

- In a **Multi-Product Operation**, products can be either campaigned or processed concurrently. For campaigned products, the focus is on cleaning validation, changeover procedures between products, and line clearance procedures. For concurrent product manufacture, the focus is on segregation, procedural controls, and avoidance of cross-contamination. In all cases, the overall guiding principle is to ensure the quality and safety of the product.
- **Manufacturing at Different Stages of Product Development** is important for many biopharmaceutical companies, particularly those facing their first major capital investment in manufacturing facilities. While the regulations are clear in stating that GMP compliance is required for all stages of clinical development, it is also recognized that in most cases the manufacturing process is not completely defined during early-stage clinical work. It is important that process issues having significant impact on the facility design be locked down as early as possible. The emphasis of process/facility design and validation during early-stage clinical manufacturing should be placed on areas that have the greatest impact on product quality and consistency.

4. Process and Equipment

The Chapter on Process and Equipment is primarily concerned with design aspects of biopharmaceutical processes and equipment, as opposed to the related operational aspects addressed in Chapter 3. More specifically, this Chapter deals with the design of biopharmaceutical process equipment, and associated piping and instrumentation, which contact a product or its components at a stage in the process where such contact could influence the quality, safety, purity, strength, or identity of the ultimate product. The primary audience for this Chapter is process and equipment engineers.

In general, biopharmaceutical processes are similar in that nearly all have fermentation/cell culture production steps, harvest steps, purification steps, formulation steps, and final bulk filling steps. Although manufacturing processes may differ, certain Critical Process Parameters are consistent from product to product, and certain key considerations for each processing step apply to all processes.

Within each process step, there are process considerations driven by the overall philosophy of the organization operating the process. The design approach that is chosen based on these considerations (GMP and business drivers) will result in a set of criteria to be used for both equipment selection and overall facility design. There is no single answer to the majority of the process considerations mentioned. However, the combinations of the choices and solutions will define reasonable, compliant process designs.

Various types of equipment share similar design considerations and requirements. Specifically, cleanability/drainability, surface finish, materials of construction, shear generation, closure level, containment level, and pressure/temperature requirements must be considered for virtually any piece of equipment or device used in biological manufacturing. Improper consideration can lead to processing systems that are either not operable (placing product at risk) or are operationally inefficient (lower process yields).

Key topics addressed in this Chapter are:

- Simplified process flow diagrams of several **typical biopharmaceutical processes**.
- **Critical process parameters** that are consistent from product to product. Key processing (critical) parameters for various processing steps are identified for typical unit operations. Critical process parameters, such as temperature, pH, conductivity, bioburden, endotoxin, product concentration, by-product levels, purity, and stability are generally similar from process to process. However, the acceptance criteria, implications, and applicable design options from process to process may vary significantly.
- **General considerations for equipment design** – design considerations common to most biopharmaceutical unit operations.
- **General equipment considerations**, such as materials of construction, cleanability, avoiding cross contamination, open vs. closed, process monitoring, safety, containment, and maintenance, can be applied to most process equipment, and design considerations are outlined. Similarly, there are design considerations applying specifically to general particular areas such as cell culture and purification. These are outlined as well in the form of checklists for the process and equipment engineer.
- **Specific equipment design considerations** – design considerations that are unique to certain specific biopharmaceutical process equipment types.

Although a detailed analysis of every unit operation used in biopharmaceutical processes cannot be covered in this Guide, unit operations generally fall within these broad process operation areas:

- Raw Material Storage/Handling
- Weigh/Dispense
- Media/Buffer/Component Preparation/Hold
- Inoculum Preparation
- Fermentation/Cell Culture
- Recovery/Harvest
- Purification
- Bulk Filling
- CIP
- SIP
- Biowaste Deactivation

Specific design issues affecting unit operations in these areas are outlined.

5. Process Support and Utilities

This Chapter provides guidance in design and operation of utility services supporting the manufacturing of biopharmaceutical products. Utility systems addressed in the Chapter include:

- Pharmaceutical Water Systems
- Cleaning, Sterilization, and Depyrogenation Systems
- Process and Utility Gases
- Process Temperature Control Systems
- Biowaste and Process Waste Handling
- Seal Support Systems
- Plumbing and Piping Systems
- Emergency Power

The Chapter focuses on process support systems that affect ability to meet GMP production requirements. The Chapter identifies the major GMP issues for each of the systems addressed. Guidance is provided in design of systems to minimize risks of product contamination or unreliable production.

For purposes of qualification and commissioning, the Chapter categorizes process support utilities as having "Direct Impact," "Indirect Impact," and "No Impact" on product. The Chapter recommends full qualification and commissioning of Direct Impact systems. Systems with Indirect Impact or No Impact should be commissioned consistent with Good Engineering Practice.

Key Concepts discussed in this Chapter

- Process support system features that affect GMP are identified, and vulnerable characteristics are explained
- Methods to minimize product contamination risks from process support utility systems are presented
- Except when required for safety or operational reasons, system design should minimize the need to service and otherwise access process support systems from within production areas
- Systems that might enable transmission of contaminants are identified with methods for prevention provided
- Methods to define commissioning and qualification requirements for process support utilities
- A summary of key concepts for biopharmaceutical water systems is provided

6. Facility

Biopharmaceutical manufacturing facilities are very complex and result from projects that focus on the attributes of the product(s) being produced, the attributes of the process, and the facility attributes needed to meet cGMP guidelines. The facility design team should become familiar with the topics discussed in the Chapter to understand how each will affect the final facility design and operation.

This Chapter will review:

- The impacts of process and unit operations on facility design
- How product attributes play a key role in facility definition
- The importance of adjacencies in defining operational flow to minimize potential contamination opportunities
- The impacts of containment and closed processing on facility design
- The definition of area environments and their impact on facility layout and design
- The issues related to single product vs. multi product production philosophy
- Air lock and gowning room alternatives
- Considerations for effective process and production support areas
- Regulatory considerations in facility design
- Layout alternatives, when is vertical flow practical
- Finishes are covered in other Baseline® Guides, and are referenced in this Chapter
- Discretionary (non-GMP) considerations

7. Process Controls

This Chapter on Process Controls and Automation provides points to consider when developing instrumentation and automation strategies for Biopharmaceutical operations. This process starts by determining the details of the biological process to be controlled. What are the critical operating conditions? What can adversely affect the process or product? Once the process and critical operating parameters are identified, the optimal level of automation versus control via manual procedures may be determined.

Automation is not a GMP requirement. However, when automation is used, it carries with it GMP requirements. If properly applied and validated, automation can help achieve ongoing GMP compliance. When not properly managed and designed, automation can result in problems with project schedule and cost.

Topics covered in this Chapter are organized as follows:

- Biopharmaceutical Automation Issues
- Level of Automation
- Biopharmaceutical Unit Operations
  - Fermentation/Cell Culture
  - Cross Flow Filtration
  - Chromatography
  - SIP
  - CIP
- Control System Maintenance
- Validation of Automation Systems

8. Commissioning and Qualification

A biopharmaceutical manufacturing facility is commissioned and qualified in the same manner as any other pharmaceutical manufacturing facility. Many aspects of the qualification of aseptic manufacturing facilities apply to classified spaces in biopharmaceutical facilities, yet there are many areas that require only commissioning in accordance with Good Engineering Practice.

It is imperative that, before detail design begins, the owner and engineers develop User Requirements (**What** the facility is to do) and a Functional Design (**How** the facility will work and protect the product). These activities will identify product/process critical parameters and their acceptance criteria (forward processing criteria), against which post-construction qualification will verify performance of the direct impact systems that are identified in Functional Design.

The ISPE Baseline® Guide for Commissioning and Qualification provides valuable guidance in identifying the systems needing qualification. Rather than restating the entire Guide, a few highlights are provided in this Chapter. The facility engineer is directed to the ISPE Baseline® Guide for Commissioning and Qualification for further information.

9. Glossary

A glossary of pharmaceutical industry terminology relevant to the ISPE Baseline® Guide for Biopharmaceuticals.

10. Appendix - European Aspects

The purpose of this appendix is to highlight the general requirements in Europe and to point out the differences between Europe and the US. Within Europe, the majority of countries are covered by the European Union (EU). There are countries in Europe outside EU, such as Switzerland, that are covered by their own national regulations. The general trend is to harmonize the regulatory requirements worldwide, but differences still exist. Organizations like ICH are the main drivers for that development.

Within Europe, the EU directives are harmonizing general requirements, giving the minimum standards. The national laws need to comply with these, but are allowed to be more stringent.

This article describes design criteria as a strategy for containment systems (isolation systems) applicable to pharmaceutical facilities handling Active Pharmaceutical Ingredients (APIs).

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Design Criteria and Evaluation of Pharmaceutical Containment Systems

Evaluation for Open Isolation Systems

by Osamu Suzuki, PhD, Morihiko Takeda, Koji Tanaka, and Mikio Inoue, PhD

Introduction

Recent drug development is becoming progressively directed toward drug potency.[1-4] For the present, this tendency is likely to continue, increasingly facilitated by the advancement of the development of drugs targeting biochemical pathways, cellular controls or gene regulators, associated with specific genes, and based on genetic research and cell biology.[3] This trend contributes to approvals for reductions in patient drug dosage with a concurrent reduction in the allowable exposure level to the drug component for the workers during the manufacturing process.[4] Pharmaceutical containment systems (isolation systems) allow pharmaceutical manufacturers to meet hazardous chemical materials exposure limits and are an essential part of pharmaceutical current Good Manufacturing Practice (cGMP).[4] This technology provides for the design of unique pharmaceutical containment facilities, including closed and open isolation systems within aseptic[2,5-10] or non-aseptic[1-3,6,7,9-10] environments. Pharmaceutical companies, engineering contractors, and equipment suppliers have recently, but independently, made an effort to establish exposure control limits through conceptual classification or case studies with various surrogate materials.[4,11-15] This article proposes design criteria to assist in the containment of potent compounds[16-20] and reflects these criteria in the design of pharmaceutical bulk and finished product manufacturing facilities. The laboratory under study has recently joined a research project to evaluate the containment performances of APIs in pharmaceutical facilities. The purpose of the research project is:

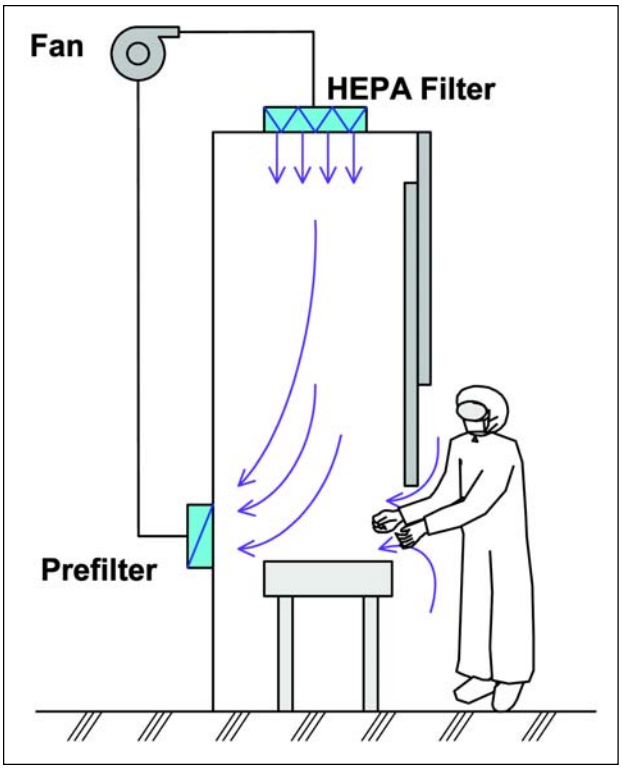

Figure 1. Schematic view of an open containment cabinet.

- to investigate quantitatively the containment level of the APIs to confirm that containment performances met design criteria
- to establish the quantitative design criteria based on the analyses of the behavior of the airborne dust in potent compounds within manufacturing processes

In the study, the containment performances of an open-type containment isolation system, which could be categorized to a Performance-Based Exposure Control Limit (PB-ECL)[11] of 3 were in-

vestigated. The review report[7] focuses on highlights in the New PDA Technical Report No.34, which defines the open isolators that are designed to allow for the semi-continuous egress of materials during operation while maintaining a level of protection over the internal environment. The isolation systems evaluated in the study included both a closed isolator (glove box) and a containment cabinet of safety cabinet-type (open containment cabinet). The open containment cabinet is designed to provide a flow of filtered air over the product, while ensuring that the flow of air is into the cabinet. This type of cabinet also ensures efficient working, while maintaining a level of protection over the internal environment.[21] Attention was focused on illustrating the relationship between the worker's operation and the containment performances under API processing in bulk API manufacturing facilities.

Design Criteria for Pharmaceutical Facilities

The general strategy of the facility design for the pharmaceutical containment systems is as follows:[16,19]

- Classification of bulk or finished pharmaceutical products into five hazard categories (PB-ECL)[11] according to their inherent toxicological and pharmacological properties, shown in Table A.

This PB-ECL classification is based on an earlier report[11] and past practices of pharmaceutical facilities in containing the various potent compounds. The categorization by PB-ECL for each pharmacological property, as the finished product, is shown in Table A.

- Classification of the barrier level into classes from zero to 2.0, at 0.5 intervals, by integrating various containment systems, including personal protection, is shown in Table B.

The protection systems for the external environment, such as layout zoning, HVAC system, and building construction, also are considered.

- Selection of the barrier level to maintain the required environment for each manufacturing process.

The barrier level should be selected according to the amount of dust generated by conditions, such as water content and handling volume, shown in Table C.

- Integrated study to reflect the selected barrier level in the facility design by utilizing a combination of barrier technologies, gowning regulations, and the layout of building facilities.

Containment Strategy and Facilities to Process Bulk APIs

Pharmacological Properties of the Drug

The categorization by PB-ECL for each pharmacological property, as the finished product, is shown in Table A. Although the intravenous toxicity was assigned to an ECL category of 3, other pharmacological properties including carcinogenicity, sensitivity, and pharmaceutical potency may be assigned to an ECL category of 2. However, as the intravenous toxicity was considered as the critical point, ECL category 3 was selected as the design basis for bulk manufacturing facilities.

	PB-ECL Category	1	2	3	4	5
	Exposure Level (μ g/m^3)	1000 ~ 5000	100 ~ 1000	1 ~ 100	< 1	NIL
1. Active	Potency (mg/day)	> 100	10-100	0.1-10	< 0.1	< 0.1
2. Hazard	Toxicity LD50 (mg/kgRat)	**> 2000: non toxic**	**500-2000: almost non toxic**	**50-500: slightly toxic**	**5-50: toxic**	**< 5: highly toxic**
	Toxicity of Oral					
	OSHA/HCS	> 500: non toxic		50-500: toxic	< 50: highly toxic	
	WHMIS (Canada)	> 500: non toxic		50-500: toxic	< 50: highly toxic	
	Toxic Control Law	> 300: non toxic		30-300: slightly toxic	< 30: toxic	
	Ocean Pollution Control (GESAMP)	> 2000: non-hazardous	500-2000: practically non hazardous	50-500: slightly hazardous	5-50: moderately hazardous	< 5: highly hazard
	Toxicity of intravenous	**> 100: non toxic**		**7-100: toxic**		**< 7: highly toxic**
3. Others	Carcinogenicity (IARC)	-----	----- -----	----- -----	2A, 2B: potentially yes -----	1: yes
	Sensitivity	low	low-middle	middle	middle-high	high

: ECL category in each pharmacological property as finished product

Table A. Performance-based exposure control limit (PB-ECL)[11] for pharmaceutical drug manufacturing.

Barrier level	Definition for protection of worker and environment against potent compounds
0	Not protected
0.5	Partially protected
1.0	Fully protected
1.5	More protected
2.0	Doubly protected

Table B. Barrier level setting for worker protection.

Barrier Level Setting for each Manufacturing Process

Table D shows the required barrier level setting for each manufacturing process. The barrier level is defined, according to the condition of the bulk APIs, with the values of the level varying between 0 and 2.0,[16-20] as shown in Table C.

Condition	Barrier Level				
	Exposure Control Limit				
	1	2	3	4	5
Large amount of powder	0.5	1.0	1.5	2.0	≥ 2.0
Small amount of powder				1.5	
Liquid/wet powder		0.5	1.0	1.0	
Very small amount of powder/liquid			0.5	0.5	
Powder/liquid enclosed	0	0	0	0	0.5
Non-hazardous substances	0	0	0	0	0

Table C. Barrier level according to the condition of hazardous chemicals under ECL.

The process for manufacturing the bulk APIs includes weighing of raw material within the glove box, charging of the raw material into a reaction vessel (suspending of the raw material), crystallization, filtration, cake receiving and drying, along with weighing, milling, and dispensing within the open containment cabinet, with further mixing, and finally, dispensing for packaging as a bulk product.

Crystallization, filtration, cake receiving, and drying processes were given a barrier level of 1.0, and with a value of 1.5 selected as the required barrier level for the weighing within the glove box charging, the powder handling processes within the open containment cabinet, and subsequent mixing and dispensing processes are considered the highest levels in the whole handling processes. This barrier level value corresponds to the handling of a large amount of powder. The containment performances were evaluated for the weighing process in the glove box, the subsequent charging process into the reaction vessel, and the powder handling processes in the open containment cabinet.

Powder Handling Processes in Containment Systems

The raw material was taken from the bag within the glove box and subdivided by weight. The accurately weighed raw material was packaged into small bags. Each bag was taken from the glove box through the pass box and placed in a closed powder loading system. The system was then connected to the inlet of the reaction vessel for the material charging. After the installation of this system, the raw material was thoroughly charged into the reaction vessel for the subsequent crystallization. The inside of the bag was well cleaned by purified water, which was introduced from a nozzle installed inside the vessel, leaving the bag 'as is,' and the loading system was uninstalled. After filtration and drying, the powder was handled on a different day for weighing, milling, and dispensing within the open containment cabinet. The equipment surfaces and floors were cleaned for both processes soon after the operations were completed. The containment evaluation was performed subsequent to the operations, but before the cleaning. Figure 1 illustrates the lateral view of the open containment cabinet. Because this cabinet is open booth, the inside is at atmospheric pressure. However, this cabinet is designed to give a flow of filtered air over the product while ensuring that the flow of air is into the cabinet. This type of cabinet also ensures efficient working, while maintaining a level of protection over the internal environment.[21]

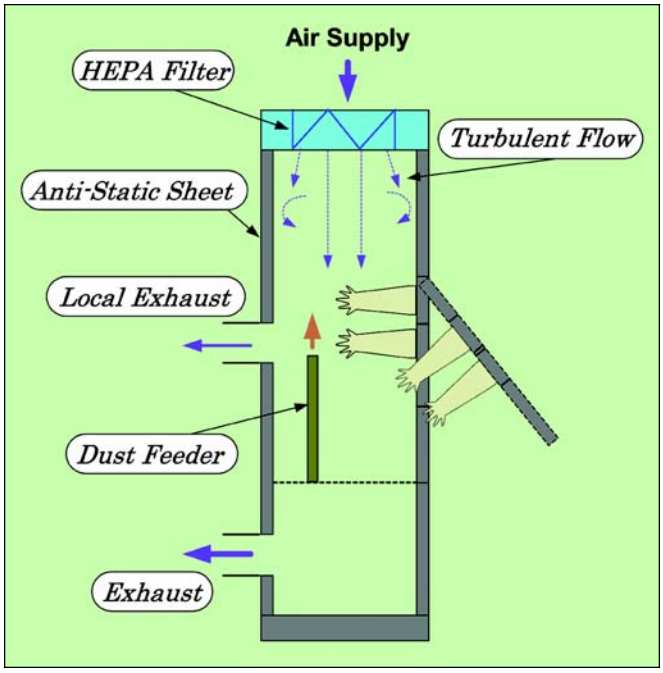

Figure 2. Schematic view of a mock-up booth representing a turbulent flow booth.

Process Flow	Required Barrier level
Weighing of raw material	1.5
Charging of raw material	1.5
Crystallization Filtration Cake Receiving Drying	1.0
Weighing/Milling/Dispensing	1.5
Mixing	1.5
Dispensing	1.5

Table D. Process flow and barrier level setting.

Evaluation Methods

Sampling Methods for Containment Evaluation

Air Sampling

Constant flow air samplers, using a 37 mm diameter, cassette type closed head or the International Occupational Medicine (IOM) head mounting and adequate filter, were used to monitor the concentrations of the airborne dust from powder handling during operations.

Static or personal monitoring was carried out. The monitoring commenced just before operations commenced and concluded just after operations were completed. The Short-Term Particulate Airborne Concentration (STPAC) was determined for less than one hour of operation, which was the usual amount of time required to complete the operations, and measured as units of amount collected per unit volume. The cassette type closed head was normally used, except in the measurement of the raw material charging into the reaction vessel during a comparison with the IOM head for performance.

Swab Test

Interior and/or exterior surfaces of equipment, surfaces of floors in the work place, and operator gowns were investigated to determine the degree of surface contamination (total amount recovered or amount per unit surface area) by a validated swab method.[22] Cloth was dipped in purified water and then squeezed. It was used for swabbing. Particular attention was focused on the entry and exit of workers from the workroom with respect to any probable carry-over of the powders being processed. For this purpose, the swab test was performed for those floors that were traversed by the operators.

Analytical Method

The concentrations of the airborne and the surface-contaminated particulate were analyzed by a validated chemical analysis. The recovery rates from both the filter and the cloth were validated and reflected in the analytical results. While the recovery rate from the surface was not determined because of the restriction of the use of water as solvent, the surface was visually checked to confirm that no powder remained after swabbing. A previous study using this swab method confirmed a recovery rate of 95% confidence of the surrogate material from the surface although an organic solvent was used for dipping swab clothes in this earlier study.[22]

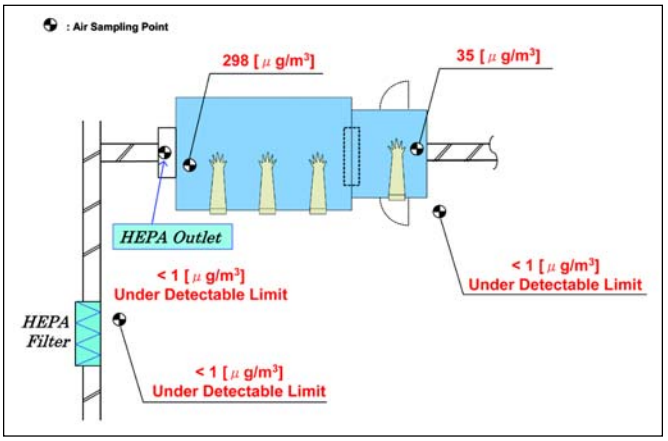

Figure 3. Containment evaluation by air sampling for inside and outside a glove box after the raw material weighing process.

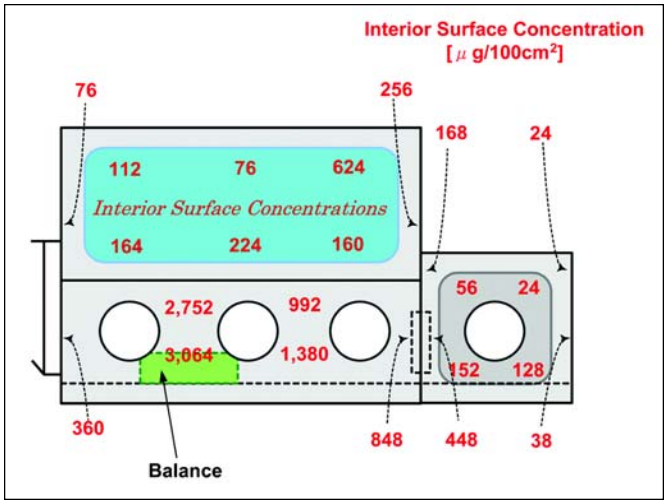

Figure 4. Interior surface contaminant concentrations of a glove box after the raw material weighing process.

Mock-up Test

Parameters for the Test and Mock-up Booth

The mock-up test covers several parameters that should be considered in the design of isolation systems. They include studies of the isolation systems, such as whether it is closed or open; flow patterns, whether it is laminar or turbulent; efficacy of local exhaust ventilation; different types of the surrogate materials and the particle size distributions, and type of sampler head, such as the cassette type closed head or the IOM head for air sampling.

Figure 2 shows a schematic view of the mock-up booth, which represents a turbulent flow booth with a local exhaust. A dust feeder was used to secure constant feeding of the surrogate material. Since the study focuses on the containment evaluation of the open isolation system, the result of the containment performance for the open booth with turbulent flow in line with the parameters listed is presented with one surrogate material. The cassette type closed head was used for air sampling. Monitoring times for air sampling were between 20 and 30 minutes. Temperature and relative humidity during the measurements were 20°C and 38%, respectively.

Surrogate Material

Fine lactose was used as the surrogate (test) material with a particle size range by weight ratio (provided by the manufacturers) of:

- below 50 μm (>30%)
- 50μm to 75μm (<35%)
- 75 μm to 150 μm (<25%)
- over 150 μm (<10%)

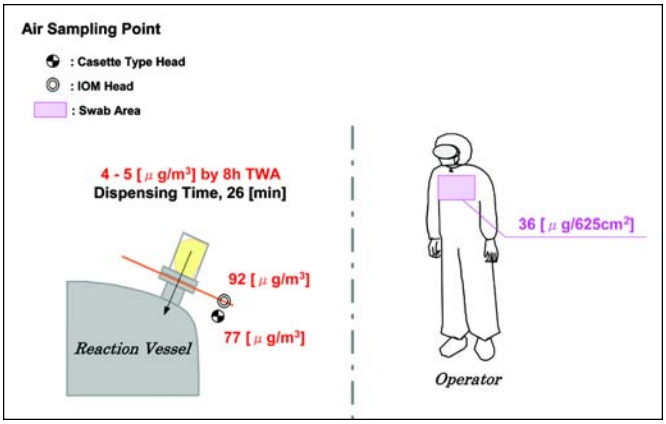

Figure 5. The sampling points and the analytical results for both air sampling and swab test of the operator gown during the charging of the raw material.

Results and Discussion

Evaluation of Containment Performances for Weighing and Charging of Raw Materials

Glove Box and its Surrounding Environment during Weighing

Figure 3 shows the sampling point and the analytical results for air sampling. Air sampling was carried out using the cassette type closed head. This figure is illustrated in plan view. The pressure within the pass box was designed to be negative with respect to the atmospheric pressure of the workplace. The pressure within the glove box was negative to that of the pass box. The containment performance of the glove box was estimated by air sampling:

- inside the glove box
- inside the pass box
- in front of (outside) the pass box
- in front of the exhaust of the room

In order to confirm the performance of the HEPA filter for possible inclusion of sub-micron particles, air sampling was carried out at the outlet side of the HEPA filter of the glove box. The sampling in the case inside the glove box was carried out in front of the exhaust (HEPA filter) to allow the results to be compared before and after the HEPA filter. The sampling for the outlet of the HEPA filter was carried out using a port for measuring the differential pressure. The analytical results demonstrated that the STPAC in the glove box and the pass box were 298 and 35 μg/m^3, respectively, while the environment outside the glove box, including the outlet of the HEPA filter, were shown to be under the detectable limit (< 1 μg/m^3). These results demonstrated that the raw material handled was satisfactorily contained within the containment equipment (the glove box) and that the containment performance met the design criteria. The weighing process was completed within 10 minutes. The airborne dust of the raw

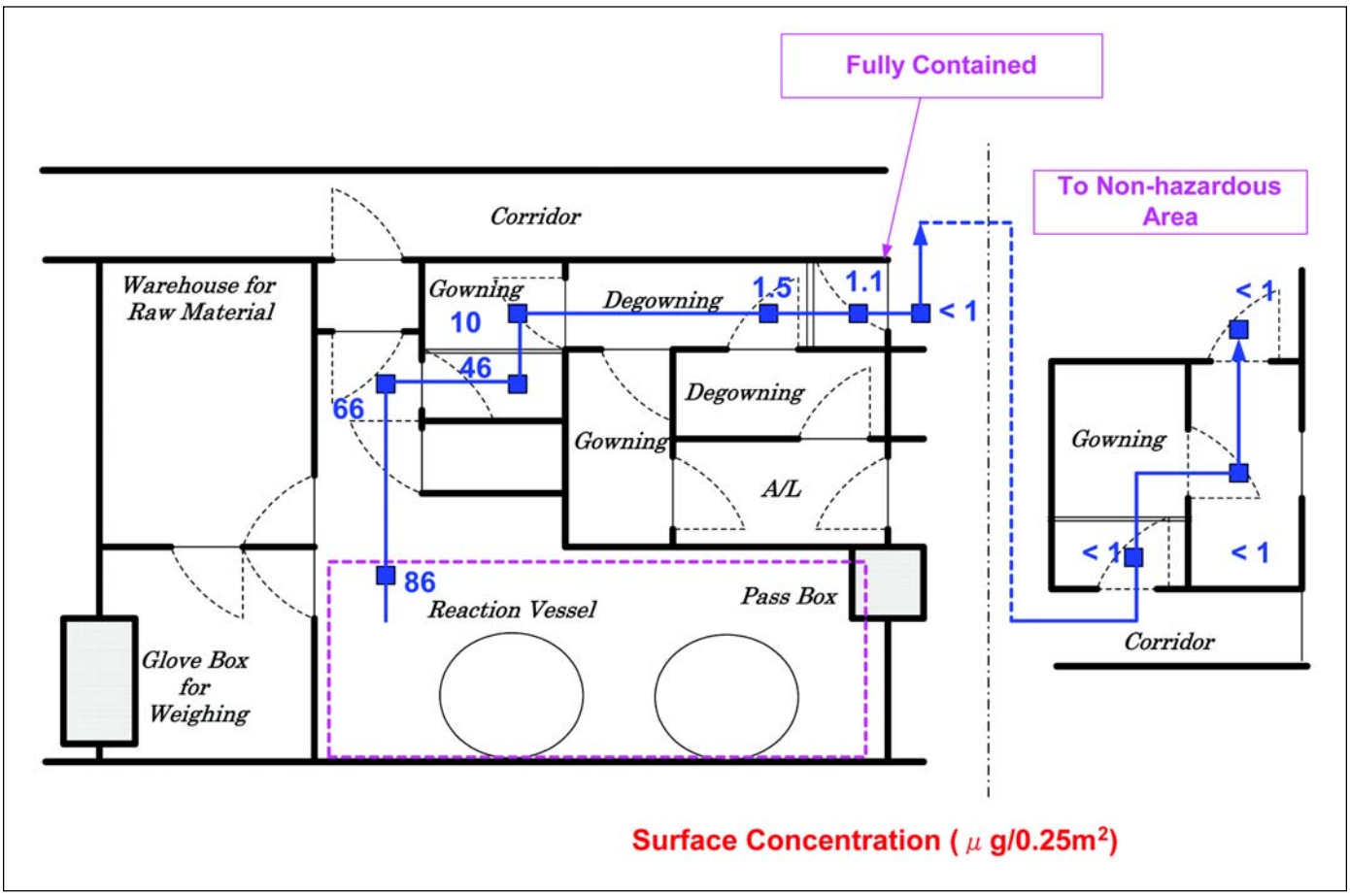

Figure 6. Containment evaluation relevant to worker operation by swab test after weighing and charging processes.

material also was found within the pass box. This might be caused by moving the bag from the glove box to the pass box relatively soon after the weighing process, despite the differential pressure between the glove box and the pass box. This emphasizes the importance of using the exhaust in the glove box effectively, by taking sufficient time to remove the airborne dust.

Figure 4 shows the analytical results for the interior surface concentrations at the front and the lateral sides within the glove box after weighing. The concentration of the lateral side close to the exhaust was obtained by swabbing the neighboring site of the exhaust. The interior surface concentrations were shown to increase toward the lower side from the upper side, suggesting this as a pattern of behavior of the airborne dust within the glove box with regard to the particle concentration of the raw material during weighing.

Surrounding Environment of Reaction Vessel during Charging

Figure 5 shows the sampling points and the analytical results for both air sampling and swab test of the operator gown during the charging of the raw material. The performance of the cassette head was compared to the IOM head in air sampling. These sampling heads were positioned at a distance 200 mm from the inlet edge of the reaction vessel, by facing the sampling heads toward the lateral side of the inlet, perpendicularly. The STPACs were estimated as 92µg/m^3 for the cassette head and 77µg/m^3 for the IOM head, indicating relatively compatible sampling performances for collecting the airborne dust of the raw materials. These STPACs were much lower than that within the glove box and within the range of the assumed design criteria. The STPACs corresponded to 4 to 5µg/m^3 when they were expressed by 8 hours time weighted average. Because the material charging process was completed within 26 minutes, the existence of the airborne dust seems to be instantaneous. It is likely that the release of the airborne dust from the inlet of the reaction vessel is the result of disconnecting the closed powder loading system relatively soon after charging the raw material and/or insufficient cleaning by purified water for the small amount of the residue within the bag. This implies that it is highly possible to decrease the STPACs by improving operation procedures. The release of the airborne dust caused simultaneous exposure of the operator gown, as shown in Figure 5. The surface concentration was found to be 36 µg/625cm^2. The area of 625cm^2 (25 cm × 25 cm) corresponded to the direct swab area. Although the amount of the raw material detected in the operator gown was small, the containment evaluation during the charging process strongly suggests the importance of gowning as a secondary barrier, and of considering adequate regulation for gowning during the facility design.

Containment Performances Relevant to Worker Operations

Particular attention was given to the containment performances associated with the operation of workers. Figure 6 shows the floor surface concentrations of the raw material evaluated along the exit route from the workplaces after the weighing and the charging processes shown in Figures 3-5. Swab sites with an area of 0.25cm^2 (50cm × 50cm) were predetermined and the sites were swabbed before starting the operations. After the operations and subsequent cleaning of the floors around the workplace, the corresponding sites were swabbed again to determine the surface concentrations. The surface concentrations shown in Figure 6 were expressed as the difference between these two swab tests.

The results revealed that the workplace surfaces were contaminated, but concentrations were markedly decreased before entering the gowning room, which is a space for degowning (from 86 µg/0.25m^2 to 46 µg/0.25m^2). However, contamination was still detected in the gowning room (10 µg/0.25m^2), in the degowning room (1.5 µg/0.25m^2), and in a space for putting on shoes (1.1 µg/0.25m^2); although the concentrations were below the detectable limit after the degowning room (<1 µg/0.25m^2). This provided clarification that the powder handled was fully contained within the hazardous areas. However, these results suggest that there is a possibility of carry-over of the handled powder outside the workplace, most probably on workers' gowns.

These results also indicate that the carry-over by workers, following exposure to the airborne dust of the powder handled, needs to be considered in the design of the pharmaceutical containment facilities, in addition to the containment of airborne dust.

Evaluation of Containment Performances of Open Isolation Systems

Surrounding Environment of Open Containment Cabinet during Powder Handling

Figure 7 shows the sampling points and the analytical results for both the air sampling and swab test in the powder handling processes within the open containment cabinet. The processes include the weighing, milling, and dispensing of the re-crystallized active compound. All processes were carried out within approximately 1.5 hours. Air sampling was carried out during these processes. The STPAC inside the cabinet was estimated at 88 µg/m^3 where the weighing and dispensing processes were performed, whereas it was only 5.1 µg/m^3 outside the cabinet and 2.6 µg/m^3 in front of the exhaust of the room. The STPACs were 4.2 µg/m^3 next to the mill inside the cabinet and 5.9 µg/m^3 outside the cabinet. These results indicate that the airborne dust was primarily produced by the weighing and dispensing processes, rather than the milling process. The results also suggest that the open containment cabinet has the ability to contain the powder handled. The floor surface concentrations in front of the containment cabinet were estimated as 86 mg for the weighing process and 19 mg for the milling process. The reason that the concentrations were expressed as an absolute amount recovered was that the powders collected by the swab test were easily visible as masses on the floor surfaces close to the open containment cabinet, in both cases.

The overall results seem to confirm a satisfactory performance of the open containment cabinet to contain relatively

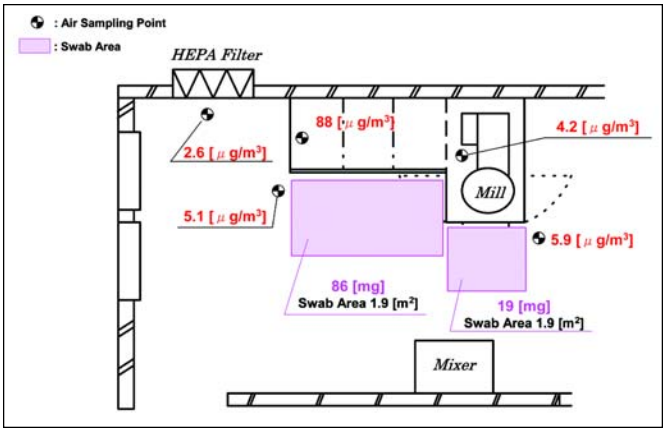

Figure 7. Containment evaluation by air sampling for an open containment cabinet and swab test for floors during weighing, milling and dispensing processes within an open containment cabinet.

large amounts of the powder being handled with a better operational performance when compared with the closed systems, such as the glove box. The best type of containment system can be adequately selected by considering both the operational performance and the PB-ECL for the potent compounds.

The release of the small amount of airborne dust from the open containment cabinet, however, caused the exposure to the operators' gown. Figure 8 shows the analytical results for both personal air sampling and the swab test of the gown after the powder handling within the open containment cabinet. The STPAC obtained by the personal monitoring was only 20 μg/m^3, which corresponded to 3 μg/m^3 by 8 hours time weighted average for 75 minutes of operation. The gown surface concentration was estimated as 250 μg/625cm^2, which

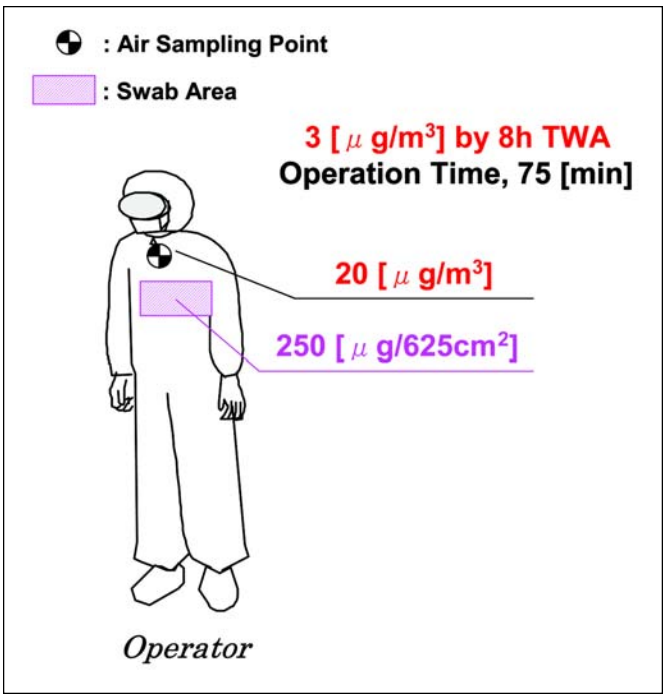

Figure 8. Containment evaluation by air sampling (personal monitoring) and swab test for an operator gown after weighing, milling, and dispensing processes within anopen containment cabinet.

was higher than that of the charging process of the raw material. This may result from the sustained exposure in this situation (75 minutes) compared to the charging process (26 minutes).

A similar tendency was obtained for the evaluation of the floor surface contaminations to the workplace exit by operators, after the powder handling of the open containment cabinet (data not included). The results indicate that although some carry-over of the powder on the operator gown was found, complete containment within the hazardous areas was accomplished.

Complementary Effect of the Mock-Up Test on Containment Performance Evaluation

Figure 9 shows the STPACs of the fine lactose for the base case (no airflow case) and its comparison (turbulent flow and exhaust working case) to the mock-up open booth. The numerical values were shown for both inside and outside the booth. The results demonstrated the quantitative efficacy of the airflows to decrease the STPAC (from 30,000 μg/m^3 to 4,500 μg/m^3 for inside and 7,500 μg/m^3 to 18 μg/m^3 for outside the booth). These results also provide a quantitative background for the containment performances of the bulk pharmaceutical facilities evaluated in the present study. Recent computational fluid dynamics studies suggest that the exhaust has an important role to contain the compound by the designed airflow in the transfer vessel when having a local exhaust system.[8] In such an open isolation system, it appears that an understanding of the airflow is critical to ensure the containment performance. Conversely, it has been shown that particle size distributions of airborne dusts differed depending on the state of the powders, despite being of the same surrogate materials,[23] suggesting the different behavior for airborne distribution. Further study at the various conditions with different surrogate materials is required for a more comprehensive understanding of the containment performances of the open isolation systems.

Conclusion

From the measurement of the containment level of the glove box and the open containment cabinet (the open isolation system), the present study can be summarized as follows:

- The containment performances of the pharmaceutical facilities including the open isolation system, designed to a PB-ECL category of 3, were confirmed to meet the required design criteria.

- The performance of the open isolation system was complemented when using the mock-up booth, resulting in an enhanced pharmaceutical facility performance and the ability to demonstrate containment performance to reduce airborne dust.

- The importance of gowning as a secondary barrier was ascertained and it was suggested that adequate regulation for gowning during facility design should be consid-

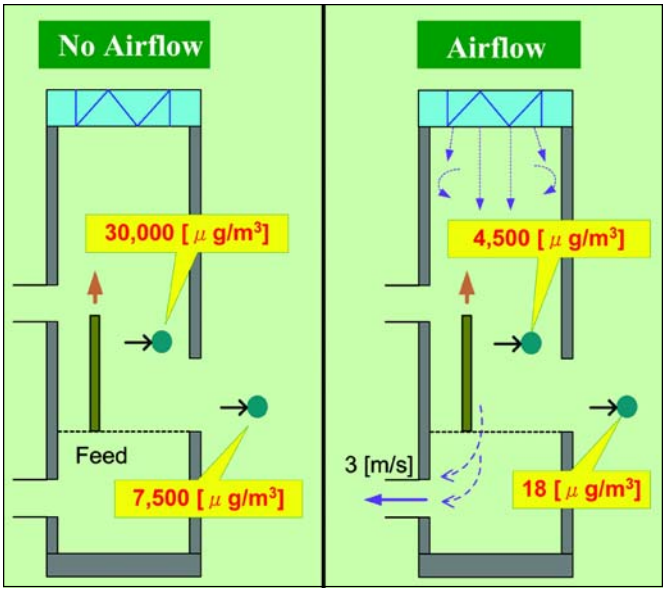

Figure 9. Containment evaluation in a mock-up open booth.

ered. The carry-over of the powder on the operators gown, after working, is one of the factors that needs to be considered for the containment design, as well as the containment of the airborne dust.

- Further evaluations of the pharmaceutical containment systems, such as aseptic isolation systems, are under way to examine the proposed containment facility design criteria based on the quantitative analyses in conjunction with the mock-up test.

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This article describes an innovative design of a fume hood control system.

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Step-Variable Air Volume Fume Hood Control - A Case Study

by Sarla M. Patel, PE and Martin J. Wendel Jr., PE

Introduction

This article describes an innovative design of a fume hood control system. This design innovation combines (for a specific chemical development laboratory facility) the best features of traditional constant volume and variable volume fume hood controls, while avoiding some of their perceived disadvantages.

Design Challenge - Laboratory Fume Hood Control

Fume hoods are critical elements in the design and operation of a pharmaceutical research and development laboratory. Fume hoods are essential in many applications to protect workers from exposure to chemical fumes or other hazardous substances. At the same time, fume hoods have a significant impact on the laboratory construction costs and operating costs because of the equipment and energy required to exhaust air through the fume hoods, and to provide conditioned ventilation air to the laboratory spaces.

One of the many important laboratory design issues associated with fume hoods is the selection of a fume hood control strategy, which then leads to the control strategy for overall laboratory airflow and pressurization. Constant volume fume hood control has been used in many laboratories for years, and is generally considered to be a solid, reliable approach to safeguard workers. For laboratories with large numbers of fume hoods, constant volume fume hood control results in enormous energy use and operating costs since the same amount of air must be conditioned and exhausted through the fume hoods whether they are in use or not (that is, whether the fume hood sashes are open or closed). More recently, variable volume fume hood controls have been developed and installed to reduce energy consumption and operating costs in fume hood-intensive laboratories by reducing air flow through a fume hood when the sash is closed. Many of these systems, which typically maintain a constant fume hood face velocity to capture fumes and protect laboratory workers, also are generally considered to be solid, reliable systems with good track records.

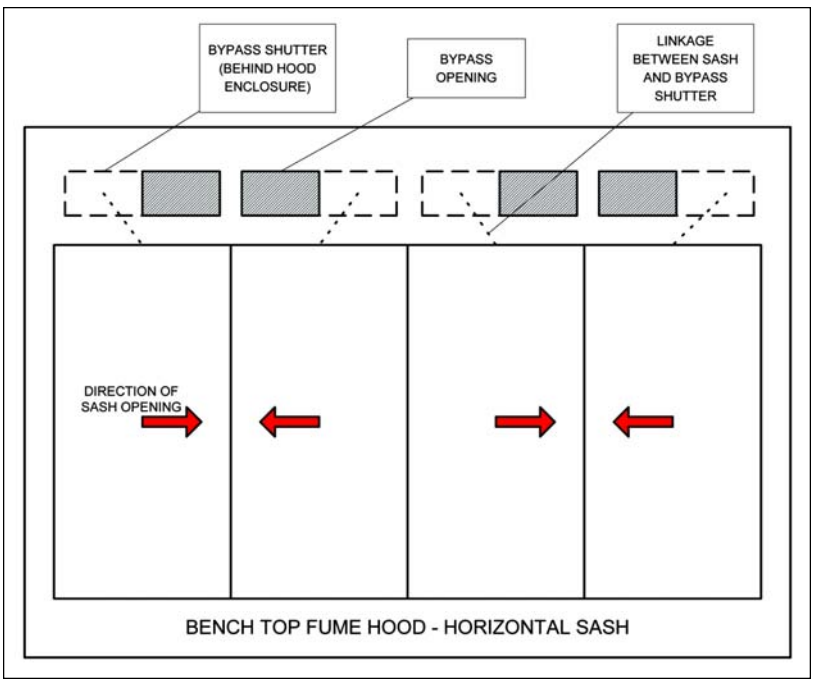

Figure 1. Bench top fume hood - shown with sashes closed.

The technical issues associated with fume hood control strategy selection can be quantified and analyzed in terms of performance, installed cost, operating, and maintenance costs. However, it is essential that this system selection (and most others) includes consideration of owner acceptance, including the scientific research community that will use the labs and the building engineers who will maintain the systems. The building design must be responsive to the needs of the people who will work in the building. Sometimes, as a result of the consideration of both human and technical requirements, the building design professional has to think outside the constraints of pre-packaged solutions to achieve design excellence. This article discusses one example of this type of innovation, and the benefits of the resulting system design.

The Case Study

The building design project was a 75,000 gross square foot (6,970 gross square meters) chemical development facility. The scientific work planned for this facility required fume hood-intensive laboratory spaces. A typical 735 square foot (68 square meters) laboratory module was planned to include a total of six fume hoods, four bench top hoods, and two walk-in hoods.

The operating profile of the fume hoods was identified by the hood users as generally being one or the other of two scenarios: sashes either 50% open or fully closed. The hood sashes would be opened 50% either when experiments are "setup" within a hood, or certain operations are performed that require the user to frequently be in-and-out of the hoods. At all other times, the sashes would be kept closed. Situations where the sashes would be partially open at a point somewhere between 50% and fully closed were not considered a "real world" condition that would occur in practice.

The building design professionals proposed to design Heating, Ventilating and Air-Conditioning (HVAC) systems accounting for diversity in fume hood use to achieve construction and operation savings. That is, if fume hood exhaust can be reduced when the sashes are closed, the exhaust systems can be sized for a diversified load since only a fraction of all fume hood sashes will be open at any one time. Since the high fume hood density in this laboratory meant that the room air change rate was exhaust-driven, the diversity also permitted reductions in supply air conditioning system and chilled water system sizing. The fume hood operating diversity was based on the agreement by the scientific researchers to institute a program of fume hood sash management so that the maximum combination of hoods with sashes open at the same time (on a per-lab basis) would be two bench top hoods and two walk-in hoods, or four bench top hoods and one walk-in hood.

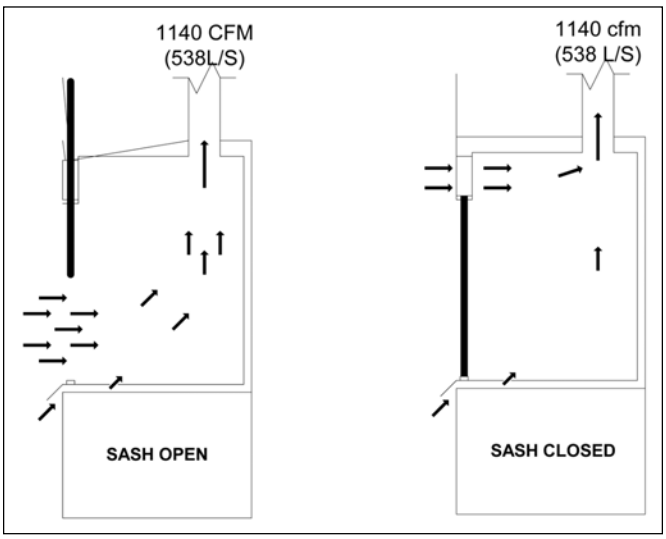

Figure 2. Constant volume bench top fume hood.

Design Criteria

The solution to the design challenge had to meet the following criteria:

1. The solution must maintain safe conditions for scientific researchers and other laboratory workers.

2. The solution must satisfy user demands for simplicity of instrumentation, controls, and operations.

3. The solution must permit reduction in fume hood exhaust airflow to allow economic HVAC system design based on operating diversity.

4. The solution must permit further reduction in fume hood exhaust airflow during operation to lower energy consumption and costs without a substantial maintenance cost penalty for ongoing component and system calibration and adjustments.

Traditional Design Alternatives - CAV and VAV Control

The two design alternatives traditionally considered for this type of laboratory facility are Constant Air Volume (CAV) control, which utilizes CAV boxes controlled to satisfy a constant airflow setpoint, and Variable Air Volume (VAV) control, which utilizes VAV boxes configured to provide variable system airflow. Since the ultimate design solution included a mix of the concepts involved in these two traditional designs, their application will be briefly reviewed.

Constant Volume Fume Hood (Figure 2)

Constant volume bypass hoods (CAV) typically feature hood sashes that operate in tandem with a "bypass" that is reverse acting with the position of the sashes. This arrangement provides a constant exhaust flow, measured in cubic feet per minute (cfm), through the fume hood regardless of the sash positions - *Figure 2*. The exhaust airflow through the hood is maintained constant through the use of a CAV box installed in the ductwork serving the hood that is calibrated and controlled to always provide a constant air volume CAV exhaust flow setpoint. This CAV box has an airflow measuring device and associated controls that modulates an "air valve" the same way a VAV box is configured. The only difference is that with a CAV box, the "control system" modulates the CAV box to maintain a programmed constant

"Sometimes, as a result of the consideration of both human and technical requirements, the building design professional has to think outside the constraints of pre-packaged solutions to achieve design excellence."

flow, regardless of "upstream" system dynamics in airflow and pressures. If we look at a typical CAV bench top fume hood, when the hood sashes are fully open, the bypass is fully closed, and the air flows through the sash opening (and airfoil). When the sashes are fully closed, the same quantity of air flows through the bypass (and airfoil). The CAV boxes are applied to the system to draw a constant exhaust airflow rate from the hood regardless of whether the exhaust air flows through the sash opening or the bypass.

CAV hoods are high energy users because there is no reduction in exhaust air out of the hoods when the sashes are partially or fully closed. No reduction in exhaust air also means no reduction in conditioned supply (makeup) air delivered to the lab to balance the exhaust air from the hood.

One energy savings alternative typically applied to CAV hoods is to index (or "set back") the hoods to a lower exhaust flow when the laboratories are unoccupied. During this unoccupied mode, the exhaust air through the hood is reduced to some percentage of full flow (60% for example), which also results in a direct reduction of supply air to the space where the hood is installed. This flow set back approach has typically been applied on a lab-by-lab basis and sometimes requires additional construction expense to provide an occupied/unoccupied indication outside of the laboratory.

One or a combination of the following methods may control the occupied/unoccupied mode changeover:

1. globally for all laboratories via a time schedule

2. manually via a hand switch provided for each hood or group of hoods

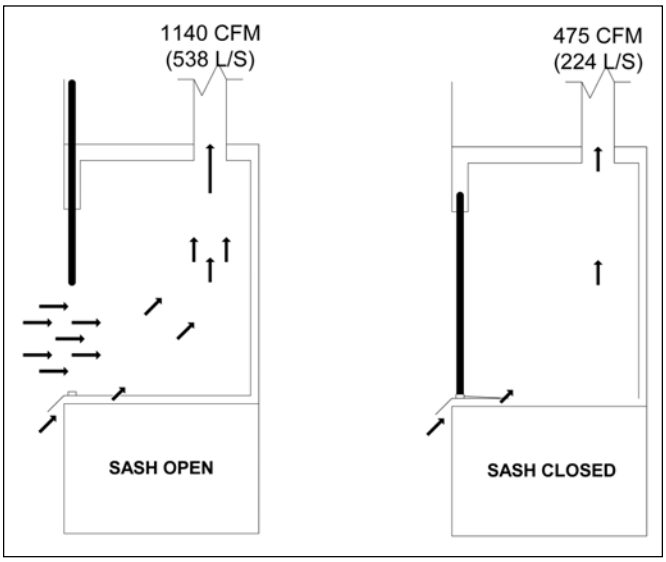

Figure 3. Variable volume bench top fume hood.

3. manually via a relay wire to the light switch in the space where the hood is installed to index the hoods to the occupied mode when the lights are turned on and the unoccupied mode when the lights are turned off.

4. automatically via motion sensor technology detecting the presence of a researcher

5. automatically via monitoring the position of the sashes to detect sash closure - unoccupied when hood sash is fully closed and occupied when hood sash is not fully closed

Variable Air Volume (VAV) Hoods

In VAV fume hoods, the airflow through the hood varies depending on hood sash position or hood differential pressure. Figure 3 depicts airflow with hood sashes open and closed respectively. In VAV hoods, the exhaust airflow through the hood is typically varied to maintain a constant face velocity through the hood sash opening through the use of a VAV box installed in the ductwork serving the hood. The supply and exhaust airflow is controlled by sensing the hood sash position or by sensing airflow via an anemometer located in the hood side wall.

Hood sash position control utilizes a potentiometer or similar position-sensing device attached to the sash through a cable. When the hood sash position changes, the sensing element responds to the change in sash position. The associated controller feeds back to the Building Management System (BMS) to determine the required air quantity and control of the exhaust air regulator to achieve a position (and corresponding exhaust airflow) that corresponds to the new sash position.

Hood side wall anemometer control utilizes an airflow sensor called a thermal anemometer to infer hood face velocity. The sensor measures air velocity passing through a hole in a side wall of the hood, which has been shown experimentally to represent an average face velocity. When the hood sash is opened, the sensor measures the reduction in face velocity and sends an appropriate signal to the exhaust air regulator, via the BMS, to increase the airflow until the face velocity setpoint is reached. When the hood sash is lowered, the sensor measures a velocity increase and sends a signal to decrease airflow.

Comparing Traditional CAV and VAV Fume Hood Control

Comparing traditional CAV and VAV fume hood control, one may observe that CAV control is free of complex instrumentation and hence inherently more reliable. The hood operat-

Hood Type	Sashes 50% Open	All Sashes Fully Closed
Bench Top	1140 CFM (538 L/S)	475 CFM (224 L/S)
Walk-In	2220 CFM (1048 L/S)	890 CFM (420 L/S)

Table A. Fume hood exhaust volumes.

ing integrity is maintained because the required amount of air is available all the time. The primary disadvantages of CAV control are the energy cost of exhausting unused conditioned air when the sashes are closed, and high air handling unit and ductwork costs since no diversity can be taken with CAV.

Traditional VAV control provides more economical operation when the sashes are less than fully open as it takes only the amount of conditioned air required to maintain a minimum face velocity with minimal bypass. Constant face velocity is maintained and continuous monitoring and alarming of face velocity is provided. However, there is an additional cost of instrumentation for sensors and controllers. Furthermore, VAV control sometimes requires a separate proprietary fume hood control system, independent of (but usually interfaced to) the BMS. This increases installed cost and operating/maintenance costs for the system.

The Design Solution

The design solution, referred to as Step-VAV control, is a combination of the best features of traditional CAV and VAV controls, while avoiding some of their perceived disadvantages.

The design solution utilized the fume hood types preferred by the researchers - *Figure 1*. The hoods were bypass CAV with taller than standard height hood sashes. Each hood was provided with four horizontal sliding sashes in a double track arrangement so that no more than 50% of the hood sash area could ever be open at any one time. Whenever a hood sash is opened, its bypass door is closed in the same proportion. Each sash door is furnished with a door switch. The door switch contact closes when the hood sashes are fully closed. The contact opens when any sash is moved from the fully closed position. As noted, there are four doors at each hood. Since the control strategy is based on detecting when all the sashes are fully closed, the position of individual sashes is not important and the fume hood manufacturer wired all switches to provide one common contact closure per fume hood. Each hood is provided with a low flow alarm light, supplied by the hood manufacturer. The low flow alarm and auxiliary alarm contacts are activated whenever hood face velocity drops below the set flow. Hood airflow cfm (cubic feet per minute) requirements are indicated in Table A.

The laboratory exhaust system is comprised of constant volume two-position air terminal boxes, one per hood. The exhaust is ducted from each hood directly to its dedicated exhaust box. The laboratory supply system is comprised of two VAV supply boxes that serve each lab module. There is a reheat coil down stream of each VAV box. Air is delivered to the room through diffusers.

Lab general exhaust was not required as the laboratory module was a "hood driven" space. This means that even when all of the hoods were closed, the minimum combined airflow setting for all hoods with all sashes closed was a value that required "make-up" supply air flow from the air handling system that was beyond that required to offset the heat gains in the laboratories.

The hood setback exhaust airflow quantity was found, through factory smoke testing, to provide good mixing conditions in the hood with air flowing through the bypass in the low flow condition.

Cost Comparison

The first cost for a constant volume hood control installation is significantly less than that of a variable air volume hood control installation for the same size hood. Table B is a summary of the major hardware elements along with "average" associated costs that comprise a typical CV and VAV control system installation for a lab module featuring two fume hoods. The HVAC system serving the model profiled here has a dedicated "exhaust box" for each hood, and a single supply air box that provides makeup air for the hoods and conditioning for the space.

Building Management System and Instrumentation Requirements

The microprocessor-based Direct Digital Control (DDC) Building Management System (BMS) monitors and controls the lab/hood air flow and space temperature. This system is an extension of the BMS used for total building HVAC system control and monitoring. This Step-VAV control design does not require a proprietary lab airflow control system.

Instrumentation requirements for laboratories using Step-VAV control are very simple compared to labs using traditional VAV control. Each exhaust box utilizes the box supplier's standard pneumatically operated two-position control product. When pneumatic control signal pressure is 0 psig (101 kPa), the box is at maximum exhaust CFM, and when pneumatic control signal pressure is 13 psig (224 kPa), the box is at minimum exhaust CFM. The pneumatic signal is provided by the BMS, 13 psig (224 kPa) when all sashes at the

Constant Volume Hood Control Installation	
Terminal exhaust box controller	$2,000
Terminal supply box controller	$2,000
Hood alarm	$1,000
Unoccupied/occupied override switch	$500
Total	**$5,500**
Variable Air Volume Hood Control Installation	
Fume hood controller with sash sensor, hood alarm panel and exhaust box control	$8,000
Lab control panel with flow tracking, supply box and room temperature control	$7,000
Total	**$15,000**

Table B. CAV/VAV hood control installation cost comparison.

hood are fully closed, and 0 psig (101 kPa) when one or more sashes is not fully closed.

Control response time of the instrumentation used to index the setback was found to be fast enough to maintain hood containment while switching the exhaust boxes between modes.

Supply boxes are controlled by the BMS supplier's standard product called a "Remote Control Panel (RCP)." This panel is a stand-alone controller and communicates on a "peer-to-peer" basis with other RCPs over a dedicated communication network. For reliability, one RCP was provided per lab. In the event of failure of a RCP, only one lab would be affected. Because the RCPs have a modular design and were sized to provide required input/output points, the cost penalty to provide an individual RCP per lab (compared to controlling several labs from one RCP) was not prohibitive. Each supply box included an airflow probe (furnished by the box suppler), a differential pressure-type airflow transmitter, a damper (furnished by the box supplier), and an electric damper actuator.

The reheat coil valve actuator is electrically operated. Space temperatures are measured by wall mounted temperature sensor/transmitters. There are also two duct mounted temperature sensors/transmitters, one in each supply duct. The reheat coil valves are controlled using space temperature sensors. The duct mounted temperature sensors are used for anticipatory BTU control of the reheat control coil valves – *Figure 4*.

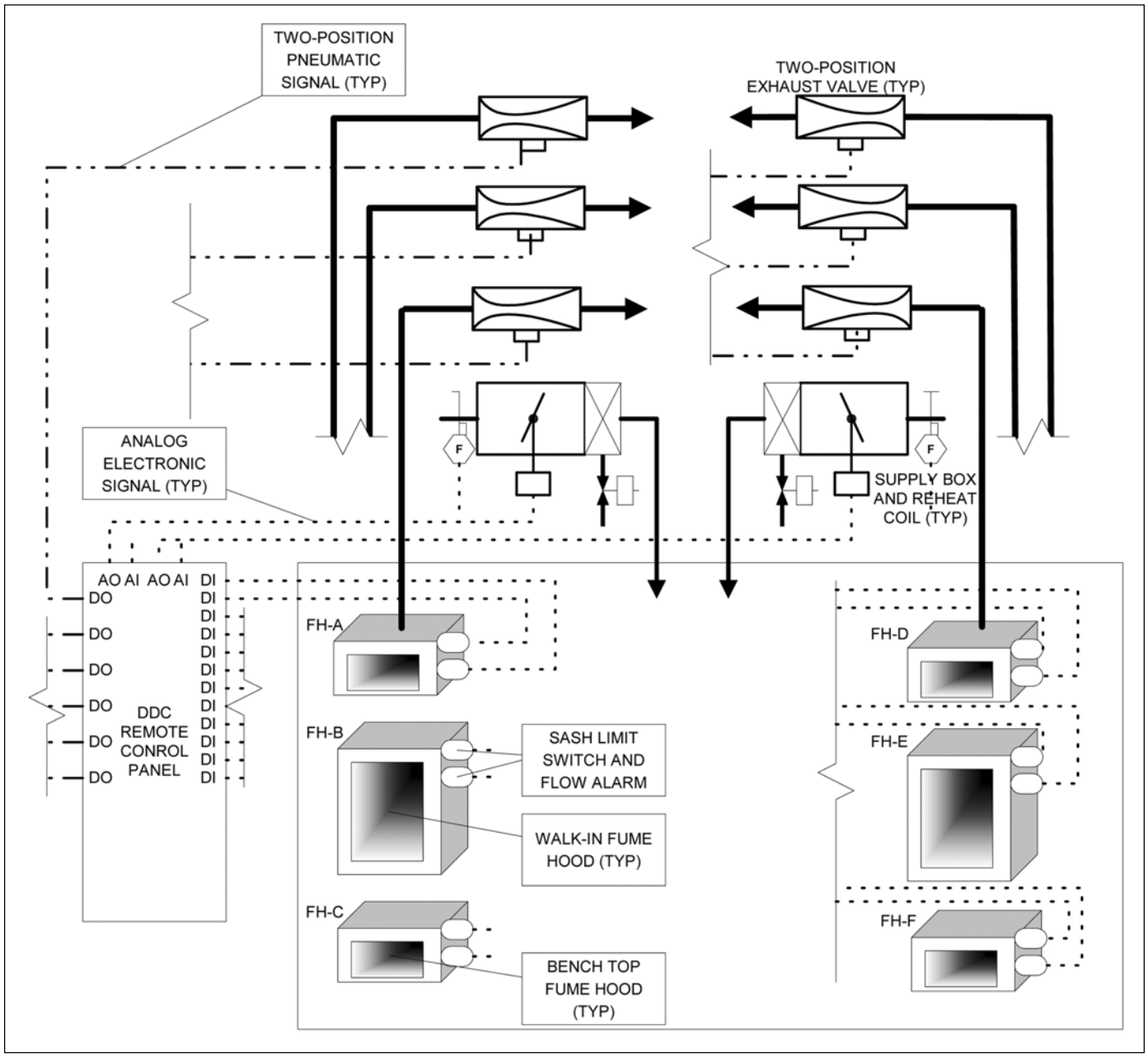

Figure 4. Typical Step - VAV Lab Module Controls.

Number of Walk-In Hoods with Sashes 50% Open <airflow>	Number of Bench Top Hoods with Sashes 50% Open <airflow>	Laboratory Air Flow Volume for this Configuration
2 <total 4,440 cfm/2.096 L/s>	2 <total 3,230 cfm/1,525 L/s>	7,670 cfm (3,620 L/s)
2 <total 4,440 cfm/2.096 L/s>	1 <total 2,565 cfm/1,211 L/s>	7,005 cfm (3,306 L/s)
2 <total 4,440 cfm/2.096 L/s>	0 <total 1,900 cfm/897 L/s>	6,340 cfm (2,992 L/s)
1 <total 3,110 cfm/1468 L/s>	4 <total 4,560 cfm/2,152 L/s>	7,670 cfm (3,620 L/s)
1 <total 3,110 cfm/1468 L/s>	3 <total 3,895 cfm/1,838 L/s>	7,005 cfm (3,306 L/s)
1 <total 3,110 cfm/1468 L/s>	2 <total 3,230 cfm/1,525 L/s>	6,340 cfm (2,992 L/s)
1 <total 3,110 cfm/1468 L/s>	1 <total 2,565 cfm/1,211 L/s>	5,675 cfm (2,679 L/s)
1 <total 3,110 cfm/1468 L/s>	0 <total 1,900 cfm/897 L/s>	5,010 cfm (2,365 L/s)
0 <total 1,780 cfm/840 L/s>	4 <total 4,560 cfm/2,152 L/s>	6,340 cfm (2,992 L/s)
0 <total 1,780 cfm/840 L/s>	3 <total 3,895 cfm/1,838 L/s>	5,675 cfm (2,679 L/s)
0 <total 1,780 cfm/840 L/s>	2 <total 3,230 cfm/1,525 L/s>	5,010 cfm (2,365 L/s)
0 <total 1,780 cfm/840 L/s>	1 <total 2,565 cfm/1,211 L/s>	4,345 cfm (2,052 L/s)
0 <total 1,780 cfm/840 L/s>	0 <total 1,900 cfm/897 L/s>	3,680 cfm (1,737 L/s)

Table C. Hood sash/lab air flow combinations.

Control Sequence of Operations

1. The BMS monitors the hood sash position for each fume hood via sash end switch contact.

2. The BMS changes each exhaust box CFM setpoint based on its sash position.

3. The BMS calculates total exhaust CFM by summing air exhausted from each hood with sash open and each hood with sash closed. Using the result, the DDC System calculates required supply air CFM (supply CFM = exhaust CFM – constant transfer CFM). As there are two supply boxes serving each lab module, each box will provide half of the total required CFM. The BMS modulates the supply box dampers to maintain the supply CFM setpoint.

4. The BMS limits supply CFM to the maximum design limit - to allow a maximum of two bench top hoods and two walk-in hoods open at the same time, or four bench top hoods and one walk-in hood. If a researcher opens sashes in more than the design allowance of fume hoods, the BMS activates a strobe light in the lab indicating "TOO MANY HOODS OPEN – CLOSE HOOD SASHES."

5. If hood sashes are not closed immediately upon activation of the strobe light, exhaust air from each hood reduces, resulting in a further drop in face velocity. When the face velocity drops to its preset low limit, a "LOW FACE VELOCITY" alarm light at each hood (provided by hood manufacturer) is activated.

6. The BMS maintains space temperature setpoint by modulating reheat coil control valves from the signal of one space temperature sensor and two duct mounted temperature sensors, one in each discharge duct in cascade mode.

Operating Reduction in Airflow

The system is designed to accommodate a maximum of two bench top hoods and two walk-in hoods, or four bench top hoods and one walk-in hood in simultaneous operation with sashes 50% open. Since the hood sashes are typically opened for experimental setup and closed otherwise, the Step -VAV design permits significant flow reduction within each lab. The required lab air flows are the sum of the flows for hoods with sashes 50% open plus flows for the hoods with all sashes closed. For example, with one walk-in hood open, the lab air flow for two walk-in hoods is 1 x 2,220 cfm (1048 L/s) + 1 x 890 cfm (420 L/s) = 3,110 cfm (1468 L/s). The different hood operating conditions and corresponding airflow volumes are indicated in Table C.

As can be seen by inspection of the values in Table C, Step VAV control for the typical labs in this case study provides stepped modulation of air flow from a maximum of 7,670 cfm (3,620 L/s) to a minimum of 3,680 cfm (1,737 L/s) in 665-cfm (314-L/s) increments. In this application, Step VAV control provides the same operating cost benefits as a traditional VAV control approach. Since the researchers typically open their hoods for experimental setup and keep them closed at other times, the lab airflow demand is stepped by its nature and any additional airflow reductions provided by traditional VAV control would be only transitory.

System Benefits

The design solution implemented for this project provides significant benefits to the building owner, including the following:

1. This design does not require the complex instrumentation and control of conventional VAV control systems, such as a VAV exhaust box controlled from hood sash position and tracking supply with each change in each hood sash position. Monitoring individual hood sash positions for the

horizontal sash arrangement with four doors is not required.

2. The first cost of Step VAV is significantly less than the first cost of traditional VAV for the same fume hood application.

3. There should be no differential cost to the Owner in the programming of Step VAV versus traditional VAV as the BMS system would have to be programmed regardless of the HVAC operating scheme.

4. This design is more robust than traditional VAV control because it is more tolerant of variations in component (such as exhaust damper) response times. Rather than trying to "chase" traveling sashes, this design provides full exhaust flow as soon as any sash is moved from the fully closed position, and maintains full exhaust flow until all sashes are fully closed.

5. Airflow control is provided by the time proven technology of the BMS (DDC System), which is simple, cost effective, and reliable, without introducing additional manufacturer's systems (that could add complexity and cost to building maintenance) into the facility.

6. It is anticipated that overall maintenance costs (typically averaging approximately $100/per sensor) will be less for Step VAV as there are fewer BMS points associated with this scheme over traditional VAV applications.

7. In this application, where the hood sashes will generally be opened only while setting up experiments within a hood and sashes will be kept closed at all other times, step VAV control is more appropriate to the owner's intended operation compared to conventional VAV. Capital cost savings and operating/energy cost savings are achieved through the simple addition of a single point, "go/no-go" measurement at each fume hood. Put another way, if a traditional VAV system were designed into the case study facility, it would be used in a manner that profiles the way a "Step-VAV" system would be used, so the operating costs would be similar. The key is, why pay the high first cost of traditional VAV if you are not going to use the system that way? The true savings are lower first cost with "Step-VAV" control over traditional VAV control.

Summary

The implemented hood control design is Step-VAV providing only the required amount of air to each hood. This minimizes the capital cost (through diversity in equipment sizing) and operating costs. The control system is simple, reliable, and easy to maintain. It utilizes the researchers' preferred constant volume bypass hoods. The only automatic sensing requires hood sash end switch position monitoring by the BMS, using simple proven technology. Exhaust flow for each hood is controlled in two steps; maximum flow when any sash is open, and minimum flow when all hood sashes are closed. In the present application of six hoods, there are 13 stepped flow conditions, providing a stepped approximation of VAV control. Supply flow is controlled by the BMS to maintain transfer airflow directionality. The installed cost of this system is lower than traditional VAV and the resulting design is very flexible.

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Redefining an Automation and Validation Strategy allowed a plant to be revised and designed for a new treatment product within three months of start-up.

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An Automation and Validation Strategy for an Automated API Manufacturing Plant

by Jorge Manuel C. Pastilha

Introduction

This article describes the design, construction, commissioning, and operation of a 200 m^3 (7063 ft^3) automated production plant for APIs meeting US FDA cGMP at Hovione, FarmaCiencia SA, Portugal.

The construction of a new automated plant was a great challenge that led the company to redefine its Automation and Validation Strategy. This new strategy allowed a plant, which had been designed to produce a single product (X-Ray contrast media), to be revised and designed for a new HIV treatment product within three months of start-up. In February 1998, the three consecutive validation batches were concluded. Three months later, the 25-day process was stable, delivering a new batch every 72 hours and a successful FDA pre-approval inspection was complete.

An increasing demand for safety and quality require that these factors are embedded in the manufacturing process, and therefore, in the product. Automation of manufacturing processes, when implemented under quality rules, has proven to be an important factor both in increasing safety and quality of the environment and the efficiency of the manufacturing process itself.

Initial Design

"The biggest problem found in most projects is a lack of clear and complete scope definition.[1]" Based on the concept that the initial project steps are critical for success of a project, the company increased the effort during the design phase.

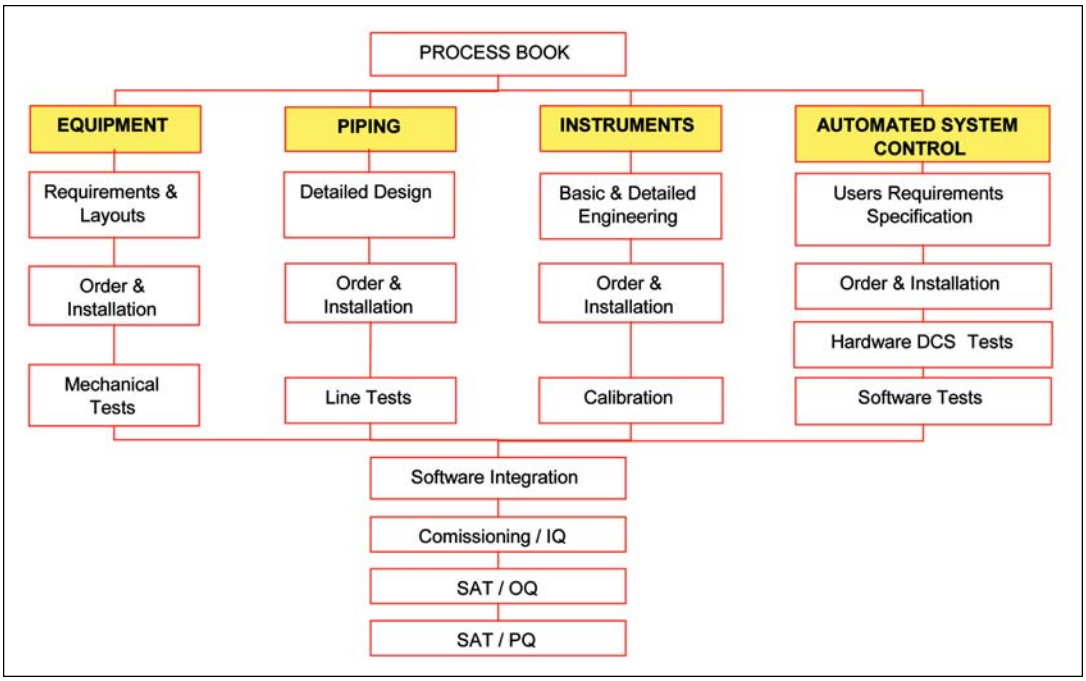

Figure 1. Parallel tasks during Validation of an Automated API Plant.

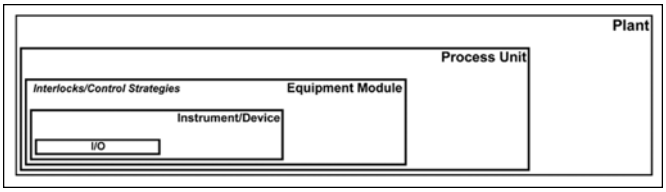

Figure 2. Overview of the Automation Strategy.

Definition of User Requirement Specifications

A key document, "Process Book/Basic Engineering," was approved almost a year after the first steps to clarify the rationale of the project and its location were taken. This document described in concise terms the X-Ray contrast media production process, and presented the main equipment to be installed with specifications, which together constituted the User Requirement Specifications.

The dimensions of the project clearly indicated that a completely new approach to validation was necessary:

- 21 reactors, 6 centrifuges, 3 dryers, more than 20 tanks, liquid film evaporator, reverse osmosis systems, a production and distribution purified water system, cleanrooms, etc.

The introduction of a high level of automation (the intention was to operate the installation from a central control room) also supported the need for a new approach.

Definition of Responsibilities and Creation of a Dedicated Team

The project required a multidisciplinary team, but defining the precise membership of the team proved one of the most difficult decisions of this initial phase. Ultimately, a team of highly motivated engineers with experience in several disciplines was created in conjunction with guarantees of 'top-level' involvement. The following three sub-teams were then identified:

1. Project and Construction
2. Automation
3. Validation

Planning Activities - The Importance of Parallel Paths

Due to the high level of automation, it became clear that automation and validation tasks (Figure 1) needed to be executed concurrently with the construction and commissioning of the facility. It was equally important that the timing of these tasks was communicated effectively to all members of the team.

Automation and Validation Strategy

Knowing the timeline and the resources involved proved essential and the project team decided to make the project an opportunity to develop an Automation and Validation Strategy.

Automation Strategy

The automation strategy focused on modularity which provided a simple solution for the complexities involved in the design, construction, commissioning, validation, and renovation of the automated API plant.

The modularity concept was applied in three distinct areas:

1. Equipment, Materials, Instruments and Spare Parts (Project and Construction)

2. Functionalities (Automation)

3. Documentation and Tests (Validation)

Modularity meant:

- proven technology and reliable equipment
- reduced number of different materials
- instrumentation should be nearly identical
- devices (valves, pumps and motors) must be normalized
- functionality (heating, cooling, temperature control, pressurization, depressurization, vent, charge materials, discharge, etc.) should be as generic and as versatile as possible, while, at the same time, simple
- the Project Team must agree on standard formats for specifications and testing documentation.

Advantages of the modularity concept:

1. guaranteed uniformity along the time between projects
2. meeting of the quality requirements
3. reduction in the implementation, testing, and validation
4. reduction in the number and cost of spare parts
5. reduction in the time required for training of operation and maintenance personnel

Example Application of the Modularity Concept

A reactor is composed of a vessel, an agitator, discharge and thermal fluid pumps, on-off valves, control valves, condensers, piping, and field instrumentation. Reactors can have different volumes, be constructed of different materials, and have different quantities of valves or associated piping. Such variations may cause individual reactors to be considered unique.

The pumps, valves, and motors that compose the reactor are considered generically as devices. The communication between the Distributed Control System (DCS) and the devices is achieved through electrical signals, known as Inputs/Outputs (I/Os).

The devices may be grouped according to their functionality on the reactor (such as adjusting temperature, controlling pressure, and charging material in the reactor). These functional groups of devices are designated as Equipment Modules (EQMs).

Each equipment module performs a different action, such as heat, cool, or maintain temperature; pressurize, depres-

"Once validated, a module is approved and released, may be duplicated or cloned, in various combinations, providing great utility and flexibility."

surize, or maintain pressure, charge, discharge, or agitate. Each action causes the DCS to act on the devices to achieve the expected result (Setpoint) for a specific variable (e.g., temperature, pressure, or level) measured by a field instrument. Each action will be executed in a specified way that constitutes a 'control strategy.' To ensure both equipment and personnel safety, interlocks are created at the equipment module level.

A reactor is generally designated as a process unit, which groups the equipment modules with the different control strategies and provides all necessary interfaces between the control system and the operators.

The strategy followed for a reactor can be applied to other process units, such as tanks, dryers, or centrifuges. Figure 2 shows an overview of the automation strategy. A **plant** is regarded as a group of **process units**, each consisting of **equipment modules** that are functional groups of **field instruments**, and **devices** that communicate with the field instruments through the **I/Os**.

Each box shown in Figure 2 corresponds to a software module that must be fully documented, developed, and tested. Once validated, a module is approved and released, may be duplicated, or cloned, in various combinations, providing great utility and flexibility. For example, if a plant has one thousand 'fail close on-off valves with closed limit switch,' then one generic valve will be documented, developed, tested, and approved. This will be 'cloned' one thousand times, assuring that all valves have the same behavior.

Validation Strategy

The project development phases were performed in parallel to, and partially overlapping with, the validation activity phases of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

The aim of the company was to develop a strategy that allowed automation and validation of new API plants without repetition of much of the work.

Figure 3 shows the steps, support documentation, and validation phases for the implementation of an automated system. Four phases in the implementation of the automated system were recognized:

- **Phase 1** - Preparation and release of Generic Tools
- **Phase 2** - Application and customization of Generic Tools for a specific project; installation and connection of system hardware, testing of functionality
- **Phase 3** - Validation of the system for the production of a specific product
- **Phase 4** - Production support and system maintenance

Phase 1: Preparation and Release of Generic Tools

All functionality that may be applicable in more than one project, had to be defined, programmed, and tested during Phase 1.

Examples of functionality that were considered "Generic Tools" and which needed to be developed during Phase 1, included:

- functioning of valves, motors, or pumps
- grouping of valves by function
- methods of cooling or heating equipment
- rules for user access
- alarming, trending, and reporting policy
- security procedures (backup and restore)
- recording of the audit trail

Step 1 consisted of defining documentation for generic system functionality (Generic Tools). Step 2 consisted of designing and implementing the Generic Tools, which were documented in the Design Specifications. Step 3 consisted of testing the functionality defined in Step 1, following the procedures given in the Generic Test Procedures. After functionality was assured (all tests had passed), the corresponding Generic Tools were considered released, and therefore, ready to use in the next phase.

Civil works	Sep 1995 - Feb 1997
Mechanical construction	Nov 96 - Aug 97
Instrumentation installation	Feb 97 - Oct 97
Automation Project definitions and Quality plan	Sep 96 - Mar 97
Automation "Generic Tools" development and implementation	Nov 96 - Oct 97
Graphics, Functional and Design Specs, Database Generation and Implementation for X-Ray product	Apr 97 - Jul 97
Re-engineering for the new product	Sep 97 - Nov 97
FDA Pre-Approval Inspection	Mar 98
500 kg batches, one every 72 hours	Jun 98
500 kg batches, one every 48 hours	May 99

Table A. Building 15-key dates.

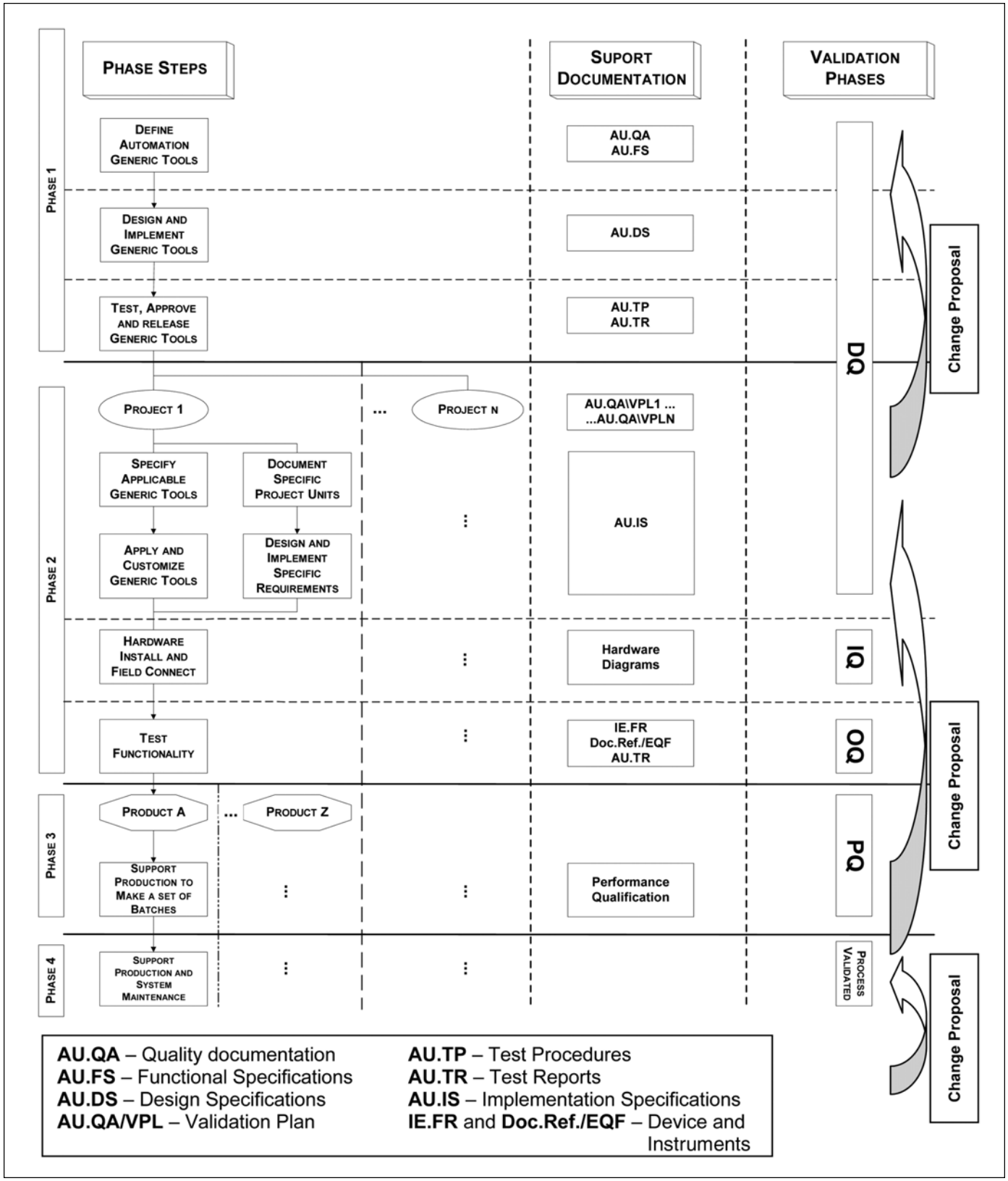

Figure 3. Implementation Phases for an Automated System.

Phase 2: Application and customization of Generic Tools for a specific project; installation and connection of system hardware, testing of functionality

This phase consisted of developing the automated system for a specific project, using the released Generic Tools, complemented with specific documentation.

Each project required specific documentation:

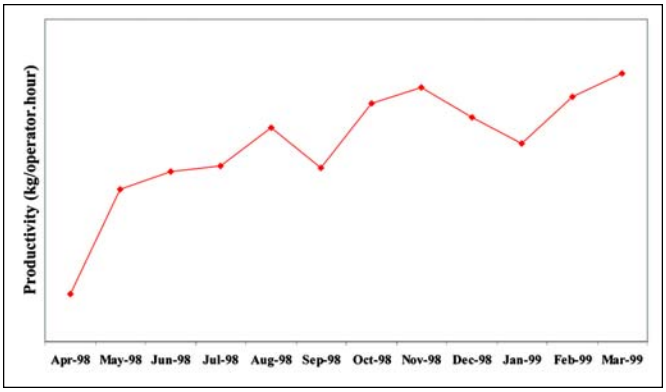

Figure 4. Productivity: Process Control Learning Curve and Training.

- Validation Plan: detailing the validation activities to be carried out and the list of tests that were applicable to the project

- Implementation Specification: defining which Generic Tools were applicable and corresponding customization

If a Generic Tool did not deal with a situation, Step 1 of Phase 1 was initiated to produce and release a new Generic Tool or revise an existing one, according to a defined Change Control procedure. Completion of customization concluded the Design Qualification.

Hardware installation, field connection, and corresponding tests composed the Installation Qualification.

Finally, system functionality for this specific project had to be tested. After functionality is assured (all tests have passed), the Operational Qualification is completed (ready to start production).

Phase 3: Validation of the system for the production of a specific product

The third Phase consisted of verifying the system capability to execute one specific product, through the production of a set of batches. This Phase occurs each time a new product is to be produced.

Whenever the adaptation of the installation or automated system was necessary to meet the process requirements, Phase 2 had to be initiated according to a Change Control procedure.

When the set of batches was successfully completed (indicating that the installation and automated system fit the process needs), Performance Qualification was considered complete.

Phase 4:

This Phase refers to regular validated process production and consisted of support of production activities and system maintenance.

Design Qualification (DQ)

This means ensuring that the plant has been designed in accordance with the Guidelines, as specified, and documented evidence exists to demonstrate this.

The sequence of activities during this stage included:

a) Piping and Instrumentation Diagrams (P&IDs); all piping design documents are validated through the signature of qualified technical personnel and changes can only be done through a Change Control system.

b) All purchases are validated through the signature of qualified personnel authorized for technical aspects. Instruments and electrical components are defined on instrument list and purchase takes place based on the approved technical data sheets from the supplier.

c) Visits to suppliers before purchase and tests done by suppliers are also part of the design validation process.

d) Safety aspects also are to be validated under the responsibility of a specific working team. HAZOP will allow the definition of efficient operating procedures, reducing the underlying risks to the process and people. Once the main risks are identified, the possible minimization and control alternatives are studied, and the project is adjusted if necessary, to ensure the accomplishment of the applicable safety and environmental protection limits.

At this validation stage, all Functional Specifications (Phase 1), corresponding Design Specifications (Phase 1), and Implementation Specifications (Phase 2) are prepared and approved.

Installation Qualification (IQ)

Examples of activities that were carried out during this phase included confirmation of the system layout, mechanical integrity, and wiring continuity.

Operational Qualification (OQ)

For each specific project, all the applicable functionality had to be defined in the Implementation Specifications and all the corresponding tests had to be listed in the Validation Plan.

Testing of the equipment operability (such as heating capabilities of a reactor) was carried out in parallel with qualification of the related control system.

Performance Qualification (PQ)

Performance acceptance of the automated system was part of a Performance Qualification Report for a specific product.

Use of GAMP and 21 CFR Part 11

The validation methodology followed was based on the Good Automated Manufacturing Practice (GAMP) Guide[2] and 21 CFR Part 11[3] and it is application to all Phases of the automated system implementation – *Figure 3*. These documents helped to develop a high-quality documentation system.

The documentation was used to verify and provide evidence that the defined project execution was followed and that the implementation had been documented and tested against the functional requirements. All validation activities

were conducted according to written procedures.

At the end of the validation, a "Validation Report of Manufacturing Facility" summarized all the validation work that had been performed.

Advantages of Starting Training in the Early Stages of the Project

From the early stages of the project, the company ensured that the people assigned for the design, construction, installation, and validation activities were fully qualified and trained to assume such responsibilities.

To ensure the success of the project, and its benefits, a successful production team had to be provided. The company production teams were accustomed to manual installations and to adapting these to an automated plant. All production operators were intensively trained, and participated in the system validation during the Operational Qualification. The advantages were obvious: the production teams became familiarized with the automated system, the equipment, and with the techniques of dealing with an automated plant.

Change Control

Modifications could significantly change performance capability and in some cases, they could completely alter the characteristics of a process. Therefore, a change control system had to be in place.

This required a formal monitoring system by which qualified representatives from appropriate disciplines could review proposed changes that might alter validated status and take preventive or corrective actions to ensure that the validated state of a system would be maintained.

Case Study Details

In 1995, the plant was initially and specifically designed to produce a single product. A decision to produce a new different product was made in September 1997. The challenge was to adapt the building, known as Building 15, before the end of October 1997. The building had a surface area of 4500 m^2, composed of manufacturing areas (production, utilities, control room, I/O rooms, and motor control centers) and supporting areas (offices, laboratories, dressing rooms, and social area). Table A presents the most important dates, including the design, implementation, validation, and production phases.

The decision to have a highly automated plant, had a high cost at different levels:

- investment was about 8% of total plant value
- an excessive number of personnel at every phase except operation
- increased space required {350 m^2 (3767 ft^2) for system and electrical cabinets and 50 m^2 (538 ft^2) for control room}

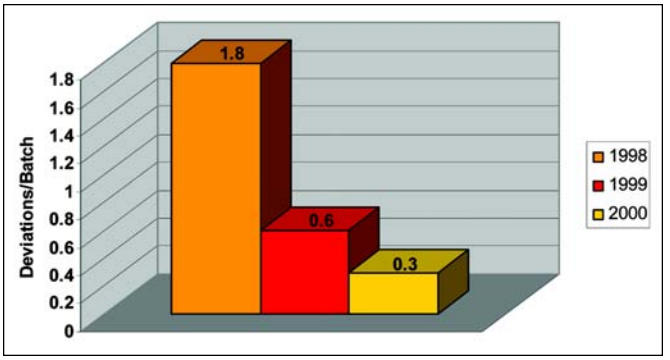

Figure 5. Reducing Deviations.

- engineering and technical documentation required considerable care with methodology and evidence of compliance with procedures

A large number of documents were prepared during the building's design, including:

- 247 wiring diagrams
- 2000 loop diagrams
- 320 functional specifications
- 290 design specifications
- 184 test procedures

Validation of an automated plant is more time consuming than that of a manual plant. The validation of Building 15 took 12 months and required more manpower and more qualified personnel. Qualified personnel from Instrumentation, Production, Maintenance, and Quality performed the validation 24 hours a day.

All operators working in the building had been operators in manual plants. There was no resistance to change when moving to an automated plant although intensive training was necessary and involved 2,000 hours of training, averaging 60 hours of training per operator.

Conclusion - The Success of the Automation and Validation Strategy

The record has shown that the decision to have a highly automated plant proved to be the correct one. Re-engineering of the building for a new product was possible in the short time period because of the key options taken several years before, namely the Automation and Validation Strategy.

There are tangible and intangible gains that can be directly related to the high level of automation and the validation strategy followed. The most important tangible gains are:

a) Higher productivity - Building 15 has a productivity level four times higher than comparable manual installations. Figure 4 shows that productivity (measured in kg of product per man-hour) improves with time.
b) Reduced number of deviations. Deviations due to human error tend to zero very quickly, as shown in Figure 5. A deviation always carries a high cost, due to the number of activities and the number of people involved in:

- Description
- Investigation
- Corrective action
- Follow-up
- Closure

Important intangible gains to consider include:

- reproducibility and liability
- yields vary less and improve with time
- process variables and actions can be continuously registered
- process data is very easy to consult and compare, which allows a rapid learning process
- ensure best-practices are adopted
- operations are safer and in case of an accident the actions can be taken automatically

Emphasis must be placed on developing the correct Automation and Validation Strategy. This provides a powerful and systematic "tool" that reduces the efforts of implementing or re-engineering an API plant by reusing fully qualified software modules and related documentation.

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About the Author

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This article provides an overview of CIP as well as a basis for establishing the flow rate for equipment cleaning.

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Practical CIP System Design

by David Greene

Introduction

"Rules of thumb" are often used to determine the flow required for cleaning equipment and pipelines in the biopharmaceutical industry. These "rules" may conflict when the desire to maintain supply and return line velocities results in accumulating liquid in the equipment being cleaned. This article provides an overview of CIP as well as a basis for establishing the flow rate for equipment cleaning.

Purpose of CIP

Clean-In-Place (CIP) is the term used in the biopharmaceutical industry to refer to the process of cleaning process systems and equipment without major disassembly of components. In addition to cleaning, CIP also assists in Steam-In-Place (SIP) operations by removing chlorides and proteins. Leaving chlorides could cause stress corrosion when heated and residual proteins would be "baked" on to surfaces when denatured by steam.

CIP involves a specific combination of predetermined manual and automated operations to perform the cleaning, monitor the operations, and document the results. The state-of-the-art involves a series of dedicated CIP skids, each assigned to a particular process area or function, with its own piping system. Figure 1 shows a typical, but simplified, CIP system with the appropriate instrumentation and valves.

A properly designed CIP system will use the minimum amount of water, chemicals, and utilities, and produce the minimum amount of effluent. It will improve safety and reduce maintenance by removing human error and provide documentation for validation by ensuring reproducibility with minimal operator intervention. It will maintain product quality and reduce turn-around time between batches.

Time

Typical biopharmaceutical production operations are based on operating 24 hours per day seven days a week, commonly referred to as 24/7. CIP is only part of a typical 8-hour turnaround (from dirty to clean) cycle, which also includes SIP and the associated heatup, cool down, and integrity testing. The majority of the time is for heating and cooling before and after SIP, but the time for CIP is important in determining the number of CIP systems required.

Factory Acceptance Tests (FATs) typically test the effectiveness of spray balls through the use of a Riboflavin coverage test. This test ensures that the vessel internals are thoroughly wetted by the spray balls, but it does not ensure that the tank will be cleaned by the plant CIP system.

Fixed sprayballs can normally achieve successful coverage test results in 30-90 seconds based on a 15-20 GPM (3-5 m^3/hr) flow and a ΔP of 25 psi (1.7 bar) per spray ball (the number of spray balls is determined by total flow requirements and discussed later). The test is done by spraying a dilute (0.2-0.3 g /L) Riboflavin solution onto vessel internals, allowing the Riboflavin to dry, and then using the spray balls to remove the residue. After the desired time interval, the tank is inspected with a UV light to determine that the Riboflavin has been removed.

Ideally, the test would be successfully done at 15 GPM (3 m^3/hr) per spray ball and 30 seconds to allow for a safety factor and provide for the possibility of increasing the number of holes in the spray balls if the original drillings did not achieve the required coverage.

Because the basis of cleaning is the coverage test results, it's common to use a safety factor of 2-3 on the test time and use the same time for all steps in the CIP cycle. Based on six cleaning steps of 5 minutes each and an allowance for set-up, air blows, heating, and chemical additions, the time to clean a circuit containing a major flow path (tank) and a few minor flowpaths (dip pipe or transfer line) is about 90 minutes.

A thorough analysis of diversity is required to analyze all utility systems including CIP. A

process simulation is performed to determine simultaneous usages of utility systems to ensure that adequate water supplies are provided. The simulation is also used to determine the number of CIP units required to operate simultaneously which will affect both the diversity of operation and the instantaneous need for Deionized Water (DIW) and Water For Injection (WFI).

Temperature

If proteins are present, the pre-rinse should be done at ambient temperature to remove as much protein as possible without denaturation. Subsequent rinses and washes should be done at higher temperatures, typically 140-180°F to improve solubility of other types of contaminants. The temperature is typically raised with a sanitary steam-heated shell and tube heat exchanger.

Solution Concentration and Type

Except for the final WFI rinse, the rinses and washes will consist of ambient DIW. After the pre-rinse, the other solutions will be heated to 140-180°F. A detergent should be selected based on its ability to solubilize residue and the ease with which it can, in turn, be removed. The alkaline wash is usually made up to a 1-2% caustic concentration while the acid wash may have a slightly lower concentration of acid, typically phosphoric, to neutralize residual caustic and remove calcium and magnesium carbonate deposits.

Satisfactory cleaning results can be obtained using a fairly wide range of chemical concentrations. However, to use cleaning solutions of different concentrations, it will be necessary to validate their efficacy over the range of concentration expected.

Solutions can be made from commercially available (typically food grade) bases and acids or proprietary solutions can be purchased from firms specialized in cleaning biopharmaceutical equipment.

Surface Characteristics of Equipment

Historically, there has been disagreement as to the advantage of polishing compared to mill finish. The advocates of using mill finish maintained that microscopic scratches provide surfaces for protein and other contaminant adherence. Although this may have been true for mechanical polishing, this is not the case for electropolishing, where the sub-microscopic "scratches" are too narrow for contaminants to hide.

Internal Finish

Cleaning is a chemical rather than mechanical action. Since it's important to minimize surface degradation caused by mechanical forces and/or chemical action, sufficient, but not excessive chemical concentrations, temperature, and force are applied to the surfaces being cleaned.

The typical biopharmaceutical finish is approximately 15 Ra (Roughness Average) µ-in (0.38 µm) electropolished 316L SS. This is produced by mechanically polishing the mill finish to 25 Ra µ-in (0.6 µm) (max) surface roughness and then electropolishing. Electropolishing will both smooth the surface and reduce the differential between the microscopic peaks and valleys. After electropolishing, the surface roughness is typically reduced by 50% to 15 Ra µ-in, but smoothing of the peaks is more important than the actual Ra value.

In addition to finish, careful attention must be given to details such as dip pipes, agitator couplings, baffle attachments, and nozzle connections to eliminate pockets and dead ends, provide smooth, crevice-free joints, and make equipment self-draining.

Flow Rate/Turbulence

Tanks

Spray balls are quite effective for cleaning equipment such as tanks when properly designed for the particular application. Low-pressure spray is generally adequate since cleaning is performed by a deluge/cascade/soak (chemical) action and not by mechanical (impingement) force. The function of the spray balls is to distribute the washes and rinses to the top of the tank, wet all surfaces by a combination of spray and falling film, and allow the chemical action to take place. It may be necessary to add a removable spray ball at a low elevation to clean agitators, spargers, or side mounted nozzles located in the lower portion of a tank, but generally, top mounted spray balls are sufficient. The top spray balls should be located a minimum of 6" above the highest liquid level to avoid the possibility of process fluids entering the spray ball when not in use and plugging the holes. Although some manufacturers say they simulate a tank head and drill spray balls with holes directed at specific nozzles, off-the-shelf spray balls generally provide adequate coverage with approximately 1 spray ball for every 10-15 ft^2 (1-1.5 m^2) of cross sectional area.

Spray balls are typically sized for 15-20 GPM (3-5 m^3/hr) each and a 25 psi (1.7 bar) ΔP. Performance is generally based on a coverage test. The plan for coverage testing should be based on the lower flow rate to allow flexibility. If full coverage is not obtained during the test, additional holes can be drilled without affecting the allowed pressure drop. Increased pressure is not desirable because it may cause atomization, which would be detrimental as small liquid particles would need additional time to coalesce and produce a cleaning film on the tank walls.

It is best to operate multiple spray balls at the same time. Because of the flow-pressure characteristics of the centrifugal supply pumps, it is important to design all paths within a circuit for the same flow rate. This may require splitting the flow to spray balls. If this is the case, cycling between multiple paths should be performed at frequent intervals, say 30 seconds, to provide a reasonably consistent coverage of internals.

An estimate of the CIP flow rate for cleaning tanks is obtained by requiring a Reynolds Number > 2100 for the film of fluid running down the tank walls. *In Principles of Chemical Engineering*, studies show that with a given film viscosity, mass flow rate and wetted perimeter, Re_f is the same whether or not a cylinder is full.[1]

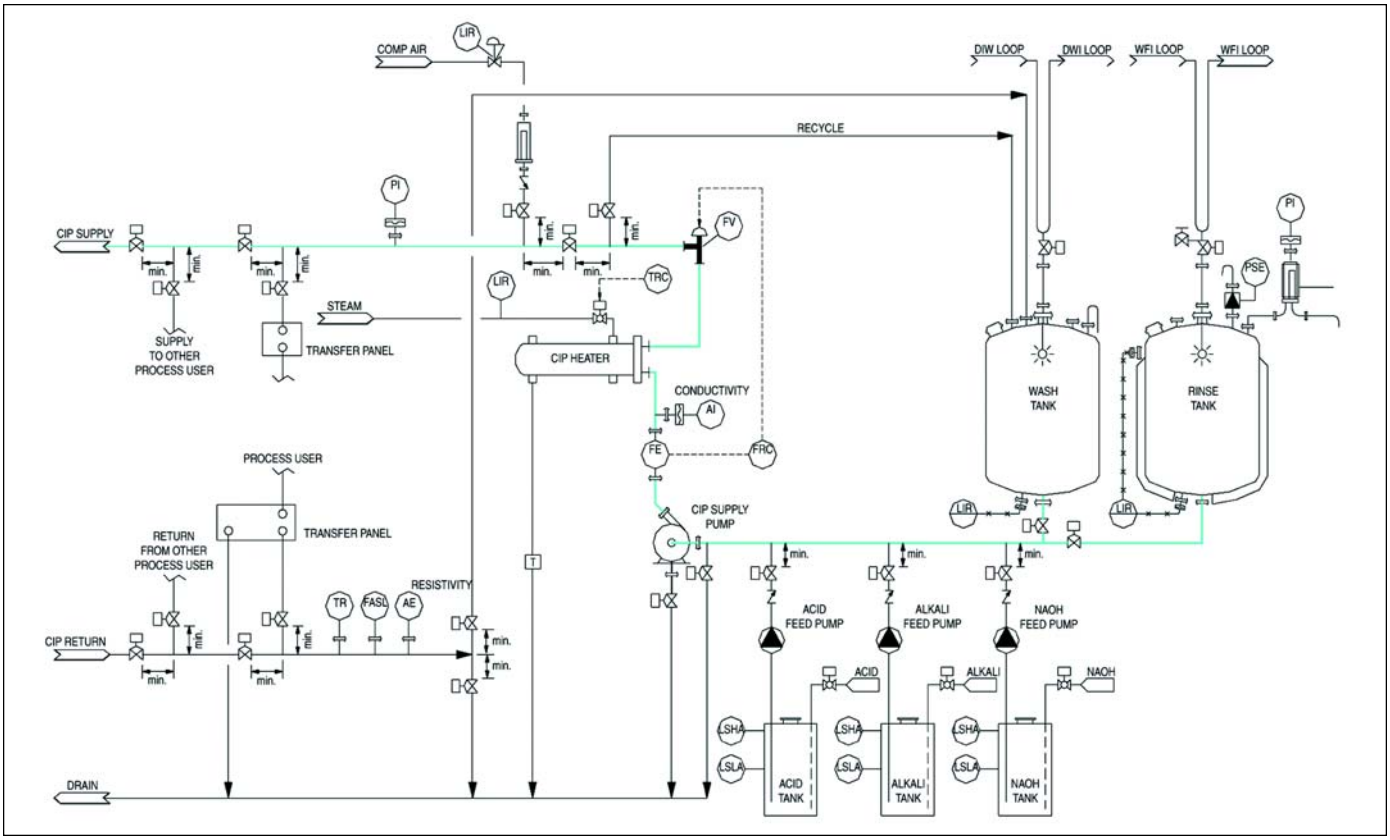

Figure 1. Typical CIP system.

$$V = \frac{m/\rho}{\pi D t} = \frac{m}{\rho \pi D t}$$

$$D_H = 4R_H = 4 \times \frac{\pi D t}{\pi D} = 4t$$

$$\mathrm{Re}_f = \frac{D_H V \rho}{v} = \frac{4tm\rho}{\rho \pi D t \times 0.000672\mu}$$

$$\mathrm{Re}_f = \frac{4m}{\pi D \times 0.000672\mu}$$

$$\mathrm{Re}_f = 5952 \frac{m}{W\mu}$$

where:

	D	Tank Diameter, ft
	D_H	Film Hydraulic Diameter, ft
	m	lb mass per second
	Re_f	Film Reynolds Number
	R_H	Film Hydraulic Radius, ft
	T	film thickness, ft
	V	velocity, ft/hr
	W	vessel circumference, ft
	μ	viscosity, cP
	v	viscosity, lb/ft-sec
	ρ	density, lb/ft^3

This equation can be rearranged and rounded to produce:

GPM / ft = 2.5μ or m^3/hr/m = 2μ

This relationship indicates that considerably less hot fluid is required, when compared to cold fluid, to achieve the same coverage. For example, water viscosity is 0.35 cP at 180°F (80°C) and 1.0 cP at ambient conditions. In terms of absolute values, a 7'-6" diameter vessel would require 25 GPM (5.5 m^3/hr) for a hot rinse and 75 GPM (17 m^3/hr) for a cold rinse.

Lines

Diffusion and convection are the controlling elements of cleaning kinetics and indicate that flow need not be turbulent to clean the straight portion of a pipe. However, turbulence will increase fluid movement to the surface where the solvent can mix and react with protein or other contaminants and also assist in moving the resultant mixture away from the surface.

For tube diameters > 1", a velocity of 0.5 ft/sec (0.2 m/s) is sufficient to achieve turbulent flow. However, other considerations may govern the selection of a suitable velocity. For example, the velocity must be greater than the saltation velocity to remove larger and heavier particles and high enough to entrain gas bubbles in case a portion of the line is not self-venting. The higher velocity in the main run of the pipe also provides better flow into dead ended branches for cleaning when maximum distance criteria are followed. Therefore, the traditional recommendation (not a requirement) of the 3A–Dairy[2] standard for a velocity of 5 ft/s (1.5 m/s) seems

"Historically, there has been disagreement as to the advantage of polishing compared to mill finish."

valid. This velocity should be based on the largest diameter when flowing through different diameter pipes or tubes in series, but if there is more than a one line size change, the circuit should be split to accommodate the different flowrates needed to achieve similar velocities.

Design for Cleaning

Piping

Threaded and flanged connections should not be used as contaminants can accumulate in the threads or the pace between flanges and gaskets. Ideally, the system should be completely welded.

Return lines should have as much slope as possible (preferably 2% but a minimum of 1%) to both encourage gravity draining and discourage air pockets from forming which would prevent cleaning fluids from reaching the surfaces to be cleaned. Pockets must be eliminated in design and fabrication by firmly supporting the lines to maintain the desired slopes.

Branches should join the return header with minimum dead legs.[3] Dead legs and pockets can retain dirt or even cleaning chemicals which will prolong the cleaning cycle or require additional rinse or wash fluids which increase both the plant effluent and the DIW and WFI usage.

Lines should be cleaned individually or in series. Do not attempt to clean lines in parallel since it is difficult to ensure that minimum velocities are achieved in each path and it might be possible for one path to backup into another and actually impede cleaning.

No permanent connections should be provided between CIP and the process: transfer panels, hoses, or mix-proof valves should be used to make and break connections. Use sanitary clamped connections at transfer panels and hoses: bolted for rarely opened and thumb screw for often opened.

Proximity switches or sanitary pressure gauges are used to confirm paths and prevent mis-operation and/or unsafe operation of the CIP circuit.

CIP Skid

The CIP skid normally contains a tank for rinse and chemical solutions. It also may contain a tank dedicated to WFI for the final rinse or WFI may be provided by a common tank to support several CIP skids. A circulating pump, heat exchanger, and chemical day tanks, along with piping and controls, complete the skid. Tanks should contain a means to disengage any air returned to the skid. Provide cleaning (spray) for CIP tanks since the tanks can be the dirtiest part of the system.

Return pumps can be mounted on the CIP skid if the skid is close to the process user(s), but this function is normally provided by pumps located close to the process equipment. The pump pressure and flow rate should be monitored to confirm circulation rate.

Tank Diameter	No. of Spray Balls	GPM	CIP Line Sizes	Tank Outlet Size
3′- 4′	2	40	11/2″	2″
4′-6′	3	60	2″	21/2″
6′ - 10′	4	80	21/2″	3″

Table A. CIP system design.

Filters

Since filters are hard to drain, it may be necessary to remove, and possibly discard, the cartridge for cleaning and then reinstall a new one before sterilization.

Accumulation

Equipment and lines should be free draining to avoid a "bathtub ring" effect. Even over-sized bottom nozzles and valves require a driving force of differential pressure to overcome dynamic losses. Return lines are typically undersized to satisfy the minimum velocity requirements. The result will be accumulation in the tank, and there is a possibility that dirt will accumulate at the air-liquid interface. Outlet nozzles and lines should be sized to minimize accumulation using valve data and appropriate engineering equations.

Accumulation or backup in a tank can be estimated by hydraulic calculations.[4]

$$h = \left(\frac{GPM}{19.636kd^2} \right)^2$$

Valve Characteristic

$$\Delta P = \left(\frac{GPM}{Cv} \right)^2$$

Combining these two equations and substituting k=0.61, the following backup is required to flow through a given valve and nozzle.

$$h = \left(\frac{GPM}{3.5d^2} \right)^2 + 28\left(\frac{GPM}{Cv} \right)^2$$

where

h = backup, in

d = nozzle diameter, in

If there is accumulation in the target tank, the supply tank may empty and stop the cleaning cycle until the accumulated

volume drains back to the supply tank. When this happens, the cycle time will be extended, adversely affecting the reproducibility of the cleaning cycle. Rather than increase the quantity of cleaning chemicals, which may require additional rinse volume and increase effluent quantity, the preferred approach is to remove the restriction at the tank exit.

The combination of sprayball and line size criteria results are shown in Table A.

The process tank can be pressurized to provide the head required to overcome resistance in the outlet nozzle and valve, but it is difficult to control the pressure to maintain the liquid level just at the outlet nozzle entrance. If the pressure is too low, accumulation will still occur, and if too high, there will be additional air entrainment, which will reduce the capacity of the return line and may interfere with cleaning.

There are some who suggest that starting and stopping the CIP feed pump can be used to remove accumulation, but this merely makes the accumulation move up and down the tank wall. It does not eliminate the problem. It also requires a sophisticated control system to keep track of the cleaning time if the system is continuously stopped and started. The solution is to use a return pump to overcome the resistance of the tank outlet.

CIP Systems

It is preferable to use a common philosophy for all CIP systems in a plant. This will avoid operational errors, provide consistent control system configuration, and maintain documentation format between CIP systems and users.

A once-through system is the least costly system from a capital cost viewpoint, but the most costly to operate because chemical solutions are made up, heated, then thrown away.

Systems use either a self-priming pump or an eductor to assist in returning and recycling washes and possibly some rinses to minimize chemical consumption, utilities, and effluent. Drainage also will be improved with return pumps located close to the process equipment. The final rinse may or may not be recovered to provide the pre-rinse for the next cycle. Figure 2 shows a typical CIP skid system which includes wash and rinse tanks, supply and return pumps, a heater, and all necessary, piping, instrumentation, and controls.

Eductor systems use eductors either alone or in combination with pumps to assist with recirculation and to make up the chemical solutions. They can pull vacuum and remove trapped air pockets and may be preferable to pumped returns since they can't lose prime. They also can provide more motive force than a pumped system as they do not have to contend with Net Positive Suction Head (NPSH) requirements. Still an eductor can vapor bind with flashing fluids or entrained air.

Pump systems using low-speed, self-priming pumps have higher flow rates and smaller diameter piping than eductor systems. They have an advantage over eductor systems in that they can be located at the target tanks to eliminate accumulation. Both pump and eductor systems will operate better at colder fluid temperatures because of the lower vapor pressure.

Multiple circuits fed from the same CIP system should be designed for the same operational flowrate. If both large and small equipment is cleaned using the same system with different flow rates, there is the likelihood that both minimum and maximum velocity criteria will be violated in the piping systems. Systems can be balanced by splitting spray balls so that they are utilized either individually, in pairs, or even two of three open at any one time to make all paths within a circuit use the same flow rate.

CIP Cycles

During each stage of a CIP cycle, each moving component should be operated in the same sequence as during normal operation. This includes valves, agitators, and pumps to ensure each fluid successively contacts all surfaces. Typically, each moving component would operate 5-6 times for 3-5 seconds during each step of the CIP cycle.

In order to minimize effluent and reduce chemical utilization, it may be possible to recirculate some portion of the rinses. Perhaps the rinse can be drained for 1/3 - 1/2 of the allocated time and then recirculated for the remaining time. In addition, the remaining rinse can be used as the starting point for caustic and acid makeups.

CIP systems both remove contaminants and prepare equipment for steaming. A discussion of the nature of "dirt" and the chemicals used to remove it is beyond the scope of this article, but a brief synopsis of the solutions for a typical mammalian cell culture process is shown in Table B.

Typical steps in a CIP cycle are:

Pre-Rinse

The pre-rinse uses either a fresh, clean, cool water (typically DIW) source, or reuses the previous final rinse. The pre-rinse is used to remove residual process fluid and debris. The fluid and temperature should be selected to avoid denaturation and precipitation of proteins. As noted earlier, this step might be once through followed by recirculation.

Recirculated Alkaline Wash

Residual rinse water could be heated and fed with caustic or

Figure 2. CIP skid.

Solution	Purpose
Water - 1st rinse	gross removal of contaminants
Base with Hypochlorite	Solubilize and denature proteins
Water - 2nd rinse	Remove base and debris
Acid	Neutralize base Dissolve mineral salts Passivate
Water - 3rd rinse	Remove acid and debris
WFI Rinse	Remove all remaining contaminants
Steam	Destroy pathogens

Table B. Chemical solutions form CIP/SIP.

other detergent to make up the alkaline (typically 1-3% caustic) wash. The step uses the alkaline wash to denature and solubilize the remaining proteins. Although denaturation increases the dirt load and makes proteins more difficult to remove, the bulk of the easy-to-remove proteins should have been removed in the pre-rinse step. If desired cleaning results are not obtained, this is the step which normally provides the most benefit from an increase in time.

Proprietary chemical cleaners are available for both alkali and acid washes. These mixes may contain a mixture of chemicals, detergents, chlorine, or other additives to improve the cleaning action.

Air blows are used after chemical washes to maximize chemical removal and make the succeeding rinse easier.

Hot Rinse

This rinse is used to remove the alkalinity and additional dirt. This step will not remove (solubilize) additional protein and may be recirculated or once through.

Recirculate Acidified Wash

If necessary, an acid wash is used to neutralize residual base, solubilize remaining dirt (inorganic), remove mineral deposits, and passivate the surface. It is sometimes omitted and it may be made up from the residual rinse fluid from the previous step.

Hot Rinse

Residual acid and any additional dirt loosened in the acid wash is removed with a hot DIW rinse. This rinse also may be recirculated.

Final Rinse

A final rinse with WFI removes traces of previous wash. It is monitored with pH, conductivity, or resistivity (compared to inlet) to ensure cleaning by measuring removal of chemical solutions. These variables will not detect protein residues.

Control

Some companies believe that it is easier to validate a manual CIP procedure because the control system is not involved in the validation procedure. However, current control systems, when properly implemented, have many advantages over a manual system and perhaps the ideal situation is a combination of manual and automatic control. It is important that the control system be easy to monitor, control, and validate.

Automated CIP is the most consistent method to achieve reproducible cleaning. The use of a control system will ensure that cycles, duration, and sequence objectives are achieved each time a CIP is performed.

The main control elements are time, temperature, and flow rate. Cleaning is usually verified by monitoring rinse conductivity. Measurements are made and recorded to verify that achievable tolerances consistent with the cleaning objectives are achieved. Typical operating tolerances of chemical solutions concentration is 1-3%, temperature accuracy should be within ±5°F (3°C), and a flow rate variation should not exceed ±10%.

The main function of the control system is to pulse valves and operate rotating equipment within a circuit with each rotating or moving component cycled 5-6 times during each step of the cleaning cycle. Communication with the process control system is essential to coordinate the cycling of pathways in the process circuit with the change in CIP steps to verify that the various operations occur for the desired time at the proper temperature and composition. Other control functions include chemical addition rate and concentration and temperature control.

Once a control system is employed, it is necessary to consider what action(s) to take in the event of a deviation. One potential deviation is an external requirement to stop the system because of a failure such as a hose leak. Another common problem occurs when low level occurs in one of the tanks on the CIP skid and the circuit must be put in recycle to avoid damaging the pump. The CIP system status can be considered as one of three or four states.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use;

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§211.180 and 211.182.

Figure 3. 21 CFR Parts 210 and 211.

1. Normal - target circuit cycles valves to clean associated paths.

2. Makeup - main path in targeted circuit is open for heatup and chemical addition.

3. Hold - drain valves are closed to prevent loss of chemicals, valves are not cycled, and timer is paused in the CIP PLC until state is returned to normal. This state may be the same as makeup.

4. Abort - systems fail to pre-established safe position.

A control system should be used to validate cleaning. In addition to the controls already discussed, the system should provide for documenting the results of each cleaning operation.

Validation

CIP systems provide for reproducible uniform cleaning and minimize the possibility of human error. The cost of maintenance is reduced, down time is minimized, and operator safety is improved.

With proper documentation, the system can be easily and quickly validated to prove that the cleaning was effective and cleaning agents have not been introduced into the product.

In order to validate a CIP system, written documentation is required to define the procedures for cleaning each piece of equipment, circuit, and flow path. Additional procedures are required to quantify the cleanliness required by the process, a means to measure the cleanliness or residue, and an analytical method to confirm the measurement results. The protocol which describes the validation procedure for CIP must be reviewed, approved, and executed by technically competent personnel.

Figure 3 is an excerpt from 21 CFR-Parts 210 and 211.[3]

Conclusion

Proper implementation of CIP seems to be a mixture of art and science. There is nothing wrong with using empirical relationships provided they don't conflict with good engineering practices. A well-designed CIP system can achieve minimum flow velocities in both supply and return lines without accumulating fluid in the tanks being cleaned. A combination of properly designed outlet connections and return pumps can be used to achieve the desired results.

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About the Author

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This article describes the results of surface compositional analysis using Auger Electron Spectroscopy and electrochemical corrosion testing of passivated versus unpassivated AL-6XN, 304L and 316L.

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The Effect of Passivation on AL-6XN Alloy Compared to the Traditional 304L and 316L Stainless Steel Alloys

by Arnie Grant and John Jermain

First patented in 1985 by Allegheny Ludlum, AL-6XN was designed to be a high strength, corrosion resistant "super-austenitic" alloy intended for service in seawater. The alloy's exceptional corrosion resistance has led to its use in a large variety of industrial applications, and most recently in the pharmaceutical/biotech industry. Given the inherent high degree of corrosion resistance, the question has been raised as to the need for passivation of this alloy. This article describes the results of surface compositional analysis using Auger Electron Spectroscopy and electrochemical corrosion testing of passivated versus unpassivated AL-6XN, 304L and 316L. A proprietary chelant passivation formulation and process was employed. Cr/Fe ratio in the passive layer and pitting potential (E_{pit}) were the criteria used to assess the effectiveness of the passivation.

Introduction

"Pharmaceutical equipment and high purity water systems are designed so that product contact surfaces are not reactive, additive, or absorptive so the drug product is not adversely altered.[1]" Austenitic stainless steel alloys, primarily 316L and much less frequently 304L, either mechanically polished or electropolished, have been the metal alloy of choice for piping, tubing, fittings, tanks, and equipment because of these requirements. Factors such as cost, physical and mechanical properties, fabricability/weldability, compatibility with process, product cleaning and sterilizing fluids, and corrosion resistance must be considered.

Unfortunately, even 316L suffers from frequent and extensive corrosion in the forms of rouging or pitting in aggressive environments including clean steam, hot purified water/HWFI, and the various product and intermediate fluids. Rouging[2-4] may be the result of general corrosion, where the metal corrodes at a consistent rate over the entire surface, or the rouge may originate elsewhere and migrate and deposit at the observed location. Pitting is a highly localized attack, in which only a small area of the metal surface is affected, but the

Figure 1.PAMO meter and test cell.

Composition	Stainless Steel Alloys				
	304	304L	316	316L	AL-6XN
Carbon	0.08 %	0.035 %	0.08 %	0.035%	0.03%
Chromium	18.00 / 20.00 %	18.00 / 20.00 %	16.00 / 18.00 %	16.00 / 18.00 %	20.00 / 22.00 %
Copper	-----	-----	-----	-----	0.75 %
Iron	66.00 / 71.00%	64.00 / 70.00 %	62.00 / 69.00 %	61.00 / 68.00 %	42.00 / 47.00 %
Manganese	2.00 %	2.00 %	2.00 %	2.00 %	2.00 %
Molybdenum	-----	-----	2.00 / 3.00 %	2.00 / 3.00 %	6.00 / 7.00 %
Nickel	8.00 / 11.00 %	8.00 / 13.00 %	10.00 / 14.00 %	10.00 / 15.00 %	23.50 / 25.50 %
Nitrogen	-----	-----	-----	-----	0.18 / 0.25 %
Phosphorus	0.045 %	0.040 %	0.045 %	0.040 %	0.040 %
Silicon	1.00 %	0.75 %	1.00 %	0.75 %	1.00 %
Sulfur	0.030 %	0.030 %	0.030 %	0.030 %	0.030 %
Relative Cost	-----	1.0	-----	1.2 – 2.5	3.5 – 5.0

Table A. Composition of stainless steel alloys.

rate of corrosion in this small area is moderately high. In those circumstances where the degree of corrosion that is occurring is unacceptable, AL-6XN has become one of the new alloys of choice. Lifecycle cost comparisons are beyond the scope of this article.

The chemical compositions and relative approximate costs (with 304L taken as 1) for 304/304L, 316/316L, and AL-6XN are listed in Table A.[5-7] The most common grade and least expensive is Type 304/304L, which makes up more than 60% of all the stainless steel made in the United States today. The improved corrosion resistance of the other grades of stainless steel in this study is developed by adding expensive alloying elements such as chromium, nickel, and molybdenum.

Alloy: Type 304L

The most common grade of austenitic stainless steel produced in the United States is type 304/304L. Type 304L is upgraded from type 304 by slightly increasing the percent composition of nickel and lowering the carbon composition. In this low-carbon austenitic alloy, control of carbon to a maximum of 0.03% has been shown to minimize carbide precipitation (sensitization) during welding and concomitant susceptibility to intergranular corrosion in the Heat Affected Zone (HAZ).

Alloy: Type 316L

By adding 2 - 3% molybdenum, type 316 has significantly better chloride corrosion resistance. Type 316 is upgraded by lowering the allowable carbon content to reduce/eliminate sensitization and slightly increasing the nickel composition. By containing molybdenum and increasing the percentages of nickel, this alloy displays higher strengths at elevated temperatures and better corrosion resistance than the 304 austenitic alloys.

Alloy: AL-6XN

AL-6XN was initially intended to be used in a seawater environment, but extensive testing has demonstrated it to be resistant to a variety of corrosive elements. Its excellent chloride pitting resistance is attributable to its 6.50% molybdenum content, while its significant resistance to chloride stress corrosion cracking is a result of its nickel content of about 25.00%. The addition of nitrogen enhances its pitting resistance as well as mechanical strength. Nitrogen also serves to significantly reduce the formation of potentially harmful secondary phases during the manufacture of large cross-section products. The AL-6XN alloy was tested against other stainless steel alloys, and it was concluded that it is the most corrosion resistant iron-base austenitic stainless alloy

Stainless Alloys	Method of Testing	Non-Passivated Samples	Passivated Samples
AL-6XN	Passivation Monitor Average	993 mV 987 mV 990 mV	1008 mV 1002 mV 1005 mV
304L	Passivation Monitor Average	27 mV 26 mV 27 mV	57 mV 52 mV 55 mV
316L	Passivation Monitor Average	55 mV 56 mV 56 mV	106 mV 113 mV 110 mV

Table B. Passivation monitor results for alloy tube samples.

presently available. According to CSI[6], unless a system is constructed entirely of AL-6XN, special precautions must be taken to avoid potential galvanic corrosion problems.

Evaluation of Passivation

The passivation acceptance or inspection methodology for stainless steel typically found in government or association specifications such as ASTM A-380, MIL-STD-753, QQ-P-35, etc., are sensitive colorimetric spot tests to confirm the complete removal of corrosion inducing surface contamination by free iron or carbon steel and timed exposure tests in water, high humidity, or salt spray for the onset of visible corrosion. The acceptance criterion for the time to onset of corrosion is left to the discretion of the facility owner or his designated authority. No other criteria for evaluating passivation are noted.

Recently, more sophisticated instrumental techniques have been employed to characterize the chemistry of the very thin (30 to 50 Angstrom) passive layer by accurately measuring the removal of iron and the enrichment of chromium, which has been shown to have a direct correlation to improved corrosion resistance. In the past, an improvement in the Cr/Fe ratio from the nominal bulk composition ratio of approximately 0.25 to a value of Cr/Fe = 1.5 has been the unofficial benchmark target for passivation of 316L. No similar criteria have been found for 304L or AL-6XN. X-Ray Photoelectron Spectroscopy (XPS/ESCA) and Auger Electron Spectroscopy (AES/SAM) are the two analytical techniques employed to measure the elemental composition as a function of depth from the surface, through the passive layer and into the bulk alloy.

In addition, electrochemical corrosion measurement techniques have been used to evaluate the effectiveness of passivation by accurately measuring the corrosion resistance, e.g., pitting potential (ASTM G-61) or Critical Pitting Temperature (ASTM G-150). As in other passivation studies by the authors[8,9], both AES to measure chromium enrichment/iron removal in a Cr/Fe Ratio Depth Profile and Cyclic Potentiodynamic Polarization to measure pitting potential (E_{pit}) have been employed to evaluate passivation

Methodology

Material

The stainless steel tubing used in this study was donated by Central States Industrial. The AL-6XN tubing was identified as 2.0" O.D. X.072, 15 GA, ASTM A270, Polished, Heat #882648. The 316L was identified as 2.0" O.D. X.065, 16 GA, ASTM A270, Polished, Heat #19126. The 304L was 2.0" O.D. X.065,16 GA, ASTM A270, Polished. The Heat # was not specified. The tubing was cut into 2.0" lengths for the electrochemical test coupons, while the AES test coupons were ¾" wide longitudinal segments.

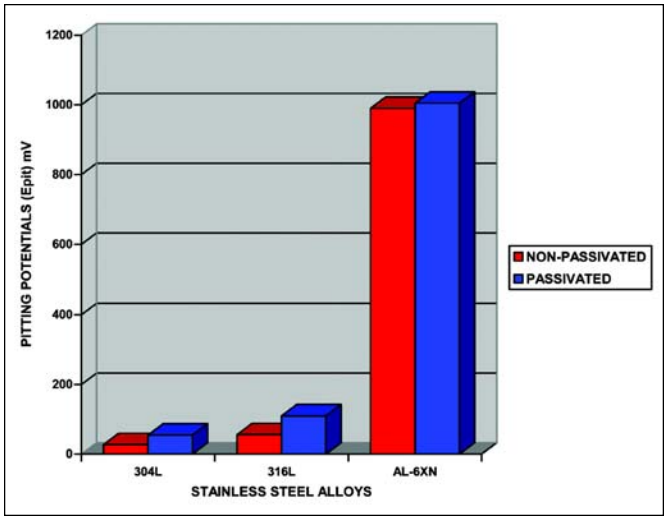

Figure 2. Pitting potentials of 304L, 316L & AL-6XN stainless steel alloys.

Passivation Procedure

After the test coupons were cut, square faced, and deburred, all samples were first cleaned in an alkaline detergent/chelant treatment and then passivated per a standard, proprietary procedure.

Electrochemical Passivation Monitor (Pamo Meter)

The pitting potentials of the three stainless steel alloys, 304L, 316L, and AL-6XN, were measured in duplicate using the electrochemical Passivation Monitor (PAMO) shown in Figure 1 with the test cell configuration. The electrolyte solution was 0.5 M KCl, the test temperature was 25°C, the counting electrode was 316L, and reference electrode was Calomel. The field portable monitor was developed in conjunction with the Materials Science Department at USC to provide more rapid data on pitting potential that was essentially equivalent to the more time consuming ASTM G-61. The procedure measures the potential in millivolts at which electrochemically induced pitting occurs. The pitting poten-

Sample Identification	Oxide Thickness (Å)	Maximum Cr/Fe Ratio	Cr/Fe Ratio @ 10Å	Cr Enriched Layer
Unpassivated AL-6XN	150	1.50	1.52	38.7
Passivated AL-6XN	100	3.03	2.56	82.2
Unpassivated 304L	44	0.38	0.24	NONE
Passivated 304L	33	1.46	1.25	13.3
Unpassivated 316L	80	0.25	0.08	NONE
Passivated 316L	24	1.66	1.12	11.3

Table C. Measurements from auger electronspectrometer.

tial is measured after fifteen minutes of an applied current to the test cylinder via the potentiometer as compared to approximately six hours for the G-61 procedure. The pitting potential, $E_{pit,}$ value may then be conveniently used to compare corrosion susceptibility before and after passivation for the same alloy as well as comparison among the different alloys.

Auger Electron Spectroscopy (AES)

AES element concentration and Cr/Fe Ratio Depth Profiles were performed employing a Physical Electronics Spectrometer with interfacing and software upgraded. Operational parameters for the quantitative elemental analysis were as follows:

Parameters:

Beam Energy:	5000 V
Magnification:	2500X
Beam Current:	1.4 µA
Ion Etch Rate:	60Σ/MIN Ta2O5

Experimental Results

Results from Electrochemical Passivation Monitor

The pitting potential data for the three alloys are presented in Table B and shown graphically in Figure 2. When tested against the traditional 304L and 316L stainless steel alloys, AL-6XN's pitting potential is significantly higher in both passivated and non-passivated conditions. When comparing the pitting potentials of the traditional stainless steel alloys before and after passivation, the pitting potentials doubled for both the 304L and 316L. In contrast, the AL-6XN alloy displayed only a very slight increase in pitting potential after passivation.

Results from Auger Electron Spectroscopy

The AES data are tabulated in Table C, while the Auger Cr/Fe Ratio and element concentration Depth Profile curves are presented in Figures 3 through 8. In all cases, the passivated samples had a much higher chromium to iron ratio then the samples that were not passivated.

Discussion

When compared to 304L and 316L stainless steel alloys, the AL-6XN pitting potential is significantly higher (an order of magnitude and greater) in both non-passivated (990 mV) and passivated (1005 mV) conditions, confirming once again its outstanding pitting corrosion resistance. When comparing pitting potentials of the traditional stainless steel alloys, the pitting potential doubled for both the 304L (from 27 mV to 55 mV) and 316L (from 56 mV to 110 mV) after passivation.

Examination of the Auger elemental analysis data provides a somewhat different picture. The two primary objectives of passivation are 1) to remove any surface contamination which may promote corrosion, and 2) to remove iron to enhance the Cr/Fe Ratio values. These two goals are illustrated in the Cr/Fe Ratio Depth profile curves. In the unpassivated condition, all three alloys display the lowest Cr/Fe ratios at the surface in the first 10 Angstroms, rising sharply to a peak at approximately 10 to 20 Angstroms. This is taken as an indication of surface contamination. As a general rule, it is desirable to have the maximum Cr/Fe value as close to the surface as possible. Not only does Cr/Fe increase dramatically after passivation (304L from 0.38 to 1.46; 316L from 0.25 to 1.66; and, AL-6XN from 1.50 to 3.03), but the peak values are at or very near the surface, indicating both objectives have been met. The depth profile curves also

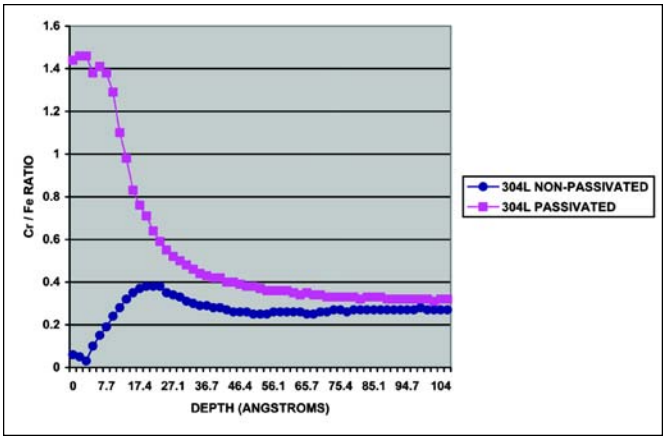

Figure 3. Cr/Fe ratio depth profiles for Type 304L.

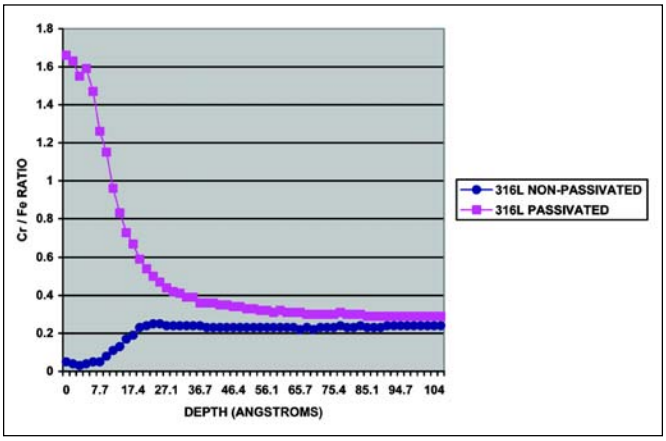

Figure 4. Cr/Fe ratio depth profiles for Type 316L.

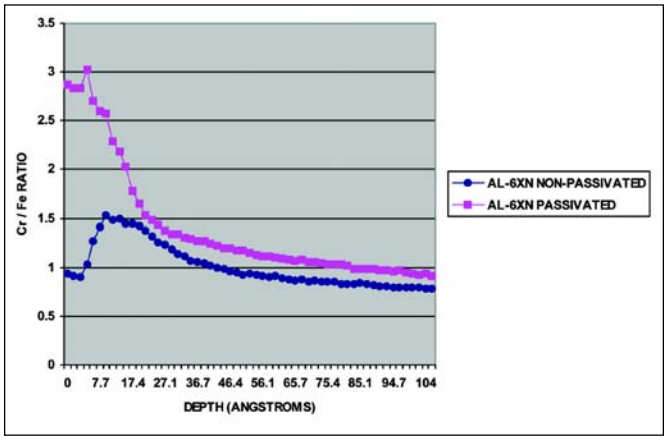

Figure 5. Cr/Fe ratio depth profiles for AL-6XN.

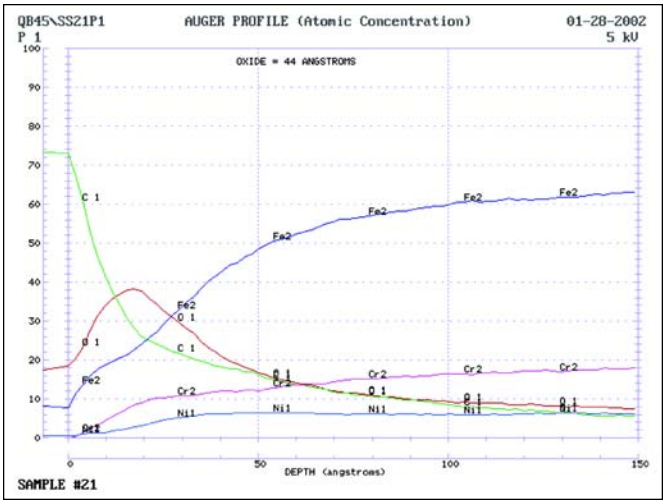

Figure 6a. 304L Unpassivated.

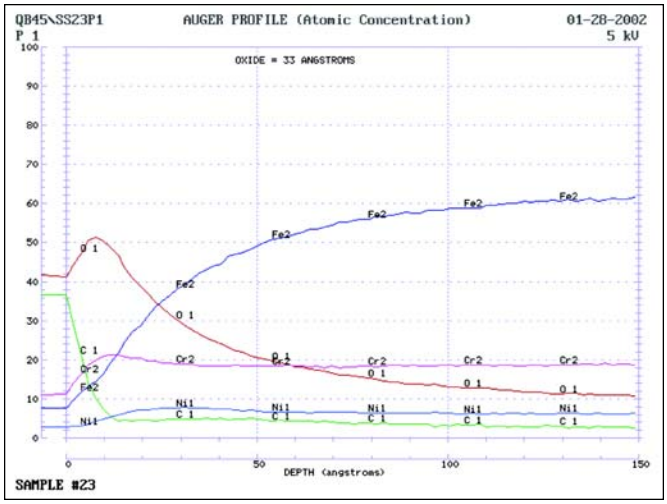

Figure 6b. 304L Passivated.

show that, at the surface of the three unpassivated alloys, iron is seen to be higher than chromium although only slightly for the AL-6XN. After passivation, a dramatic shift is seen where chromium is much greater in concentration than the iron. The chromium enriched layer value shown in Table C represents the cross-over point, the depth to which the Cr is greater than Fe. For AL-6XN, the enrichment depth is doubled by passivation, from 38.2 Angstroms to 82.2 Angstroms.

Should 304L and 316L alloys be passivated? Without a doubt. Should AL-6XN be passivated? The electrochemical pitting test results do not show a clear need based on the difference in E_{pit} before and after passivation. However, given the significant removal of iron from the surface of the AL-6XN by the passivation process and the certain requirement for a thorough cleaning to remove surface contaminants after installation, it seems most prudent and cost effective to require both cleaning and passivation for new AL-6XN systems. Evaluation of the effect of welding on surface segregation of alloy constituents in AL-6XN and the need for passivation is currently underway. As experience is gained in the operation of equipment constructed of AL-6XN in pharmaceutical applications, we will be able to determine if rouging or corrosion occurs, under what conditions and frequency, and if maintenance derouging and repassivation will be required.

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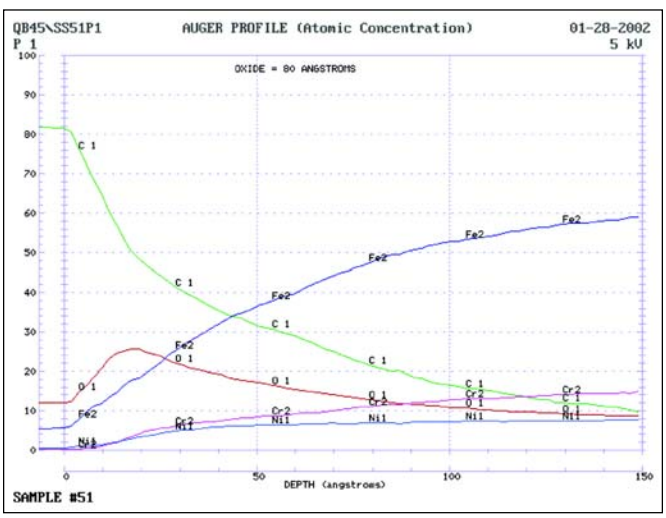

Figure 7a. 316L Unpassivated.

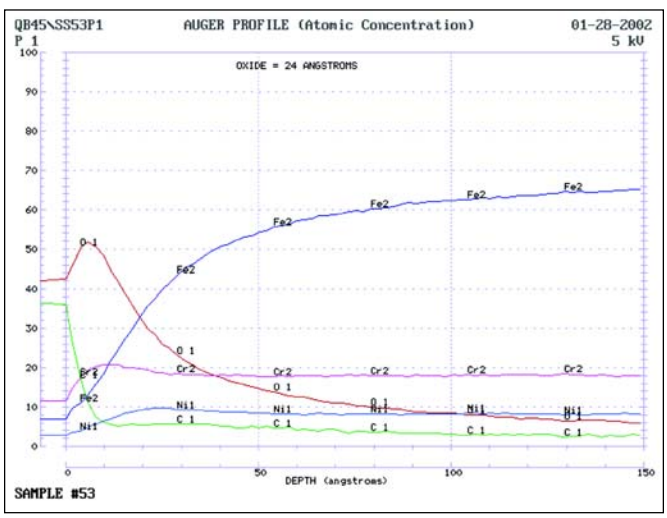

Figure 7b. 316L Passivated.

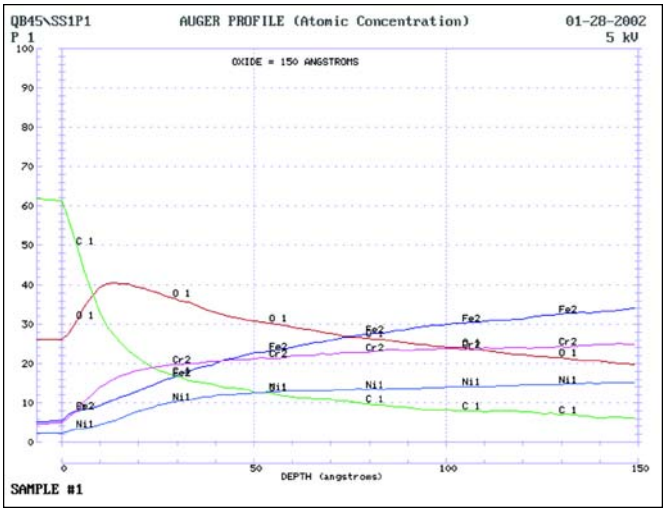

Figure 8a. AL-6XN Unpassivated.

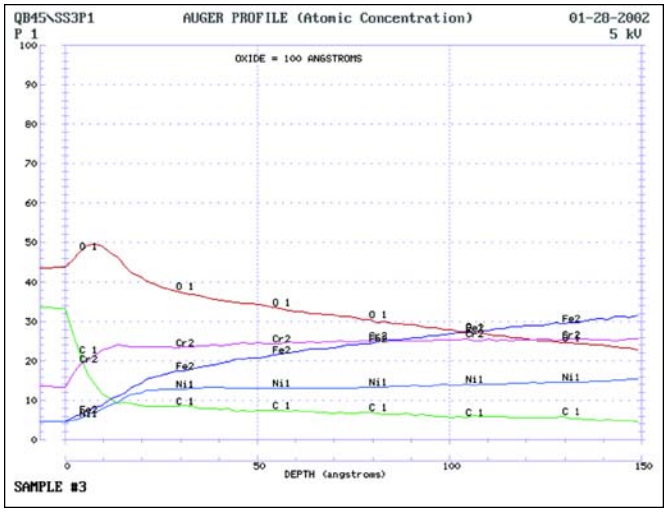

Figure 8b. AL-6XN Passivated.

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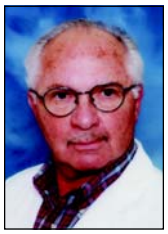

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This article discusses a method adopted by IT Software Suppliers to meet a fundamental requirement of all IT users - to receive a good quality product or service.

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Quality Systems in the Pharmaceutical Industry

by Lorna Foote

Within the pharmaceutical world, quality and validation requirements for software products are fairly well covered and understood. IT directors, their managers, and staff know that if they are implementing IT systems in a regulated area, they have to validate these systems and the systems and associated documentation have to meet certain quality requirements. There are well-documented reasons for carrying out the validation and meeting the quality requirements, and there are well-documented methods and standards describing the goals and activities. There may still be areas where these methods and standards are not rigorously applied; for example, how many end-user developed databases become business critical, but have had little testing and have no documentation? However, no matter how well known these issues are within the pharmaceutical industry now, the pharmaceutical customers' requirements will change, and the capabilities of the suppliers will change with time.

The suppliers of IT products and services are constantly changing; they are gaining new skills, broader experience, answering the challenges of the technology, and meeting the needs of competition. But, through all that change do they continue to meet the quality and validation requirements of the pharmaceutical industry?

This article will discuss one method being increasingly adopted by IT software suppliers to meet a fundamental requirement of all IT users – ***to receive a good quality product or service***. That method is the Software Engineering Institute Capability Maturity Model (SEI CMM). The Carnegie Mellon Software Engineering Institute Web site describes CMM as follows:[1]

"The Capability Maturity Model for Software describes the principles and practices underlying software process maturity and is intended to help software organizations improve the maturity of their software processes in terms of an evolutionary path from ad hoc, chaotic processes to mature, disciplined software processes."

It is reasonable to speculate that suppliers who have mature, disciplined, proven, and certified software processes will deliver software of a high quality. To elaborate on that speculation, and to argue that this will help software suppliers meet the regulatory needs of our industry, this article will briefly summarize the CMM and its levels of maturity. Additionally, the article will draw comparisons between the processes required to achieve the higher levels of CMM and the processes required by disciplines such as ISO 9001 and the ISPE Good Automated Manufacturing Practice (GAMP) Guide. These comparisons are neither easy nor obvious since there is little direct correlation between the elements of the CMM, the ISO standard, and the GAMP Guide. In fact, the purpose of each is so different that the basis of comparison may at first seem questionable. However, it is hoped that the way in which the comparison is documented will aid an understanding of how high levels of quality in software can be achieved through the CMM approach. It should be noted here that there are many standards, guides, and regulations that could have been used for this comparison; however, the GAMP Guide is included because it is specific to meeting the requirements of the healthcare industry for automated systems and ISO 9001 is arguably the best known standard against which quality systems are compared.[2,3]

So, the article aims to show how a very high proportion of the pharmaceutical industry's

quality and validation requirements for the supply of software can be an integral part of the delivery process, even when the specifics of the pharmaceutical industry's regulatory requirements are not explicitly addressed. The aim is not to suggest that we shift our focus toward the CMM, instead of GAMP or ISO 9001, rather that it is an additional way of looking at the quality of software suppliers, giving the pharmaceutical industry a broader choice of potential suppliers.

For those readers well versed in validation requirements and processes, the following definition will be familiar; however, it is included here as a reminder of the objective of validation.

Validation: "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."[4]

The Capability Maturity Model has been designed to help software developers achieve the consistency of quality that is required by validation. However, it must be stressed here that the Capability Maturity Model does not in any way directly address the requirements of validation, since they are understood within our industry. The introduction to one of the main CMM texts states that the "CMM guides software organizations that want to gain control of their processes for developing and maintaining software and to evolve toward a culture of software engineering and management excellence." It will help organizations identify the critical areas to address to achieve the improvement in their processes and in the quality of their software products.[5]

This article will demonstrate that by implementing a CMM approach to software engineering processes or by contracting suppliers who have achieved the higher levels of CMM, systems will:

- be engineered according to defined and documented processes
- be delivered with documented evidence
- provide a high degree of assurance
- work consistently
- meet pre-determined and agreed requirements and specifications
- meet pre-defined quality attributes
- while this does not mean that the systems **are** validated it will provide us with a system that **can be** validated.

The next two sections will briefly describe the background to and the objectives of the GAMP Guide and ISO 9001 respectively. The following section will describe the CMM in much more detail. This is intentional since this article sets out to introduce the model which is considerably less well known within the industry.

The GAMP Guide

The GAMP Guide was originally a set of guidelines for suppliers of automated systems to the pharmaceutical industry. It was the work of the GAMP Forum, an industry group set up to promote the understanding of validation of automated systems, and was first published in 1994. Further revisions were published in 1996, 1998, and GAMP 4 was published in 2001. This most recent publication has been revised and refined to include current regulatory expectations and good practice and now aims to provide guidance not just to the pharmaceutical sector, but also to related healthcare industries.

The GAMP Guide is an excellent source of information about what has to be done to validate a system. This includes what the end-user or owner of the system ***must*** do and what the supplier ***should*** do. The italicized and emboldened emphasis in the last sentence is intended to show two things. The first is to place responsibility clearly with the owner/end-user who must make the decisions about how and if the system can be used for their purposes. The second is to indicate that should the supplier fail to meet some of the requirements of validation normally associated with a supplier, the owner/end-user would then have to, through extra effort, provide the assurances that the system is satisfactory for use.

Perhaps it is because the responsibility for validation lies fairly and squarely in the hands of the system owner/end user that the GAMP Guide is well known within the pharmaceutical industry and much less known by "generic" IT suppliers. And, perhaps this situation will not and need not change. However, there are two downsides associated with IT suppliers not understanding the requirements of system validation.

- Some IT suppliers lose out because, although they may be more than **capable** of supplying systems meeting the quality and validation requirements, they do not have the specific knowledge of validation, its terminology, or the applicable regulations. To make matters worse, they may not be told about them as part of the tendering or procurement process, and so they miss out on opportunities to supply.

- Some pharmaceutical companies lose out because, understandably, they tend to look for suppliers who are knowledgeable about validation and the applicable industry regulations. This limits the source of suppliers by leaving out many IT companies supplying goods and services to a quality that could more than satisfy the industry's needs.

It is not the intention to try to summarize the GAMP Guide – it is beyond the scope of this article. However, below is a list of points particularly pertinent to this article.

- In order to play their part in the production of a validated system, it is recommended that the suppliers follow a formal management system, preferably based on standards such as ISO 9000 Series.

- The supplier's management system should follow a standard life cycle approach which can be tailored as appropriate to the system being produced.

- Contractually agreed Quality Plans and Project Plans should be produced and meet the minimum standards specified in the Guide.

- Specifications should be produced for the required functionality, design, build, and finally, for the testing of the system. These also should meet minimum standards and they should be formally agreed.

- The supplier should carry out testing and this should be sufficient to show that the product is fit to be installed and used at the customer's site.

- A further phase of testing carried out at the customer's site should demonstrate the system meets the customer's requirements.

While the Guide does include some detail concerning the sections and content that should be contained in a formal management system, it clearly leaves the supplier with scope to build a management system appropriate to their specific ways of working and product range. Allowing this autonomy is essential; otherwise, the range of suppliers with which the pharmaceutical companies could work would be even more severely limited.

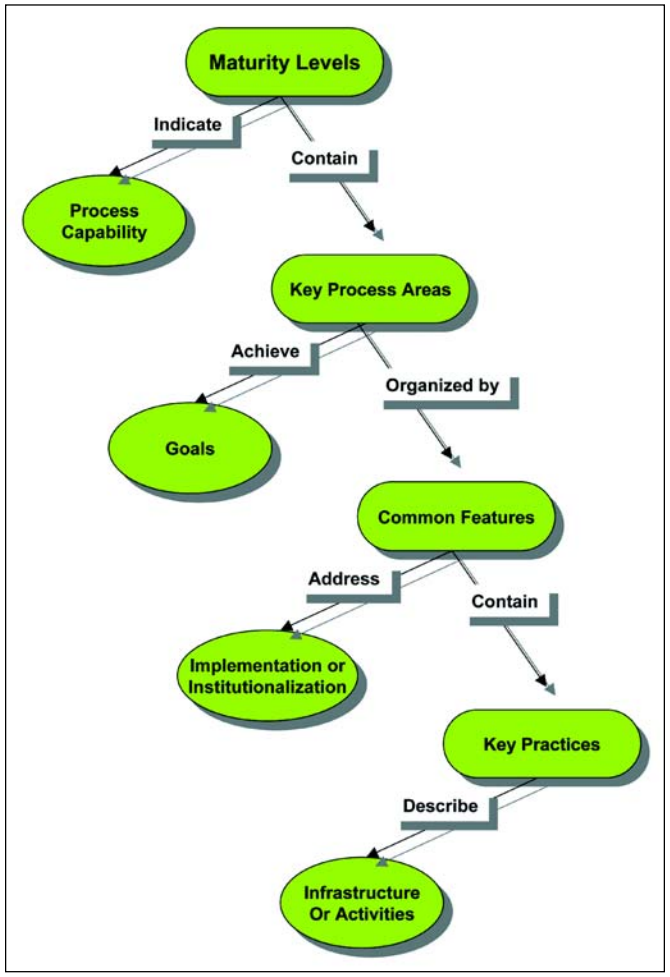

Figure 1. Structure of the Capability Maturity Model.

One of the real strengths of the Guide (GAMP 4 in particular) is that it provides the pharmaceutical company or the supplier to the pharmaceutical company a number of very useful Guidelines and Procedures that can be adopted and adapted to meet the specific processes of the organization. This approach (describing "how" as well as noting "what") is one of the main differences between the GAMP Guide and ISO 9001 and the CMM.

ISO 9001

ISO 9001 is a "model for quality assurance in design, development, production, installation, and servicing." It was formerly British Standard BS 5750 and is now a European and international standard. BS EN ISO 9001 was published in 1994 and there is now a new ISO 9001:2000. It is one of three standards dealing with quality system requirements that can be used for external quality assurance purposes. These standards are generic and independent of any specific industry or economic sector.

BS EN ISO 9001: 1994, which was used in the preparation of this article, consists of 20 quality system requirements, each of which is expanded giving a total of 46 subsections defining requirements. The objective of these requirements is to help a supplier meet customers' expectations and thereby achieve customer satisfaction.

Organizations seeking to demonstrate compliance with the standard are likely to go through a registration process which will typically involve the following four steps:

- pre-audit to determine areas where practices are falling short of the audit - an optional stage likely to be done if the organization is not confident of their ability to meet the standard

- audit - done by an independent, qualified, and certified auditor. This will result in a pass or fail status.

- registration - in the event that the audit status is pass the organization can progress registration

- surveillance audit - to determine the continuing state of the organization in their attempts to comply with the standard

SEI CMM

The Software Engineering Institute started the development of a maturity framework in 1986 with assistance from the MITRE Corporation. It was initiated because the US federal government needed a method of assessing the capability of software suppliers. This evolved by the early 1990s into the Capability Maturity Model, which is based on the actual practices of organizations looked at during the development of the model. The model reflects the best of those practices and is both fully documented and publicly available. The CMM has continued to evolve with the introduction of additional models (looking wider than the software engineering processes) and a new integrated model. Because there is

CMM Level	CMM Key Process Area	Related GAMP or ISO Requirement
2 – Repeatable	Requirements Management – Establishing a common understanding between the customer and the software project of the customer's requirement that will be addressed by the software project	GAMP – Planning – Validation Plan and User Requirements Specification GAMP – Design Review and Traceability Matrix GAMP – Functional Specification ISO – Contract Review – to determine if requirements are adequately defined, agree with the bid, and can be implemented.
2 – Repeatable	Software Project Planning – Establishing reasonable plans for performing the software engineering and for managing the software project	GAMP – Planning – Quality and Project Plans GAMP – Risk Assessment GAMP – Categorization of Software and Hardware ISO – Management Responsibility ISO – Quality System ISO – Contract Review ISO – Design Control ISO – Process Control
2 – Repeatable	Software Project Tracking and Oversight – Establishing adequate visibility into actual progress so that management can take effective actions when the software project's performance deviates significantly from the plan.	GAMP – Quality and Project Plans GAMP – Project Change Control ISO – Management Responsibility
2 – Repeatable	Software Subcontract Management – To select qualified software subcontractors and manage them effectively.	GAMP – Subcontractor Control GAMP – Supplier Audit ISO – Purchasing ISO – Control of Customer Supplied Product
2 – Repeatable	Software Quality Assurance – To provide management with appropriate visibility into the process being used by the software project and the products being built.	GAMP – Quality & Project Plans GAMP – Reviews GAMP – Good Engineering Practice GAMP – Production, Control and Review of Software GAMP – Design Specifications GAMP – Testing ISO – Management Responsibility ISO – Quality System ISO – Process Control ISO – Corrective and Preventative action ISO – Internal Quality Audits
2 – Repeatable	Software Configuration Management – To establish and maintain the integrity of the products of the software project throughout the project's software lifecycle.	GAMP – Configuration Management GAMP – Document Management ISO – Design Control ISO – Document and Data Control ISO – Product Identification and Traceability ISO – Inspection and Test Status ISO – Control of non-conforming product
3 – Defined	Organization Process Focus – To establish the organizational responsibility for software process activities that improve the organization's overall software process capability.	GAMP – Good Engineering Practice ISO – Management Responsibility
3 – Defined	Organization Process Definition – To develop and maintain a usable set of software process assets that improve process performance across the projects and provide a basis for cumulative, long term benefits to the organization.	GAMP – Good Engineering Practice ISO – Quality Systems ISO – Statistical Techniques
3 – Defined	Training Program – To develop the skills and knowledge of individuals so that they can perform their roles effectively and efficiently.	GAMP – Training of Supplier Staff GAMP – Good Engineering Practice ISO – Training
3 – Defined	Integrated Software Management – To integrate the software engineering and management activities into a coherent defined software process that is tailored from the organization's standard software process and related process assets, which are described in the Organization Process Definition.	GAMP – Good Engineering Practice ISO – Management Responsibility

Table A. Comparison between CMM and GAMP/ISO 9001. *(Chart continued on page 29.)*

CMM Level	CMM Key Process Area (continued)	Related GAMP or ISO Requirement (continued)
3 – Defined	Software Product Engineering – To consistently perform a well-defined engineering process that integrates all the software engineering activities to produce correct, consistent software products effectively and efficiently.	GAMP – Good Engineering Practice ISO – Management Responsibility
3 – Defined	Intergroup Coordination – To establish a means for the software engineering group to participate actively with the other engineering groups so the project is better able to satisfy the customer's needs effectively and efficiently.	GAMP – Good Engineering Practice ISO – Management Responsibility
3 – Defined	Peer Reviews – To remove defects from the software work products early and effectively and to develop a better understanding of the software work products and of the defects that can be prevented.	GAMP – Reviews ISO – Inspection and Testing ISO – Control of Quality Records
4 – Managed	Quantitative Process Management – To control the process performance of the software project quantitatively. Software process performance represents the actual results achieved from following a software process. The focus is on identifying special causes of variation within a measurably stable process and correcting, as appropriate, the circumstances that drove the transient variation to occur.	ISO – Process Control ISO – Statistical Techniques
4 – Managed	Software Quality Management – To develop a quantitative understanding of the quality of the project's software products and achieve specific quality goals. Software Quality Management applies a comprehensive measurement program to the software work products described in Software Product Engineering.	ISO – Management Responsibility ISO – Design Control ISO – Statistical Techniques
5 – Optimizing	Defect Prevention – To identify the causes of defects and prevent them from recurring. The software project analyses defects, identifies their causes, and changes its defined software process, as described in Integrated Software Management	ISO – Corrective and Preventative Action
5 – Optimizing	Technology Change Management – To identify beneficial new technologies (i.e. tools, methods and processes) and transfer them into an orderly manner, as is described in Process Change Management. The focus of Technology Change Management is on performing innovation efficiently in an ever-changing world.	ISO – Process Control
5 – Optimizing	Process Change Management – To continually improve the software processes used in the organization with the intent of improving software quality, increasing productivity, and decreasing the cycle time for product development. Process Change Management takes the incremental improvements of Defect Prevention and the innovative improvements of Technology Change Management and makes them available to the entire organization.	

Table A. Comparison between CMM and GAMP/ISO 9001. *(Chart continued from page 28.)*

much information available on the SEI Web site about these developments, they shall not be included in this very brief introduction.

The CMM sets out the criteria that characterize mature software organizations. These criteria can then be used as a means of appraising organizations and this can be done in two different ways.

- A **software process assessment** can be used to determine the state of the processes in an organization. The likely outcome of this assessment will be an action plan to address priority areas for improvement.

- A **software capability evaluation** can be used to determine if a software supplier is likely to be able to fulfill an organization's requirements.

Organizations being appraised against the CMM are subject to a rigorous, formal, and independent review by an accredited body that will certify them at the appropriate level. The SEI has an Appraiser Program that aims to select the highest quality candidates for training and authorization. SEI-authorized Lead Appraisers are required to submit a report to the SEI for each appraisal performed. The SEI strives to ensure that there is a uniform level of quality applied by all Lead Appraisers. The appraisal method includes:

- a maturity questionnaire, which samples the CMM, to be completed by the organization being appraised

- analysis, by the appraisers, of the responses to the questionnaire

- a detailed on-site investigation, using the CMM as a guide
- preparation of findings identifying strengths and weaknesses in terms of key process areas in the CMM
- preparation of a maturity profile
- presentation of appraisal results to organization

Some organizations will be initially assessed at Level 1 or 2 and work their way from there, through each level in turn. Others may start with an assessment at perhaps Level 4 and make improvements over time to gain Level 5. It must be stressed that each level is a building block upon which the processes for the next level will be built. And, so even if an organization is first assessed at a high level, they will almost certainly have gone through the lower levels in their evolution. Achieving the higher levels can take a considerable amount of effort, and as implied by the name, a considerable amount of time to reach maturity.

The structure of the model is represented in Figure 1. This shows the relationship between the elements of the model. Each Maturity Level (Initial, Repeatable, Defined, Managed, and Optimizing) indicates the capability of the organization and each contains the Key Process Areas. These Key Process Areas are at the heart of the CMM, are designed to achieve one or more Goals, and are organized by Common Features. The Common Features (see below for more detail) address the Institutionalization of the processes within the organization. (This is very important – for an organization to reach the higher levels of maturity, the processes must be an integral part of the company culture.) Each Common Feature contains Key Practices which are descriptions of activities or the organizational infrastructure in place for each Common Feature.

The Common Features (addressing how the key processes are institutionalized) are:

- **Commitment to Perform** - describing what the organization should do to ensure the process is established, e.g. setting policies and ensuring that leadership is in place.
- **Ability to Perform** - describing the necessary preconditions to allow the process to become effective, e.g. having in place the appropriate resources, organizational structures, and training programs.
- **Activities Performed** - describing the activities, roles, and procedures required to implement the Key Process Area, e.g., planning the work, preparing procedures for the work, carrying out the work, tracking progress, and taking necessary corrective action.
- **Measurement and Analysis** - describing the basic measurement practices carried out to determine the status of the process that can then be used to control and improve the process.
- **Verifying Implementation** - describing what should be done to ensure that the activities comply with the established process, e.g., reviews and audits by management and quality assurance.

At the heart of the model are the **Key Process Areas** which identify the issues that must be addressed to achieve a maturity level. The Key Process Areas are very briefly described in Table A.

Level 1 - Initial

The software process is characterized as ad hoc, and occasionally even chaotic. There is not a stable environment for software development and during a crisis, the plans and procedures are likely to be abandoned and all efforts will be focused on coding and testing. Few processes are defined, and success can happen depending on individual effort and heroics.

Level 2 - Repeatable

Basic project management processes are established to track cost, schedule, and functionality. The necessary process discipline is in place to repeat earlier successes on projects with similar applications. There are likely to be differences in approach taken by different projects; however, the projects will be guided by organizational policies. Key Process Areas are:

- requirements management
- software project planning
- software project tracking and oversight
- software subcontract management
- software quality assurance
- software configuration management

Level 3 - Defined

The software process for both management and engineering activities is documented, standardized, and integrated into a standard software process for the organization. All projects use an approved, tailored version of the organization's standard software process for developing and maintaining software. Responsibility for the software process activities is assigned and an organization-wide training program will ensure that staff and managers have the knowledge and skills required to fulfill their roles. The capability of Level 3 organizations is standard and consistent because both engineering and management activities are stable and repeatable. Cost, schedule, and functionality are under control and quality is tracked. Key Process Areas are:

- organization process focus
- organization process definition
- training program
- integrated software management
- software product engineering
- intergroup coordination
- peer reviews

Level 4 - Managed

Productivity and quality data are collected and analyzed for all important software process activities across all projects as part of an organizational measurement program. Projects achieve control over their products and processes by narrowing the variation in performance to fall within acceptable quantitative boundaries. Meaningful variations can be distinguished from random variation and the risks involved in introducing change are known and carefully managed. Causes of variation are identified and addressed. Key Process Areas are:

- quantitative process management
- software quality management

Level 5 - Optimizing

The entire organization is focused on continuous improvement. It will identify weaknesses and proactively strengthen processes with the goal of preventing the occurrences of defects. Innovations that exploit the best software engineering practices are identified and implemented across the organization. Defects are analyzed to determine and eliminate root causes. Lessons learned are disseminated throughout the organization. There will be organized efforts to remove waste and inefficiency. Key Process Areas are:

- defect prevention
- technology change management
- process change management

CMM Benefits

One of the main published texts on the Capability Maturity Model includes details of a number of organizations and the advantages they accrued from the implementation of a CMM approach to improving their software engineering processes. The text includes the following as stated benefits:

- return on Investment (ROI) - one company has reported a return of 4.5 to 1 in moving from Level 2 to Level 3. Another company reported an ROI of 6.35 to 1
- reduction in defects - customer reported defects from 25% to 10%
- increased productivity - projects on schedule from 51% to 94%, schedule slippage from 50% to 1%
- more work - more contracts awarded and more time to carry out work because of reduced rework time (rework costs reduced from 41% to 11%)

The text also lists the following less tangible benefits reported by organizations:

- improved employee morale
- improved quality of work life
- fewer overtime hours
- more stable work environment
- lower staff turnover
- improved communication
- improved quality as reported by customers

All of the above should lead to improved customer satisfaction. The Capability Maturity Model is not the only way to achieve this level of customer satisfaction, but it is another way that may benefit our industry if it were to be more widely adopted internally or if we contracted more suppliers who have adopted the approach.[5]

The Capability Maturity Model is a complex and extremely lengthy model (it runs to several hundred pages, whereas ISO 9001: 1994 is contained in under 20 pages) that can only be very briefly described in an article of this nature; however, it is hoped that this summary will serve as a useful introduction for any reader who is unfamiliar with the model and its uses.

Comparisons

Just as there have been comparisons drawn between the GAMP Guide and ISO 9001, there have been several comparisons drawn between CMM and ISO 9001 (some of these can be found on the SEI Web site), and it is widely believed that an organization at Level 2 of CMM would benefit from achieving ISO 9001, whereas an organization at Level 3 would be likely to have all of the necessary processes in place to achieve ISO 9001. It is reasonable then to assume that organizations achieving Levels 4 or 5 would have processes in place that are far more rigorous, and effective in ensuring delivery of consistent quality, than organizations doing only that necessary to gain ISO 9001.

It is worth noting here that there will be clear areas of difference between the GAMP Guide and CMM. For example, the GAMP Guide covers keeping a computer system in its validated state, post-implementation, and through its useful life. CMM does not cover the post-delivery elements in great detail because its focus is very much on the software engineering processes.

The objective of this article is to look at how IT organizations, which have achieved the higher CMM Levels (4 and 5), could be potential suppliers to the industry. And, the question that this article must answer is: How do the processes needed to achieve CMM Level 4 or 5 match with the processes needed to build a system that can be easily validated when used in the pharmaceutical industry?

Table A provides the CMM levels and the key process areas for each level. The table structure is based on CMM rather than GAMP. This is intended to give readers, who are not familiar with CMM, an insight into its requirements and objectives.

It is worth noting here that a key focus of CMM is revisiting, reviewing, and refining the processes. So while it may appear that all of the basic IT processes are in place by the time an organization reaches Levels 2 or 3, the activity required to reach Levels 4 and 5 will mean that these processes are more effective, more efficient, and products of a better and more consistent quality are being delivered to the customer.

Key Points of the Comparison

The following is a comparison based on the Key Process Areas associated with each maturity level. The comparison starts at Level 2 because one of the characteristics of a company at Level 1 is that it has no defined key processes.

Level 2 - Repeatable

At Level 2, organizations must be able to effectively:

- manage requirements
- plan projects
- track project progress
- manage subcontractors
- plan and manage quality assurance activities
- plan and manage software configuration management activities

They will be able to repeat successes when faced with similar pieces of work. This level of maturity compares with organizations who have addressed the following GAMP and/or ISO 9001 requirements:

- quality and project planning
- reviews
- good engineering practice
- management responsibility
- quality systems
- process control
- corrective and preventative action
- internal quality audits

Level 3 - Defined

At Level 3, organizations will have formal, documented, standardized, and integrated processes for software engineering. These will cover the following areas:

- process improvement initiatives at organizational levels
- data gathering for analysis in support of the improvement initiatives
- planned and managed training activities
- integrated software management – a refinement of project planning and project tracking being done at Level 2
- software engineering processes that ensure consistent product delivery
- intergroup coordination ensuring that all interactions are controlled and effective
- peer reviews leading to defect identification and removal

This level of maturity compares with organizations who have met all of the previously stated requirements of GAMP and/or ISO 9001, plus the following:

- statistical techniques
- training
- training of supplier staff
- inspection and testing
- control of quality records

At Level 3, CMM starts to diverge from both GAMP and ISO 9001. This divergence is related to the focus of the approaches – CMM is entirely focused on the organization's processes whereas GAMP and ISO 9001 tend to focus (at least in part) on the product of the processes. This process focus arguably will lead to a much more consistent delivery capability than a product focus.

Level 4 - Managed

At Level 4, an organization's processes and products will be quantitatively understood and controlled. The processes required to achieve Level 3 will be built on in the following areas:

- quantitative process management - within a measurably stable process, causes of variation are identified and corrected
- software quality management - a comprehensive measurement program setting goals for software products

It is worth noting here that while the underlying objective of the various approaches is similar, the focus of both GAMP and ISO differs from CMM. ISO 9001 Process Control and Design Control aim to define and document processes so that they can be **verified** and appropriate **controls** can be implemented. While this verification will involve quantitative statistical and elements, the CMM aims to ensure that processes are **measurably stable** allowing transient variations to be identified and dealt with.

It is quite likely that the ISO and GAMP requirements for Software Quality would be met by a CMM Level 2 company with their approach to Quality Assurance. However, ISO 9001 can be interpreted as requiring some of the elements associated with Quality Management implemented by CMM Level 4 organizations.

Level 5 - Optimizing

At Level 5, organizations will have fully embraced continuous process improvement and they will be piloting innovative ideas and technologies. The processes required to achieve Level 4 will be enhanced in the following areas:

- Defect Prevention - identifying, analyzing, and eliminating the root cause of defects.
- Technology Change Management - proactively seeking innovation and improvement opportunities and implementing them in a controlled manner.

- Process Change Management - taking the improvements identified through defect prevention and technology improvements and making them available throughout the organization.

Organizations who have met the requirements of GAMP and/or ISO 9001 will have addressed Defect Prevention. However, the approach will probably have been reactive and may well have been based on customer complaints. The focus of a CMM Level 5 company will be on root cause analysis and eradication.

Conclusion

So, how do the processes needed to achieve CMM Level 4 or 5 match with the processes needed to build a system that can be easily validated when supplied to the pharmaceutical industry?

The comparison summarized above and detailed in Table A shows that there are links from nearly all elements of CMM to the GAMP Guide (or to ISO9001). It also shows that the only element of ISO9001 not covered in some way in CMM is that of Servicing. Because of CMM's focus on the development processes, the ongoing support and maintenance of systems is not addressed in any great detail. As already mentioned, there are areas covered in GAMP that are not covered at all in CMM. However, these are related to specific validation activities (and therefore not the responsibility of the supplier), to hardware or infrastructure issues (and therefore outside of the scope of CMM and Software Engineering), or to on-going operational issues (again outside of the scope of CMM).

The basic premise of both CMM and GAMP, and the greatest similarity between the two (and this applies also to ISO) is that organizations should have defined and documented processes in place and their practices should match these – "say what you do and do what you say." It is reasonable then to conclude that organizations certified at CMM Level 4 or 5 will be doing all that is required to satisfy an ISO9001 audit or indeed a GAMP-style Supplier Audit.

But they will be doing more. They will be constantly looking at their processes, refining them, and looking for opportunities for improvement. They will be constantly gathering data relating to their processes and products and analyzing that data looking for the root causes of problems so that they can be eliminated. And, it is very likely that they will be looking for opportunities to demonstrate to existing and potential customers that this emphasis on quality and improvement is beneficial to all concerned.

In a final conclusion, I would heartily recommend that CMM Level 4 or 5 companies be included as potential suppliers to any pharmaceutical company looking for IT suppliers of good quality software products and software development projects.

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Steve Watson, IT Solutions

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This article describes a continuous, five-phase treatment system producing purified water to USP XXIV.

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Production of Purified Water in the Biotechnology Industry

by Patrick Chkroun, Denis Acker, and Philippe Jaunin

Biotechnology in the Service of Health

Today, three main methods exist to produce medicines:

- extraction and purification of natural substances
- chemical synthesis
- biotechnology

In healthcare, modern biotechnology utilizing DNA recombination techniques has improved prevention, diagnosis, and treatment of numerous illnesses since the late 1970s.

Since the middle of the last century, Serono has been producing medical products by traditional methods of extraction and purification of natural substances. They have been using the recombinant DNA methods for more than 10 years now. The first "recombinant" product, the growth hormone, is being distributed today in more than 50 countries.

State-of-the-Art Technologies

The new biotechnology laboratories in Corsier-sur-Vevey, Switzerland, are among the most modern worldwide from the technological viewpoint, which constitutes a new approach to pharmaceutical production based upon cell culture and development. Taking into consideration the specific and very complex characteristics of the equipment, Serono went into partnership with architects, engineers, planners, and constructors, who are experienced and have a good track record in project engineering of pharmaceutical facilities, and more specifically, in biotechnology.

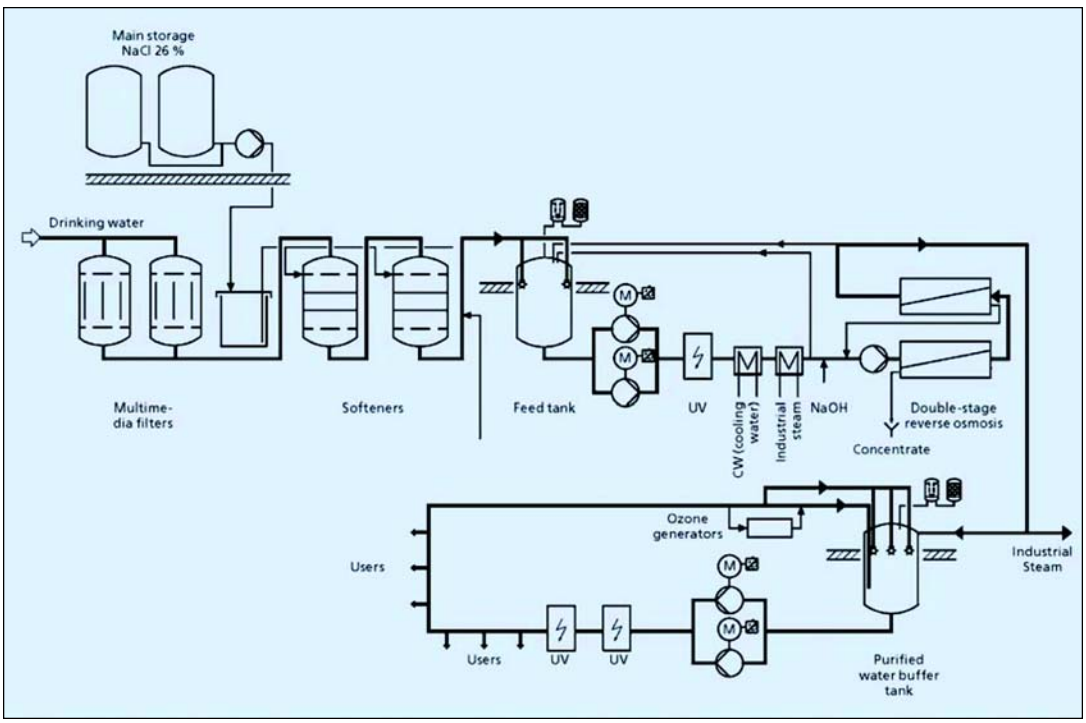

Figure 1. Diagram of production and distribution of purified water.

Basic Concept

The process engineering design concept was conceived by an engineering office in conjunction with the engineering department of Serono in Geneva. The following equipment and services were supplied:

- purified water production
- injection control and destruction of ozone
- service water softening (cooling towers steam)
- control panels - switching and control
- engineering of material and programming conception
- commissioning
- validation DQ and IQ
- assistance in validation OQ

Project Goals

Starting with potable water distributed by the Service des Eaux de Vevey (municipal water supply), the aim was to produce purified water according to the US Pharmacopoeia USP XXIV, the site specifications of Serono, and to conform to the concepts of installation, manufacturing, and validation mandated by the cGMP. The purified water will be used to feed the following:

- Multistage Still
- Purified Steam Generator
- Pre-Washing System
- Steam Boiler (mainly with softened water).

In the first stage, the production capacity for purified water is 6.5 m^3/h at 15°C. To guarantee the nominal capacity over all seasons, the system was dimensioned for a water temperature of 10°C - *Table A*.

Description of the Purified Water Production Process

The installed water treatment system consists of five phases:

- Pre-treatment with multimedia filtration, softening, dechlorination, feed tank with UV-radiation and heat exchangers. These elements are sized for the requirements of the final extension.

	Units	Value
Aspect/Color		clear/colorless
Smell/Taste		odorless/tasteless
Conductivity (25°C)	μS/cm	< 1.25
TOC	mg/l	< 500
Aerobic microbial contamination	CFU/100 ml	< 10
Pathogenic micro-organisms		
E. coli, enterococci, pseudomonas aeruginosa, pseudomonas cepacia	n/100 ml	n.d.
Endotoxin content	EU/ml	< 0.25

Table A. Physico-chemical parameters required by QA.

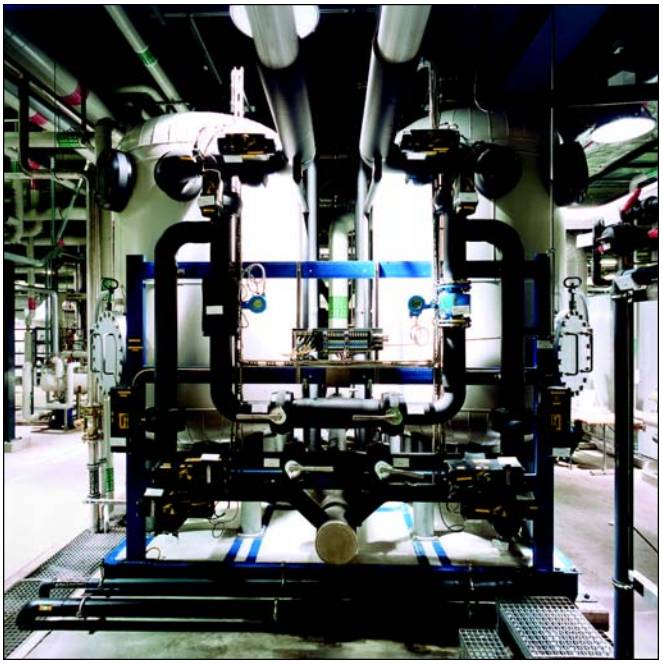

Figure 2. Multimedia filtration.

- Demineralization by two-stage reverse osmosis including neutralization of carbon dioxide. These units are laid out to allow for future extensions.

- Hot water sanitization.

- Purified water storage tank with distribution and circulation equipment.

- Disinfection of the treated permeate and of the purified water storage tank by electrolytically produced ozone; ozone destruction by UV-radiation in the feed of the distribution loop.

Process Description of the Purified Water Production Plant

Pre-Treatment - Multimedia Filtration

Suspended matter in the raw water is removed by passing the water through two multimedia filters in parallel. Each unit is filled with quartz sand and activated carbon, and has a capacity of 36 m^3/hr. The system is configured to work in parallel. During backwashing a single unit works.

The control of each unit is independent, allowing each unit independent response to differential pressure and feed water solids capacity. The signal to backwash a unit can be given by one of three parameters: differential pressure, water consumption, or cycle time. Differential pressure, which indicates that the filter is becoming saturated, has priority over cycle time in initiating a backwash. Starting the backwash procedure requires an operator to activate the automatic counter-current washing process at the control panel. The different steps of this operation can be followed - *Figure 1*.

Softening

The exchange of calcium and magnesium ions with sodium ions takes place in a series of softeners filled with ion exchange resins specially developed for potable water and food applications. The unit allows softening with both columns either in series or in parallel. Each unit is equipped with the necessary instrumentation to measure differential pressure, water consumption, and flow. In the softened water collector, a resin trap retains the resin fines and any resins that might have accidentally come from the softeners. The resin retention is indicated by the pressure loss measurement installed with the trap. A valve arrangement allows purging of the filter on request. Three parameters of each softener are permanently controlled: differential pressure, softened water production, and cycle time. When the programmed capacity is reached, the working column is regenerated. The polishing column automatically becomes the working column. At the end of the regeneration cycle, the regenerated column becomes the polishing filter. The residual hardness is constantly monitored with an alarm level of 1 mg/l. To guarantee this value monodisperse resins specially developed for potable water and food applications are used, regenerated co-currently with 90 g NaCl per liter of resin. Concentrated brine, stored outside of the building is used for regeneration. A pump transfers the brine, controlled by level sensors, to the day tank located in the technical zone.

The regenerations are interlocked so that softener regeneration and multimedia backwash cannot occur simultaneously. Softener regeneration has priority - *Figure 2*.

Dechlorination

The possible presence of free chlorine in the feed water is detected by continuously measuring the Redox potential. If chlorine traces are present, a signal interrupts the softened water feed. This can only be reset into operation once bisulfite dosing has been actuated and the measured chlorine level is back within control limits. A second Redox measurement installed right at the feed of the reverse osmosis unit ensures security by stopping reverse osmosis production when chlorine is present. In this case, the softened water is recirculated into the feed tank.

Feed Tank

This tank receives three flows:

- softened feed water
- recirculating permeate
- concentrate during recirculation or for out of specification returns (Redox - pH)

The softened water, possibly dechlorinated, is automatically fed into the tank via two "spray-balls" depending on the water level. The measurements of level, service pressure, and temperature are linked to the control screens. The reverse osmosis is fed by a group of variable speed electropumps, pump rate being dependent on whether the reverse osmosis or the recirculation is being fed. The tank vent is equipped with a sterile microfilter in a heated housing to eliminate condensation and with a carbon dioxide adsorber in the outlet. Connections with the sterile filter allow in-line integrity tests and validation of the filter element. This equipment limits pH-variations in the feed water.

This very specific layout was chosen to continuously keep the feed network for both the reverse osmosis unit and the production of purified water in a dynamic circuit with the objective to avoid water stagnation and to limit as far as possible the loss of water in concentrate or rinsing water.

UV-Sanitization

Downstream of the feed pumps, a UV-sanitizer at 254 nm with an intensity of more than 30,000 microWatts/cm^2, ensures reduction of bacterial contamination in the reverse osmosis feed. The radiation intensity of the lamps, the operating status, and the alarms are given to the control screen.

Heat Exchangers

The feed of the reverse osmosis is equipped with two tubular heat exchangers with double-plates, water/steam and water/cooling water, of sanitary design, installed in series.

In manual operation, the feed temperature of the reverse osmosis unit is kept steady at 15°C.

Reverse Osmosis

In the final installation, two lines of reverse osmosis units, each with a capacity of 13.5 m^3/h, will be in operation. At present, one unit is installed with a capacity of 6.5 m^3/h, which may be extended to 13.5 m^3/h. Any suspended residue is retained by microfilter cartridges with a porosity of 1.2 micron.

The pH of the feed water is continuously controlled to neutralize and transform carbonic acid into bicarbonate. Caustic soda, pharmaceutical grade - is only injected when the system is not in recirculation.

The double-stage reverse osmosis unit is fed by only one pump. The permeate and concentrate capacities are controlled by the panel as well as all parameters of pressure and temperature. The panel stops the high-pressure pump when it reaches the pressure and temperature limit values - *Figure 3*.

Permeate capacity @ 15°C:

		expected	reached
1st stage	m^3/h	6.5	6.5
2nd stage	m^3/h	13.5	13.5
3rd stage	m^3/h	25	25

Sanitization

The water/steam exchanger produces hot water at 80°C for the sanitization of the feed tank, the feed pumps, the UV-generator, the security microfilters, the reverse osmosis feed, and the recirculation piping. During this operation, the membrane stages are by-passed by a "spool piece." The same system is used for the sanitization at 80°C of the pretreatment, that is the multimedia filters and the softeners. The

Figure 3. Softeners in series.

contents of the feed tank are used for the sanitization itself. It is actuated at the panel; the UV-lamp is switched off, and the process runs automatically. When the control indicates a temperature of 80°C, circulation is maintained at that temperature for one hour. At the end of the cycle, cooling is automatically initiated by means of the exchanger (water/cooling water) until a temperature of 15°C is reached. The production processor is then directly reset into normal operation by means of the panel. All sanitization phases are automatically recorded.

Purified Water Storage Tank

The permeate mainly feeds the stainless steel 316 L tank through an automatic diaphragm valve depending on the level indicated by the differential pressure measurement. The double-walled tank - for cooling and maintaining the purified water temperature at 18°C - is equipped with the following elements for reasons of security and a sterile atmosphere:

- bursting disk in case of excess pressure with a control contact to an open air outlet
- continuous pressure and temperature control
- security controls for high and low levels
- sterile microfiltration vent filter kept at 80°C (to avoid condensation) with connections to allow in-line testing and validation
- CO_2-adsorber, installed upstream of the vent filter allows air passage over a bed of chemically pure calcium granules. The adsorption capacity of these granules is 1 mol of calcium hydroxide neutralizes 1 mol of carbon dioxide.

The circulation return is split into two streams. One of them feeds the water with a high ozone concentration and a capacity of approximately 4.7 m^3/h into the tank beneath the minimum water level. The other one feeds the main return into the tank by three spray balls at a pressure of 2 bar.

Disinfecting by Ozone

This system was chosen to allow a continuous disinfection of the purified water in circulation, in the storage tank, and of additional permeate from the double-stage reverse osmosis. Furthermore, it allows sanitization of the entire distribution network without additives, without modifying the purified water quality, and without loss of rinsing water. Ozone is a tri-atomic modification of oxygen. It's an extremely strong and effective oxidant. The high reactivity allows effective destruction of microorganisms and guarantees continuous sanitization. This strong oxidant is produced by catalytic separation of water inside an electrolytic cell composed of an anode, a cathode, and a solid polymeric membrane which acts as an electrolyte and separator between the two half-cells. The Direct Current (DC), which is fed to the cell, causes the splitting of the passing demineralized water into ozone, oxygen, and protons at the anodic side and the reduction to hydrogen gas at the cathodic side. The high-purity ozone thus produced within the flow-electrolysis cell is immediately dissolved in the passing purified water stream. This system works for demineralized water with a maximum conductivity of 20 µS/cm.

The disinfection system is composed of three groups of electrolytic ozone generators fed from the main loop return. The intensity is controlled to keep an ozone concentration of approximately 0.1 to 0.2 ppm in the purified water tank. The ozone content is measured at five points in the loop by microprocessor analyzers with a measuring range of 1 ppb. All values are given to the panel together with alarm signals (outlets). The polarographic measuring probe is composed of three precious metal electrodes, immersed in an electrolyte

Figure 4. Double-stage reverse osmosis (extensible).

solution, separated from the liquid by a gas-permeable membrane.

A protective electrode enveloping the measuring electrode blocks the influence of other gases and improves the stability. A voltage difference is applied between the electrodes to reduce the ozone passing the membrane thanks to a partial pressure gradient. A proportional electric current is generated, measured by the analyzer, then calibrated, displayed, and converted. The value is available in analog and numeric outputs - *Figure 4*.

Piping and Purified Water Distribution

Two centrifugal pumps in stainless steel 316L each with a capacity of maximum 24.9 m^3/h with open wheels and speed-variable motors ensure the purified water distribution. The capacity is set by means of a pressure detector. They can be independently isolated from one another by an automatic diaphragm valve arrangement controlled by the panel. The ozone is destroyed by two UV-generators in series working at an intensity of above 90,000 microWatts/cm^2, and in the position to treat a maximum flow of 49.8 m^3/h.

All equipment parts in contact with the purified water are made of electropolished stainless steel 316L. All control parameters – intensity, temperature, and operating status - are transmitted to the control panel - *Figure 5*.

On the fittings and valves of the multimedia filters, the softeners and the reverse osmosis plants, the straight valves are placed in strict compliance to the 3D guidelines in order to reduce the dead ends in all of the fittings to a minimum. Starting with the softening station, all valves are membrane valves made of materials complying with the US FDA and with housings made of wrought stainless steel 1.4435. The valves connected on a bypass as well as the sampling valves and the taps are T-valves (zero dead-leg body) of identical quality. The valve weir placed immediately at the point of

Figure 5. Ozonization plant (3 x 4 gO_3/h).

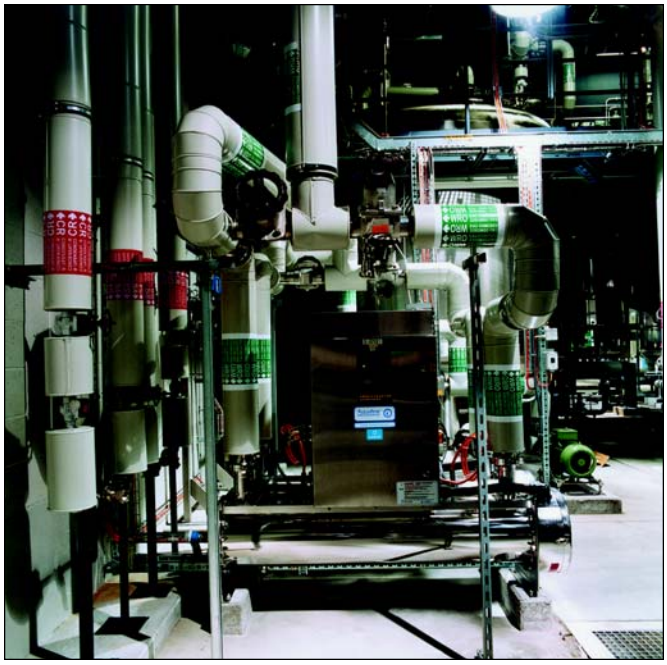

Figure 6. UV generator for the ozone destruction.

flow (straight throughflow enables almost complete deadleg-free take). The material of the pipes is specified by the engineering office and is adapted to the conveyed liquids. For the stainless steel hygienics tubing and fittings material grade 1.4435 is used with low ferrite, fully annealed (< 0.5 %). The interval surface has a polished scratch- and pit-free roughness not exceeding 0.6 µm Ra. For the purified section, pipes, instrumentation, and valves are assembled by orbital welding without insertions with a ferrite content < 1 % or by using BBS connections. An endoscopic control has been effected for each welding and the ferrite content measured. Ten percent of the weldings and all manual weldings (approximately 3 % of all weldings) have been controlled with X-rays (Rx). The entire weldings are documented.

Sanitization of the Purified Water Distribution System

The tank and its equipment as well as the distribution system may be sterilized by purified steam or ozone. The usual process is a periodical sanitization at night, or when stipulated by the user. During this operation, the panel automatically interrupts all feeds to consumers and the UV-lamps. The ozonated purified water circulates within the whole distribution loop for a preset period to obtain a constant optimum ozone concentration in the circulation return. Due to the length of the distribution loop, it takes 17 minutes to obtain an ozone value in the return. Then, the UV-systems are returned to operation. The end of the sanitization is marked by the absence of ozone in the output of the second UV-generator. The panel can control and vary all procedure durations. Sanitization by purified steam is used only in extreme cases, for example, after opening the loop for maintenance, piping modifications or replacing elements. The purified steam is introduced by a flexible connection into the permeate line directly downstream of the reverse osmosis

unit. The manual valves by-pass the ozone generators at shared in- and outputs. All purge valves as well as the venting valve of the sterile microfilter are opened and the pressure of the purified steam is set at 2.5 bar. The sanitization process is then actuated and entirely controlled by the panel. All condensates are recovered and drained. When all measuring points indicate the sanitization temperature (121°C), this is steadily maintained over 30 minutes. Then, after stopping the steam, sterile process air is fed into the sterile microfilter in counter-current. Simultaneously, cooling water circulates between the double jackets of the purified water storage tank. The cooling operation is stopped when the purified water temperature reaches 18°C in the return. The normal distribution process is then reset into operation.

System Management

All functions are managed by a programmable logic controller situated immediately next to the installations. The display and touchscreen allow supervision of the entire purified water production system and also allows modification of certain parameters when needed. The link to the control center is where all data is recorded via a netware system. Data may be reproduced in different ways depending on the information priority and the hierarchic treatment - *Figure 6*.

Description of the Service Water Treatment

The service waters comprise the feeds for the following:

- Cooling Towers
- Supplement to the Steam Production
- Compressor Cooling

Figure 7. Operating and control panel, Dosing group for caustic soda and sodium bi-sulfite, Double-stage reverse osmosis (extensible).

The raw water is directly fed to a series of softeners working alternately. The same specifications as those applied for the softening unit for the "purified water production" are used.

Steam Boiler Feed

The steam boilers are fed first by the condensate return, secondly permeate, and then finally, softened water. If permeate is required for the purified water storage tank, an automatic valve manifold switches the feed to softened water coming from the softening unit. This unit has its own control cabinet with programmable logic controller and touchscreen. All information is also transmitted to the control center.

Qualification and Validation

Why Validate?

Only by process validation can you ensure that all units meet the required quality standards; quality control alone is not sufficient to guarantee that the product quality is achieved. These procedures reduce costs by reducing expensive problem solving. The concept of defining the basis is regulated by several organizations: no matter which organization is further mentioned, validation is compulsory.

Three terms are often used for this concept, the definitions of which are as follows:

- Calibration - all operations that establish under certain given conditions the relation between values indicated by a measuring apparatus or system or the values given by an equipment measurement and the corresponding values of a standard measure.

- Qualification - operation with the aim to demonstrate that equipment operates correctly and in fact provides the expected results.

- Validation - Establishment of the proof in conformity with the principles of Good Manufacturing Practice (GMP) that the execution and the use of all processes, procedures, materials, raw materials, products, activities, and systems effectively ensure reaching the expected results.

Validation

Installation Qualification - IQ

Aim: to identify each piece of equipment and to determine whether it is installed in conformity with the approved specifications.

- System Description
- Utility Requirements (electric capacity, cooling water, air steam, nitrogen drainage)
- Specifications of the Different Plant Components
- Calibration of the Measuring Instruments
- Training and Qualification respectively of the Operators
- Adequate Environment

The installation qualification must demonstrate the following:

- the system was laid-out and built in conformity with the specification
- the equipment performances are within specification and were tested by the manufacturer
- the components are installed correctly and the utilities are in line with the equipment requirements
- the operators are of the technical standard required for the correct operation and maintenance of the plant
- the equipment control and monitoring instruments are precise
- the environment is of the required quality

All these operations aim to show us that the system and its environment meet the specifications.

Operational Qualification - OQ

Aim: to determine whether the plant functioning conforms to the approved specifications. The objective of this stage is to ensure that the tested system performances are adapted to the process for which the system is intended.

One will thus:

- test the equipment performances
- test the cycles
- test the programs

All these operations aim to prove that the system in isolation functions according to specifications.

Performance Qualification - PQ

Aim: to test the equipment functioning in its normal capacity range over one year. Still called "performance qualification" by the Americans, this operation whether prospective, retrospective, or consecutive must give proof that the system in production conditions, allowing for seasonal variations, gives the expected results.

All these operations aim to show that the whole system performs to specification in production conditions and at all times.

Documentation

Good documentation is one of the essential and indispensable elements of the system quality assurance.

Functions:

- To give instructions and working procedures:
  - uniformity of intervention maintenance and utilization practices
  - adherence to regulations
  - adherence to validation files
  - avoidance of deviations
  - reference bases
- Recording of information:
  - historic
  - traceability
  - evidence

Elements constituting the documentation system:

- specification of plant components
- specification
- general procedures
- reports of calibration, qualification, and validation
- material follow-up
- diagrams, drawings (P&ID), and programming listings
- files of malfunctions, anomalies, and change control protocols
- recordings of maintenance activities
- recordings of certain material controls and certifications

Labeling

The documents are labeled according to a pre-established system allowing their management. The labeling procedure may comprise the following headings:

- Service Symbol
- Nature of the Document Symbol
- Field of Application Symbol
- Edition Number
- Version

Production

The production of the document is carried out by a qualified person, the closest possible to the user.

Verification

The newly written or revised document may be verified by any qualified person (in direct contact with the user of the document).

Approval

Any document must be approved by qualified persons. Their role is to make the documents compulsory and official.

Distribution

Ensured by the Quality Assurance Department, it makes adequate numbers of copies available to all users.

Archiving

The circulating copies are destroyed, the original archived.

The Procedures

Documents that give instructions to allow a trained person to perform an operation in conformity with an established rule in a way that the expected result can be reached in a reproducible manner.

Conclusion

The plant has worked continuously since its start-up (end of 1998) without any interruption other than the security stop for passing into the year 2000. All operating parameters,

daily controls by the user are in line with the expected values as far as quantity is concerned and always superior as far as quality is concerned.

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Barrier Isolation History and Trends

by Jack Lysfjord and Michael Porter

This article summarizes survey results taken in 2002 on the use of barrier isolators in fill/finish applications in the parenteral industry.

For complete survey raw data, click here.

This is the third survey (1998 and 2000 are previous surveys) on the use of Barrier Isolators for automated pharmaceutical fill finish operations that was implemented. Manual operations in a glove box are not considered. We began this journey in the late 1980s and early 1990s when the use of pharmaceutical "barriers" or "isolators" was a discussion concept rather than a practice for improving sterility assurance. New ground was broken developing some of the first "production" fill/finish barrier isolators for pharmaceuticals with the Barrier Users Group Symposium (BUGS) and LUMS groups (Lilly, Upjohn, Merck, et. al.). However, there was always a benchmarking question as to usage in the industry. A decision was made to try and survey users and equipment manufacturers to get some answers. Keep in mind that the data is only as good as the input from many sources and that while trends certainly apply, numbers should not be viewed as absolute, but rather as trends over time. Every fill finish application for Barrier Isolators may not have been found, but the vast majority for trend analysis were identified. Preliminary data was presented at ISPE conferences in Arlington, VA in June 2002 and in Zurich in September 2002. Here are the results for 2002:

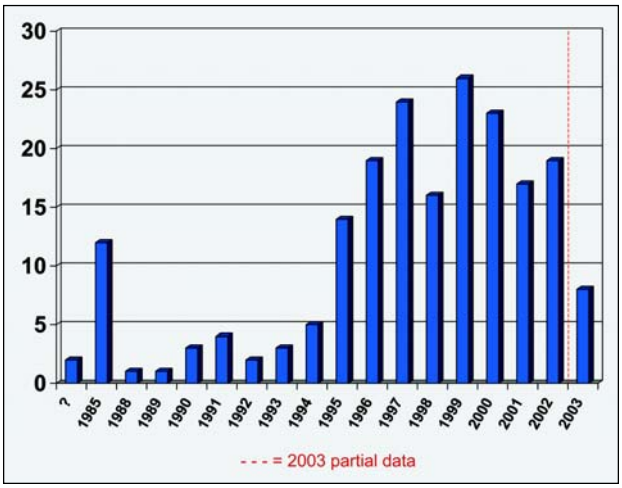

Figure 1. Barrier isolator filling line - deliveries by year.

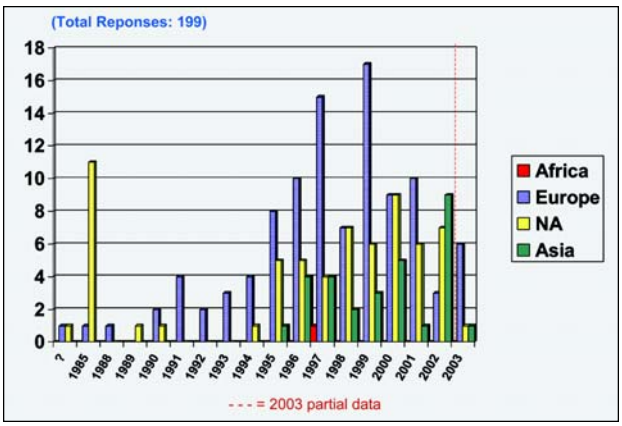

Figure 2. Barrier isolator filling line - deliveries by year and region.

Filling Barrier Isolators Delivered:

1998	2000	2002
84	172	199

Figure 1 shows that global deliveries of Barrier Isolators for automated fill finish are continuing from 1996 through 2002 with about 20 per year being delivered.

Figure 2 shows the number of deliveries for various continents. Of note in 2002: European deliveries dropped, North American deliveries maintained, and Asia (Japan) is taking the lead in more recent application of this technology.

Figure 3 shows companies with the highest usage. It is interesting to note the commitment some companies put into this type of technology. It is also interesting to note the reluctance of others to begin the learning process with barrier isolation.

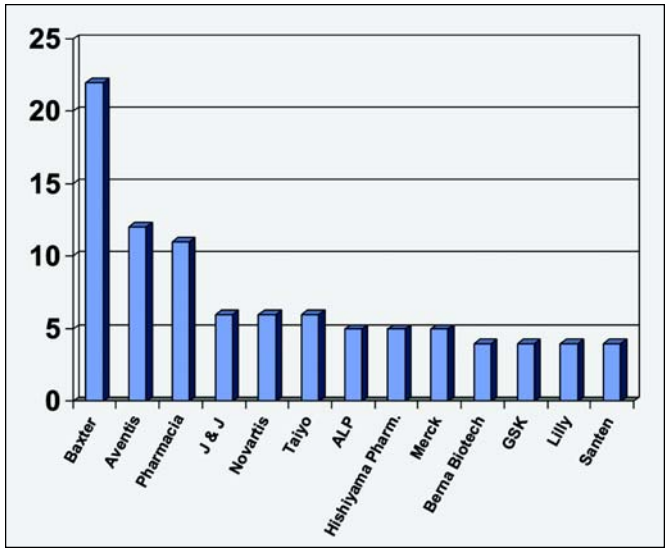

Figure 3. Barrier isolator filling line - companies with highest usage.

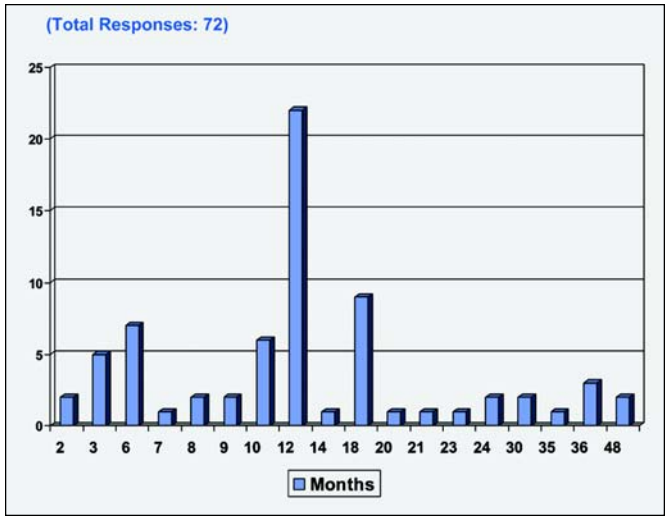

Figure 4. Months from delivery to start-up.

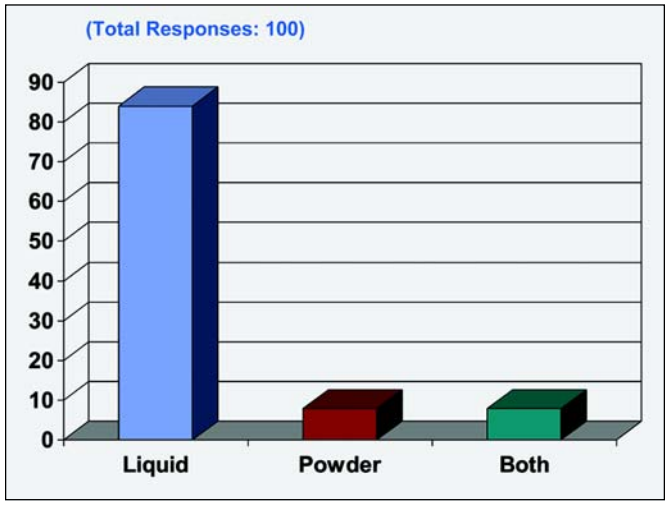

Figure 5. Filling line type.

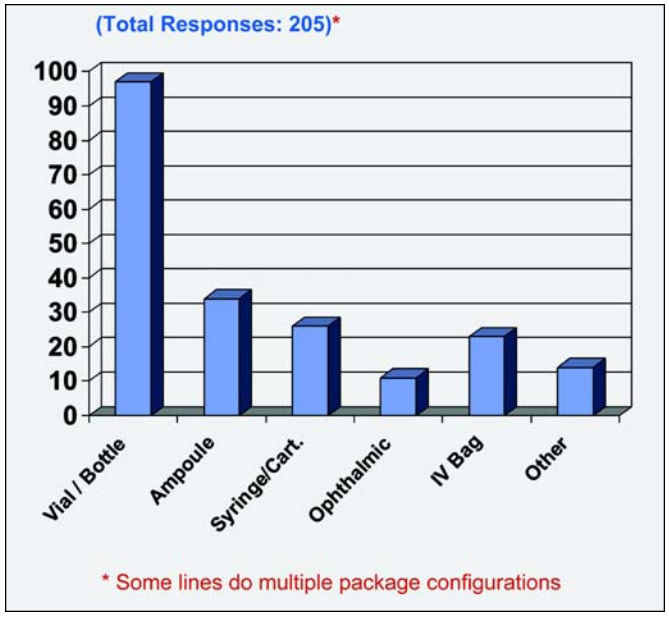

Figure 6. Type of container.

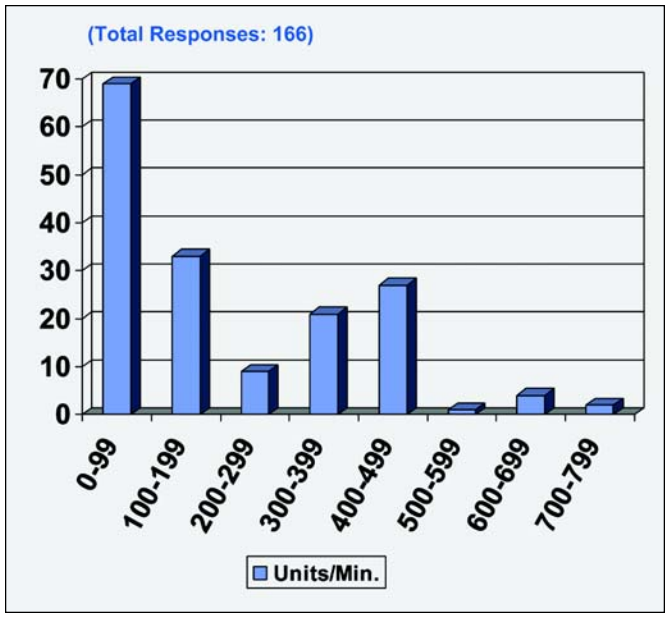

Figure 7. Maximum speed.

The following are the number of companies using barrier isolation:

1998	2000	2002
38	56	67

The following are the number of units in operation:

1998	2000	2002
34	70	90

The number of units in operation is close to half of the number of delivered units. The remainder are being installed, commissioned, validated, and approved.

One of the more interesting pieces of data is the number of filling lines with FDA approval (out of 128 responses):

1998	2000	2002
6	26	52

Figure 4 indicates the number of months from delivery to start-up. Data is wide spread and has a strong correlation to line speed and degree of difficulty in dealing with processing inside the enclosure. Slower speed lines (clinicals) were easier to start-up and vice-versa. Typical clinical applications do not go through the rigorous validation process that higher speed production systems require.

Figure 5 shows "Filling Line Type" by liquid, powder, or both applications.

Vials are the predominant container used with Barrier Isolation Systems as shown in Figure 6.

The maximum speed of Fill Finish Systems is shown in Figure 7. Note: the large number of applications for 0 - 99/min.

Table A shows hard wall construction (stainless steel and glass) predominates due to:

1. Robustness/Reliability
2. Less Absorption of Sterilant
3. Rigidity prevents breathing of Barrier Isolators (creating negative pressure inside and ingesting particles through openings when removing hands from gloves)

Table B shows surrounding room classification. Class 100,000 (1SO class 8) is the predominant choice. Note that some early applications with unclassified surrounding rooms have been upgraded to class 100,000 (ISO class 8).

Hydrogen Peroxide Vapor is the sterliant of choice as shown in Table C. Use of half-suits is shown in Table D.

Gloves are the typical method for intervention. One or two-piece gloves usage is shown in Table E.

Table F indicates smooth sleeves or gauntlets are preferred by 4:1 over pleated style.

Glove Replacement period is critical to assurance of glove integrity. Typical replacement periods reported are shown in Figure 8. Typical replacement frequency depends on intervention frequency, design of the glove/isolator junction and manipulations typically performed at a particular glove location (particularly when broken glass is present).

Integrity testing and method of testing are shown in Table G and Figure 9, respectively.

Use of a second disposable glove (latex) is shown in Table H. This is typically placed on the hand prior to going into the glove port, but some use it over the glove port inside the isolator.

The use of mouseholes and depyrogenation tunnel openings creates an "open isolator." Typical ratio of open vs. closed applications is shown in Table I.

The internal environment pressure to the surrounding room and pressure with a washer/tunnel are shown in Figures 10 and 11, respectively.

	1998	2000	2002
Soft Wall	9	9	9
Hard Wall	73	134	166
Total	**82**	**143**	**175**

Table A. Barrier isolator construction.

	1998	2000	2002
100	3	4	5
1,000	3	4	7
10,000	13	30	40
100,000	55	84	105
Unclassified	5	17	7
Response Total	**79**	**139**	**164**

Table B. Barrier isolator surrounding room classification.

H_2O_2 Vapor	135
H_2O_2 Spray	13
Miscellaneous Peracetic Acid	6
Alcohol Wipe	3
H_2O_2 + Steam	1
Formalin	1
ClO_2	1
Other	5
Total	**165**

Table C. Barrier isolator sterilants.

1998	2000	2002
	17	21
*Question Not Asked	(102 Responses)	(126 Responses)

Table D.The number of ILines with half-suits.

One Piece	Two Piece	Total
3	72	**110**

Table E. Number of filling lines that use - one or two piece gloves.

Yes	No	Total
14	56	**70**

Table F. Two piece glove - is gauntlet pleated?

Yes	No	Total
91	29	**120**

Table G. Gloves - do you integrity test?

Yes	No	Total
78	31	**109**

Table H. Do you use a second disposable glove?

Open	Closed	Total
100	30	**130**

Table I. Is barrier isolator open or closed?

Yes	No	Total
19	20	**39**

Table J. Do you use a sterilizable cool zone with depyrogenation tunnel?

Yes			32
	Chemical	20	
	Biological	5	
	Chemical Biological	5	
	Chemical Nuclear	2	
No			76
Total			**10**

Table K. Barrier isolators indicating the need for containment.

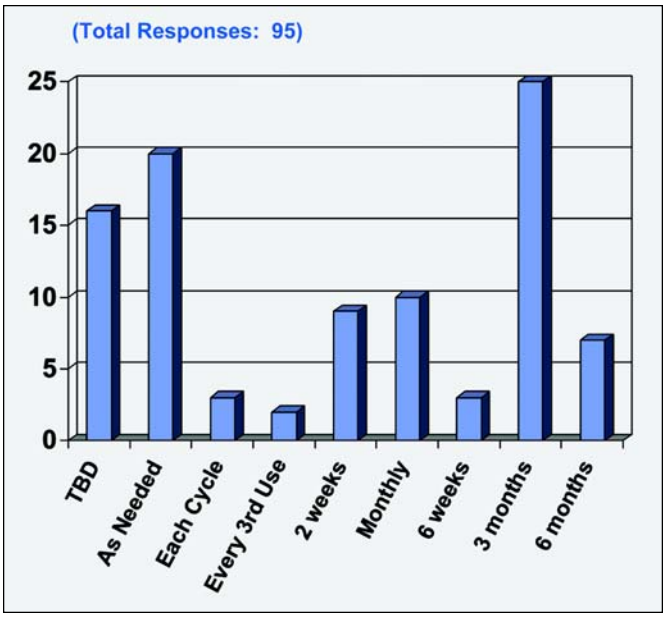

Figure 8. Glove replacement period.

When a depyrogenation tunnel is used, sterilizable cool zone usage is shown in Table J.

The need for containment is increasing. The need and type of need is shown in Table K. 30% of those reporting indicate some need for containment!

In 2001, Stewart Davenport, Pharmacia, Kalamazoo, MI, reported at the Arlington, VA ISPE Barrier Isolation Technology Conference on media fill data for 3 RABS (Restricted Access Barrier Systems) equipped lines. **Data indicated equivalence to isolators for sterility assurance.** This year our survey indicates 52 RABS lines delivered. This can be an alternative to isolators when only Asepsis and not containment is needed. This number is in addition to the 199 Barrier Isolators delivered in 2002.

Cumulative deliveries of Barrier Isolators for fill finish are shown in Figure 12. The increase in numbers continues at a fairly consistent rate. An interesting comment from Lennart Ernerot of The Swedish Inspectorate at the 2002 ISPE Zurich Barrier Isolator Conference was that he would mandate the use of isolators for products such as vaccines and other biopharmaceuticals that are slated for children because of the known tremendous improvement in sterility assurance over conventional cleanroom aseptic processing. As regulators and users of barrier isolators evolve toward this mindset, the slope of the cumulative deliveries line is likely to increase.

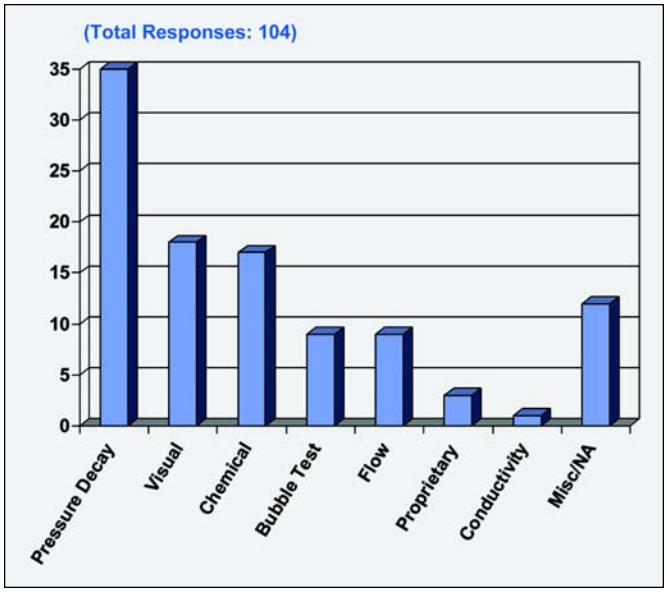

Figure 9. Method for integrity testing of gloves.

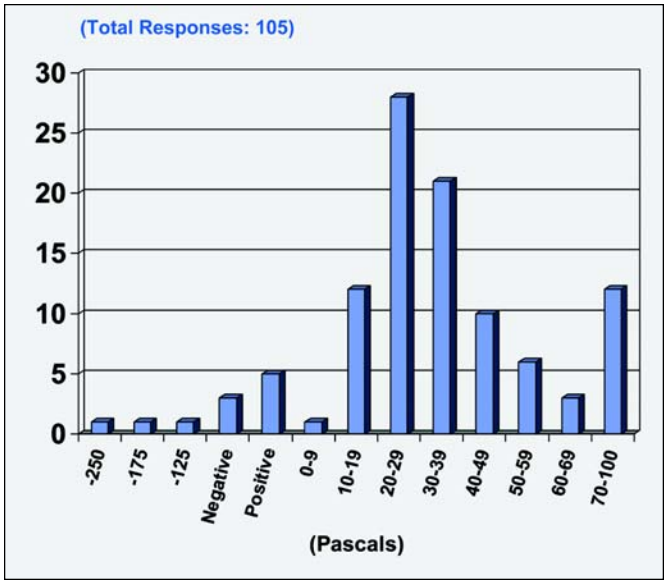

Figure 10. Pressure to surrounding rooms (12.5 Pascals = 0.5″ Water).

Survey Conclusions:

- slight slowing of orders in 2001- 2002
- Europe typically has twice the NA order rate (1995-2001); however, Europe dropped in 2002 to less than NA.
- Asia really accepting technology, particularly Japan (27)
- some companies really accepting technology (Baxter) while others avoid it
- vials predominate applications

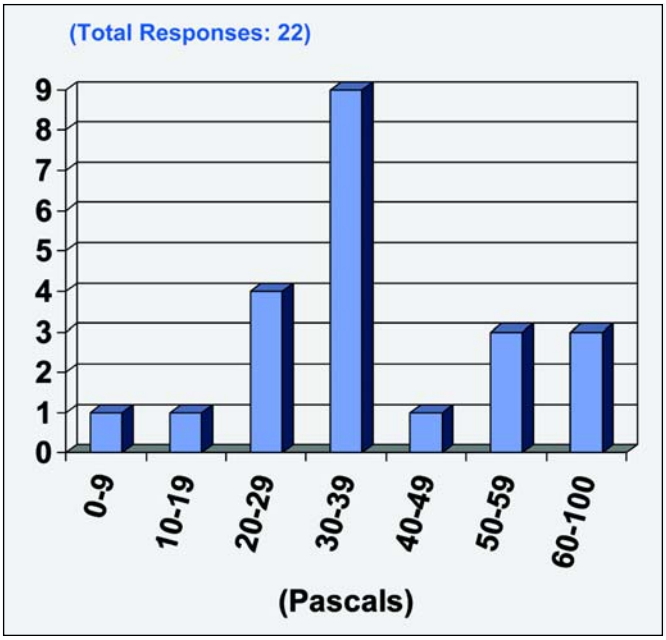

Figure 11. Pressure to washer rooms (12.5 Pascals = 0.5″ Water).

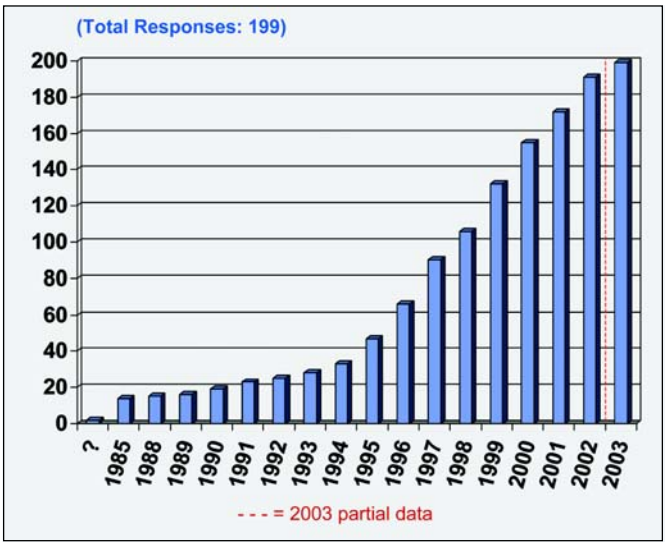

Figure 12. Barrier isolator filling line - cumulative deliveries.

- usage for lines below 100/minute are most frequent users of isolators
- hard wall Isolators/H_2O_2 Vapor Sterilants/Class 100,000 Room
- predominate applications
- two-piece gloves without pleats is typical as is second inner glove

Trends for decision makers – benchmarking information for those who are just getting started:

- hard wall isolator
- vaporized H_2O_2 sterilant
- class 100,000 surrounding room
- gloves only – minimize half suits
- two-piece gloves with smooth sleeves or gauntlets
- doing glove integrity tests
- using disposable glove (2nd glove)

Remember, you are not only deciding how to produce today's products, but consider that the decisions you make today will determine what you can do for the next 25-30 years in your facility. Asepsis and containment are the concerns for the future. Will you make the correct choices for your company?

If you have additional information, please contact the authors.

About the Authors

Jack Lysfjord is Vice President of Consulting for Valicare, a division of Bosch Packaging Technology. Since 1981, Lysfjord has held a variety of management positions with Bosch Packaging Technology (formerly TL Systems Corporation). Prior experience was with Dahlberg, Litton, Medtronic, and Onan. Lysfjord is a member of ISPE, recipient of the 2001 Richard Purdy Distinguished Achievement Award, a past member of the Board of Directors, a past Member of the Year in 1994, past Chairman of the Vendor Committee, and past Chairman and current member of the Marketing Advisory Council. He holds other memberships in the Parenteral Drug Association (PDA), the American Glove Box Society (AGS), The Parenteral Society (UK), R3 Nordic (Clean Room Processing) the Society of Automotive Engineers (SAE), and the Barrier Users Groups Symposium (BUGS) of which he is the Chairman. He is a frequent speaker and course leader in the US, Europe and Asia, and has been author and co-author for numerous technical papers and articles. Lysfjord holds a BS in mechanical/industrial engineering from the University of Minnesota and an MBA from the University of St. Thomas.

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