Country Profile

A look at the Pharmaceutical Industry in

POLAND

Produced in collaboration with ISPE Poland

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Dear Friends,

The idea of establishing an ISPE Affiliate in Poland was first conceived in 1999. After two years of hard work, which included complying with the intricacies of Polish law, we officially launched the Affiliate to an international audience at the ISPE Amsterdam Conference in December 2001. Over the years, I have come to realize the value of the organization and the importance of bringing together various key participants in the pharmaceutical industry and having a forum for exchanging experiences with global participants. A forum for the collaboration of individuals, industry, government, and academia was and is even more important for the country of Poland that finally became a member of the European Union on 1 May 2004. The Polish pharmaceutical industry is comprised of long-lasting tradition and has made significant contributions to the country as a whole; however, the adoption of the principles proposed and recommended by the Society and its local Affiliates has allowed a global audience to more efficiently and efficaciously implement the principles of Good Manufacturing Practice.

I am convinced that the articles presented in this profile will introduce you to the vast opportunities and contributions of the pharmaceutical industry in Poland. Today, there are more individuals employed in the pharmaceutical industry in Poland than ever before. We are excited and optimistic about the future of the pharmaceutical industry in Poland, but at the same time, we are challenged to compete in this ever-changing, global environment.

After reading the following profile of Poland, should you have any questions or would like to receive more information, please do not hesitate to contact me.

Sincerely Yours,

Marek Ruzikowski

Marek Ruzikowski
Chairman, ISPE Poland

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 Netherlands in the July/August issue of *Pharmaceutical Engineering.*

Poland - Main Opportunities and Risks in the Industry

by Andrzej Szarmanski

Poland, a country with a population of 39-million, a size similar to Spain, is currently one of the most important pharmaceutical markets in Europe. Its size and dynamic growth in terms of sales value provides excellent business opportunities. In 2003, the market growth was one of the highest in Europe reaching 13% and 3.1 billion Euro ($3.6 billion USD). This article will present the main opportunities and risks of the industry in Poland.

The EU Enlarged Market

At last! The barriers for making good business are being knocked down. There is no doubt that the new European market will soon become a source of new possibilities and benefits. In 2003, 15% of Poland's pharmaceutical production output was meant for export, but the value of sales on the EU market was absolutely marginal.

In practice, the increased accessibility to the western European markets for the new member states, and in particular for Poland having a strong and large pharmaceutical sector, might mean the "low hanging fruit" within the reach of the business, and also a chance for a long-term development driven by the strengthened export engine.

The EU Enlarged Market
- 450 million population
- 25 countries
- 21 languages
- market value more than $120 billion

The Industry in Poland
- mostly generic products manufactured
- 15% of production value for export
- around 350 manufacturers
- $1 billion invested over the last eight years
- 23,000 employees

The Market in Poland
- 13% growth of market value in 2003
- 8,800 products registered
- OTC sales make 50% of total sales
- local industry has 30% of market value
- local industry as 70% of market volume
- top 10 companies have 40% of market value

Table A. Key industry information in Poland.

The industry in Poland manufactures mostly generic products, i.e., products for which the patent has already expired. After accession, it should be much easier to obtain marketing authorization for such products on the EU markets.

There are approximately 350 pharmaceutical manufacturers operating on the Polish market, registering more than 8,000 medicinal products. These companies have four years to update the registration files and to comply with the EU regulations. Some products which will lack sufficient quality, safety, and efficacy data will not be registered. Although demanding, the new regulatory requirements will keep the patients safer than before.

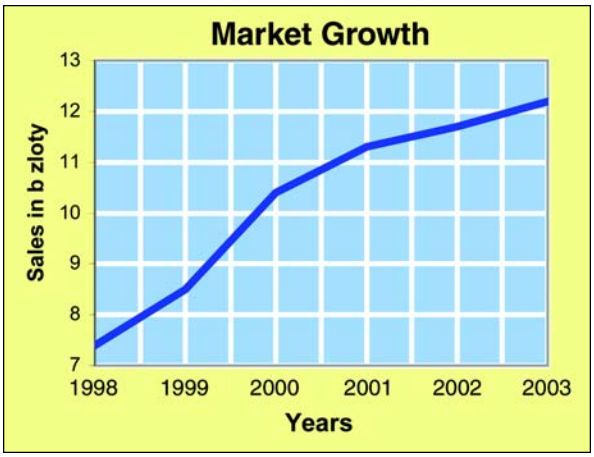

Figure 1. Market growth in Poland.

Growing Competition

The top five players already present on the market include GlaxoSmithKline (GSK), Novartis/Lek, Polpharma, Servier, and Eli Lilly. There is a chance that some other foreign companies will follow the example of GlaxoSmithKline, which established a strong position on the market and in the region of central-eastern Europe by acquisition of a local manufacturer in Poznan. GSK invested around $400 million in Poland and transferred more than 70 products to the site. Nevertheless, it must be emphasized that in the enlarged European Union, the importance of the site's geographical location might be much lower. In the future, the manufacturing operations may be relocated anywhere where there is assured a good infrastructure, stable tax and judicial system, as well as friendly treatment of investors.

Poland is still able to attract new investors because of the low cost of labor compared to Western Europe; however, keep in mind that labor costs have the potential to increase in the future, and there are other countries that have cheap labor. In addition, pharma-

Figure 2. Top 5 pharmaceutical companies in Poland.

ceutical manufacturers from Asia are looking forward to improve their position on the Polish market.

The competition will be tougher and tougher, and for companies which will not show a value to the patient, payer, or the regulator, it will mean a struggle to survive.

Political Interactions

The actions on the edge of politics and business usually pose more risks than opportunities for the business processes. In the case of pharmaceuticals, the state is one of the indirect customers who subsidize a large part of patient expenditures.

The Polish government, certainly in harmony with European trends, has been undertaking various actions regarding reduction of the state expenditures for the healthcare system. First, there has been enormous pressure put on the pharmaceutical companies to reduce drug prices on the reimbursement list. Second, no new medicines have been included on the reimbursement list over the last six years, but at the same time, some life changing products have been made available in other acceding states.

Opportunities
- growth potential of the market
- increase of export opportunities
- the same regulation for 25 member states
- registration of products in EU will be easier
- labor costs are low in Poland
- up-to-date technical infrastructure
- the culture will support new challenges
- products of proven efficacy will be kept on the market

Risks
- new competitors will enter the market
- few experienced GMP professionals
- other acceding states have also low cost of labor
- government actions to reduce healthcare costs
- affordability of investments to meet the EU safety standards
- other states might have better tax systems and investing environment

Table B. The industry in Poland after accession.

An unstable and unpredictable legal environment also can create a barrier for investment and development. Recently, frequent changes and re-interpretation of regulations led to the huge dispute between the Polish government and importers of medicines. This unsolved issue results in worsening of the situation for investors as well as makes the country a place less attractive for further investment.

Stable, predictable regulations, and transparent information are inevitable for business growth, especially in the pharmaceutical industry which is strongly regulated by governmental decisions.

The government efforts to bring the reimbursement costs down also takes other forms. One way considers merging several large state owned pharmaceutical companies as a way of strengthening the local state owned industry in the tough competition on the local market. It also might be perceived as another method of manufacturing cheap generic products on the market and another instrument of influencing the drug products prices. The new merged company would be one of the major players on the market.

Good Manufacturing Practice Regulations

All acceding states must comply with the EU GMP regulations on the day of accession. The industry in Poland invested more than $1 billion over the last eight years in the manufacturing facilities and technical infrastructure to bring them into compliance with the EU regulations.

This is a good message to the patients that the industry is developing new quality standards, and manufacturing safe, effective, and good quality products.

Once the technical challenges are out of the way, companies are able to focus on the business opportunities on the enlarged market.

One of the challenges is certainly to get the return from the investments taking into consideration that the prices of most domestic products are regulated and kept by the government at a very low level.

Implementation of EU GMP requirements in terms of their practical and cost effective application might be a challenge for the industry for the next several years, it also might mean an opportunity for reduction of manufacturing costs.

On the Polish market, due to the relatively short period of GMP implementation, there are not many professionals with practical knowledge and experience; therefore, in many cases, the manufacturers seek for external support or guidance.

Patent Protection and Data Exclusivity

The patent on a new medicinal product provides 20 years of protection plus the possibility for another five years through a Supplementary Protection Certificate. Regardless of these regulations, the Polish pharmaceutical law from the day of accession provides six years of registered data exclusivity (three years before accession), and this law encompasses products regis-

ISPE in Poland

by Andrzej Szarmanski

The Poland Affiliate was established in 2001. The organization, although relatively new, having many excellent specialists and managers, makes a good platform for development and cooperation of industry professionals. There have been already several meetings organized by ISPE Poland to promote and facilitate training, professional effectiveness, and links between members. ISPE in Poland as a part of the international organization is open to cooperation with local regulatory authorities which may be particularly valuable after EU enlargement.

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tered back to 1 January 2000. There are plans to extend the exclusivity data protection up to 10 years across Europe which triggers a strong discussion regarding different views.

Bringing a new medicinal product on the market involves huge investments reaching in the hundred million dollar range. The longer new patented products are protected by law, the more chances are for return on investments. This in turn allows for reinvesting the revenues into research and potential new drug products, bringing value to the patients and changing their lives.

The Culture

Change was a close friend of the industry in Poland over the last decade. A reform of the pharmaceutical law, huge investments in the pharmaceutical sector, inflow of foreign investors, and know-how contributed to the culture change in the industry.

After 10 years of continuous changes, resulting change is easier to swallow. Therefore, the advantage and also the opportunity of the Polish industry is that the country is prepared to deal with change management and experienced at doing business in a much more complex environment. Growing competition has already made many of the local manufacturers implement new management techniques, lean manufacturing, and new organizational solutions. As a result, pharmaceutical manufacturers seem to be competing on the enlarged European market, and thriving at it.

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The Polish Pharmaceutical Market

by Marek Ruzikowski

Continued market growth, wholesale privatization of domestic companies, investment by leading international groups, consolidation occurring in the distribution channels, and major restructuring of the funding of the Polish healthcare system add up to Poland being one of Europe's most dynamic and challenging environments for the pharmaceutical industry.

Poland is one of the largest countries in Middle Eastern Europe totaling approximately 39 million individuals. The total value of the Polish pharmaceutical market in last three years is on the rise. As you can see, in Figure 1, the Polish market is still growing. From 11.3 billion Polish Zloty in 2001 to 13.3 billion Polish Zloty in 2003.

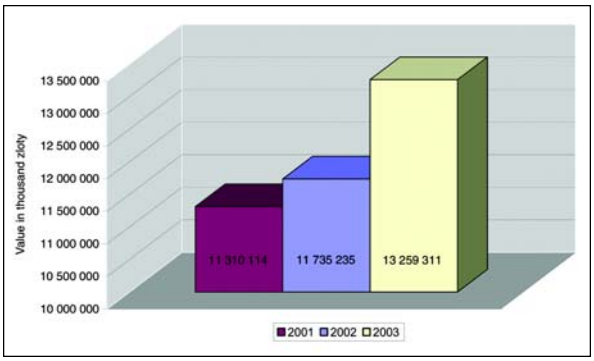

Figure 1. Polish market growth.

All of this product was sold in 10,627 pharmacies. There are about 3.3 staff per pharmacy. The better situation is in the big cities such as Warsaw, Katowice, Gdañsk; the less comfortable situation is in the smaller cities and villages.

Even after the changes in the Polish economy in the last century, the Polish market is still changing. Currently, there are about 600 companies active in the medicines field. In addition to this, there are small private companies that manufacture two or three pharmaceutical products.

The production profile of the Polish pharmaceutical industry differs from that of European standards. A majority of Polish pharmaceutical companies lack sufficient research and business resources to compete with innovative drug producers. They produce mostly generic drugs. As a result, foreign products dominate the Polish market, both in terms of the number of registered pharmaceutical products and the value of sales (the share of imports accounts for around 60 to 70 percent). The value of foreign trade in pharmaceutical products reached $2 billion in 2001, which represented an increase of 19 percent or $318 million compared with the year 2000. Poland's trade balance was negative with the deficit amounting to $1.6 billion. The value of imports amounted to $1.8 billion (a rise by 19.1 percent) and the value of exports was $159 million (a rise by 18.6 percent). Former Soviet Union countries are a traditional market for Polish pharmaceutical products, accounting for around 40-50 percent of the total exports. Regarding Western markets, most Polish drug exports are delivered to two countries – Switzerland ($19.92 million) and Germany ($16.1 million). In 2003, the Polish market sold slightly more than 1,219,870 units of medicines.

Please keep in mind that information regarding the value of sale does not mean that all of these products are manufactured in Poland. Specifically, when this information concerns big multinational companies. In case of production, this information does not include sales on exports mainly to the former Soviet Union countries.

The organization structure of the Polish pharmaceutical industry, in particular, the former state facto-

	YEAR/01 Units	YEAR/02 Units	YEAR/03 Units
Selected Market	*1,307,918,608*	*1,203,250,537*	*1,219,870,434*
POLPHARMA S.A.	154,035,593	135,399,102	133,882,490
GSK PHARMA	134,808,773	120,018,775	115,812,957
WARSZAWA ZF PLF	52,585,042	47,533,026	45,618 ,743
GSK PHARMA RX	48,214,264	45,327,178	43,028,604
PLIVA KRAKOW	46,590,936	40,420,435	41,678,141
JELFA	44,479,179	40,540,766	38,026,805
U.S. PHARMACIA	32,971,839	30,273,509	34,629,614
I.C.N.POLFA RZESZOW	28,938,648	28,504,822	30,444,944
SANOFI-SYNTHELABO	25,897,816	26,768,581	28,380,087
POLFA KUTNO	26,275,365	23,234,673	25,737,338

Table A. Top ten pharmaceutical companies per units produced.

	YEAR/01 Value (zl)	YEAR/02 Value (zl)	YEAR/03 Value (zl)
Selected Market	*11,310,144,438*	*11,735,235,391*	*13,259,311,340*
GSK PHARMA	791,058,236	871,860,151	1,014,730,931
POLPHARMA S.A.	501,550,346	591,834,021	693,674,054
SERVIER	447,498,399	464,172,140	504,670,916
ELI LILLY	267,875,048	339,478,263	475,739,630
NOVARTIS PHARMA	434,926,813	416,748,088	465,740,910
SANOFI-SYNTHELABO	294,432,482	327,462,826	373,284,512
NOVO NORDISK	284,879,588	305,288,337	367,405,964
MERCK SHARP DOHME	303,776,703	319,895,353	331,039,338
ROCHE	232,975,407	253,339,199	328,029,979
JANSSEN CILAG	251,574,979	273,242,430	319,188,530

Table B. Top ten pharmaceutical companiees per production value in Polish Zloty.

ries Warsaw Pharmaceutical Works "Polfa," "Polfa" Pabianice, and "Polfa" Tarchomin, is complicated. In the near future, these three companies will be reorganized under one name Polish Pharmaceutical Holding.

R&D

At this time, there is little innovative drug research taking place in Poland although some pre-approval testing for new products is being conducted. For example, reformulated insulin (developed through biotechnology) is cited as an attempt to expand the innovative research and capacity of the industry, as well as some innovative research taking place at the Drug Institute. The scarcity of innovative research is often explained by the lack of necessary capital and facilities, despite the relative abundance of educated scientists and the sizable internal market. Anecdotal evidence suggests that researchers active in Poland must travel periodically to other countries to use laboratories abroad to support their research.

The recent formation of a biotechnology incubator clearly represents an attempt to use the intellectual capital of Polish researchers. According to industry insiders, a number of potential ideas are waiting for commercialization, but what is needed are capital and partners capable of introducing and exploiting such ideas.

	2001	2002
State healthcare budget (in million Polish Zloty)	4,600.80	3,594.10
Average monthly income per household	2,005.77	2,065.44
Average gross monthly per capita income	644.48	664.21
Average net monthly per capita income	620.47	638.41
Average monthly per capita expenditures	609.72	624.99
Average monthly per capita health-related expenditures	27.58	28.32
of which		
medical devices	19.33	20.39
pharmaceutical products	17.69	18.73
out-patient services	7.67	7.44

Table C. Average per capita healthcare expenditure in Poland in Polish Zloty. (1 USD = 4 Zloty)

The shortage of venture capital funds specializing in biotech and pharmaceutical companies is likely to slow the growth of the native Polish biotech industry. Also needed to foster biotech start-ups are changes to the tax law and licensing of intellectual property rights. It would be very helpful to have governmental initiative to support biotech start-ups, similar to the initiatives undertaken by the governments in many countries, such as Japan, to foster the biotech industry.

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List of Contacts in Poland

Medicines and Medical Devices

Ministerstwo Zdrowia
Ministry of Heath
www.mz.gov.pl

Organs and Units Supervised and Subordinated to Minister of Health

Urzad Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych
Office for Registration of Medicines, Medical Devices, and Biocides
www.urpl.gov.pl

Glówny Inspektor Farmaceutyczny
Chief Pharmaceutical Inspector
www.apteka.biz.pl/giff/

Veterinary Products

Ministerstwo Rolnictwa i Rozwoju Wsi
Ministry of Agriculture
www.minrol.gov.pl

Organs and Units Supervised and Subordinated to Ministry of Agriculture

Glówny Lekarz Weterynarii
Chief Veterinary Inspection
www.wetgiw.gov.pl

Producers Organization

POLFARMED
Polska Izba Przemyslu Farmaceutycznego i Wyrobów Medycznych
Polish Chamber of Pharmaceutical and Medical Devices Industry
www.polfarmed.pl

Polski Zwiazek Pracodawców Przemyslu Farmaceutycznego
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In this article Computational Fluid Dynamics (CFD) software was used to estimate the distances traversed by transgenic corn pollen.

Numerical Simulation of Genetically Modified Corn Pollen Flow

by Brian A. Fricke, PhD, Arun K. Ranjan, Deep Bandyopadhyay, and Bryan R. Becker, PhD, PE

Arun K. Ranjan, a graduate student and ISPE student member at the University of Missouri-Kansas City, won the graduate level award at the ISPE Midwest Chapter's Student Poster Competition in the spring of 2003. This award consisted of sponsorship to the ISPE Annual Meeting in November 2003 where he competed with other local winners in the International Poster Competition.

Introduction

Due to numerous advances made in the field of biotechnology, genetically modified or transgenic crops have been developed for their pharmaceutical value or with beneficial characteristics such as herbicide tolerance or disease resistance. However, the possible repercussions of human intervention in nature should not go unchecked when evaluating the numerous benefits which could be derived from genetically modifying crops. The most immediate risk posed by transgenic crops is that of cross-pollination between the genetically modified species and the natural species, the implications of which suggest serious modifications in the surrounding environment. However, in order to determine the ramifications of genetic implants, a live field trial could become the possible cause of one such disaster by its very application.[1] Even with strict regulations and tough rules imposed by the US Department of Agriculture, Animal and Plant Health Inspection Service (APHIS), contamination of natural species by genetically modified crops has occurred. To ensure the purity of the natural species, transgenic crops developed for their pharmaceutical value (pharma crops) must be sufficiently excluded from the natural belts of the parent species.[2] Therefore, a numerical simulation of plant pollination dynamics should be developed to predict the behavior of the natural system.

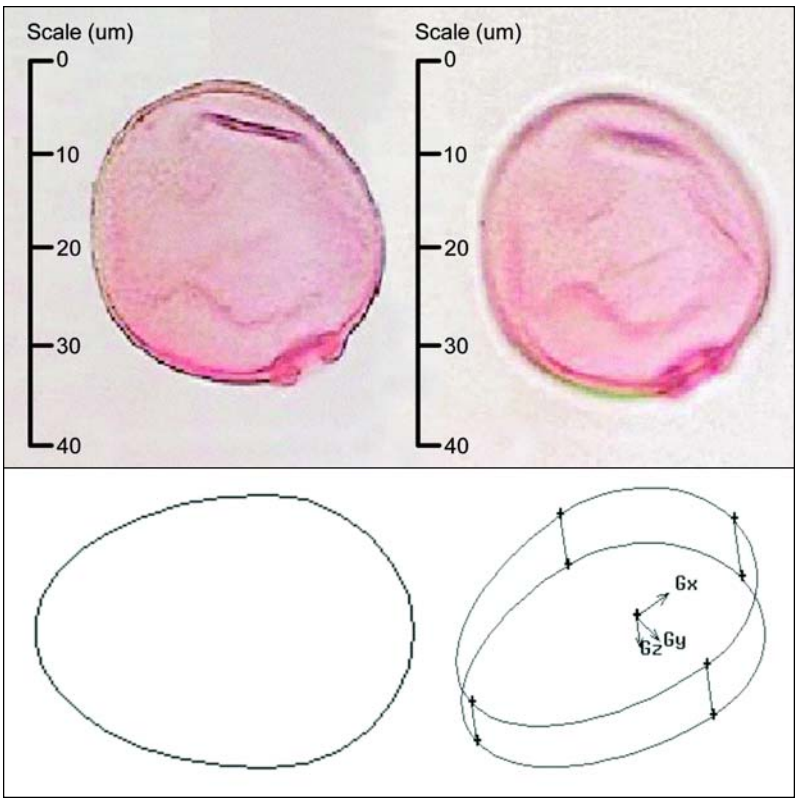

Figure 1. Electron microscope image of corn pollen and two dimensional and three dimensional pollen models.

Methods for Producing and Characteristics of Transgenic Crops

Creating genetically modified plants involves cutting edge technology that focuses on engineering the plant species in order to obtain the desired characteristics. The process of genetic alteration is achieved by introducing foreign genes into the plant genome. The subsequent expression of these transgenes to a satisfactory extent results in a genetically modified plant.[3]

Agro bacterium as a gene vector has been used since the early

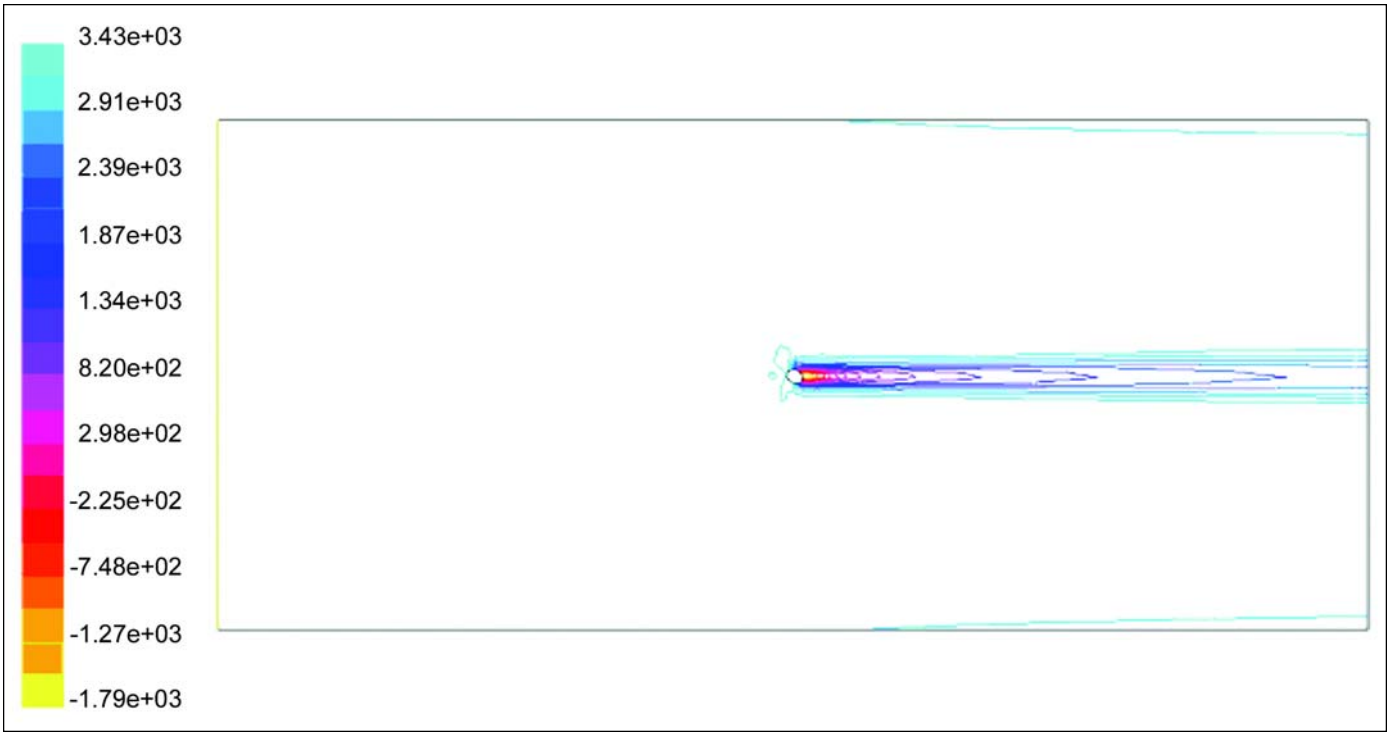

Figure 2. Contour of Total Pressure (Pascal) for a single pollen.

stages of biotechnology for successful gene transfers. In this technique, an expression of interest is inserted into the Agro bacterium plasmid, which in turn inserts the genetic material into the DNA of the host plant after crossing the plant cell barrier. These modified cells then develop into transgenic plants. However, this method cannot be used for all types of plant families. For example, monocots are difficult to hybridize by this method because agro bacteria generally infect dicots and do not easily form pathogens necessary for infecting the monocots.

The technique of electroporation has been used for many years and it uses electrical current to open pores or tiny holes in the plant membrane to allow transfer of genetic material into the cell. Although this technique is simple, it is only applicable to grasses such as wheat, rice, or lettuce.

The technique of micro-projectile transfer employs bits of genetic material that can be attached to tiny spheres, which are then shot into selected plant cells for hybridization. Corn can be converted into a transgenic crop by this method.

A current technique involves in-vitro manipulation of a crop's tissue culture by micro injecting DNA directly into the nucleus. Recent technological advances have made possible the use of recombinant DNA techniques in which interest specific gene transfer occurs without causing backcrossing of new genes into nature. This technique can be effectively used for genetic expression of characteristics between totally unrelated species; plants and animals are thus mutually comprehendible. Clever manipulation of any of the aforementioned techniques can generate transgenic plants with more than one trait of interest.

Almost all genetically modified plants have at least one marker gene inserted into their genetic makeup to provide traits of interest. Common traits generally altered by insertion of marker genes include herbicide tolerance, insect resistance, disease resistance, stress tolerance, and physiological occurrence. Crops also may be genetically modified to enhance nutrition and taste, extend shelf life, and ease storage as well as provide attractive appearance. Some of the more valuable products to have been developed from genetically modified plants include drugs which have the potential to cure rare diseases, i.e., alpha-galactosidase and glucocerebrosidase used to treat Fabry's and Gaucher's diseases. Special proteins known as defensins also are being produced from pharma crops to obtain alternative antibiotics. With such techniques and traits, it is possible for a transgenic crop, which is tolerant to saline conditions to be cultivated in agricultural wastelands and create economic opportunities, which would otherwise be non-existent.

However, hybridized plants are capable of transferring their genes over long distances to related plants, which have different characteristics. Therefore, engineered plants, with inserted experimental or engineered genes, may find a compatible relative and transfer their code to the natural species.[4-12]

Environmental Impact of Transgenic Crops

While the advent of new technologies provides us with the ability to enhance particular traits, this technology also may create significant problems that can be of major concern if unchecked. It is an absolute certainty that fertilization will occur between naturally occurring plants that are in the vicinity of transgenic plants.

The event of fertilization depends on factors such as sexual compatibility of the genetically modified plant and the wild

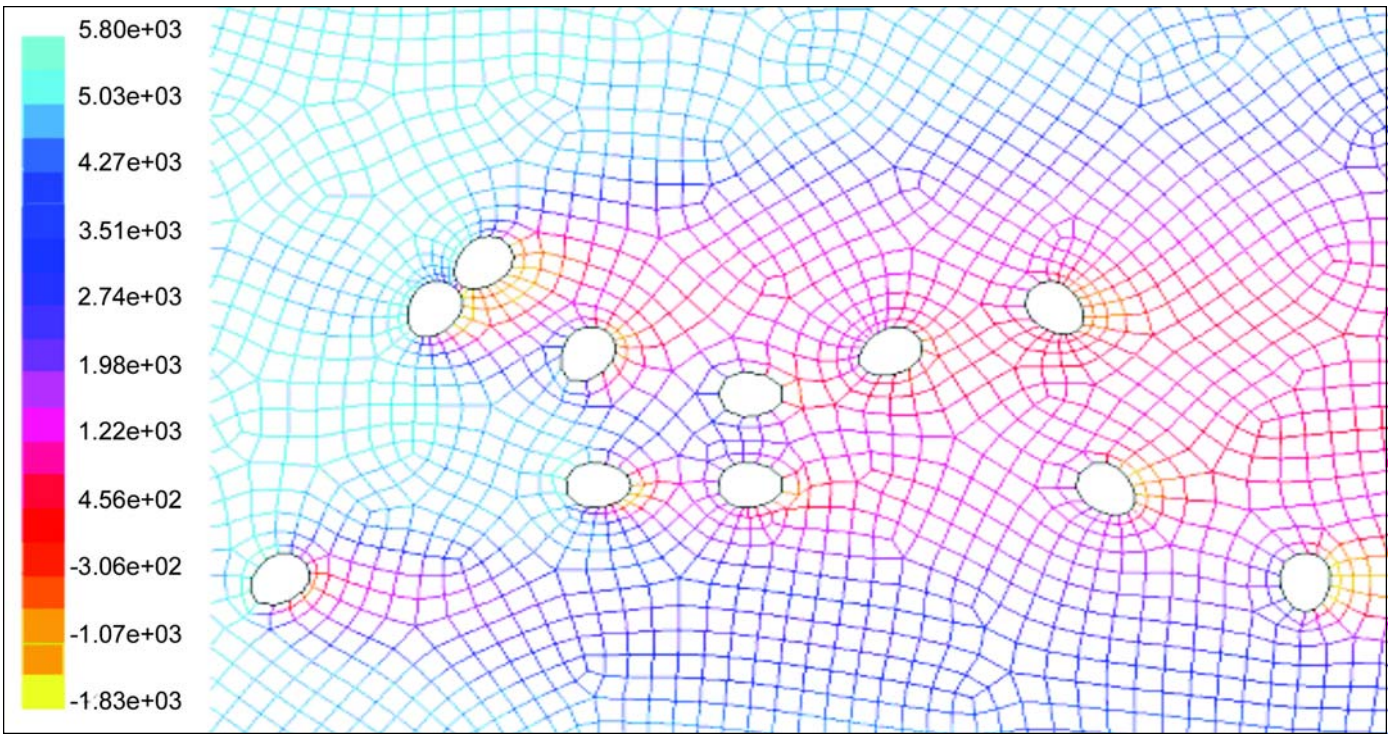

Figure 3. Contour of Total Pressure (Pascal) for randomly distributed pollen.

relative, geographical occurrence, natural vectors of pollination, and identical fertilization seasons. In spite of so many requirements for successful mating, cross breeding has occurred in nature, and hence, the problem of genetic transfer to the wild species is genuine. Cross breeding would result in dominant wild relatives with traits acquired from the genetically modified species, and these wild relatives would become super weeds whose elimination would become difficult.[13,14] This also means that loss of biodiversity and significant evolutionary changes are inevitable and will eventually result in the modification of the total genetic information present in a breeding population or species.

The problem of hybridization is not limited to containing fertilization between a transgenic crop and a wild relative. The transfer or genetic fallout of transgenes to different plant populations has a higher probability of occurring depending on the economic value of the transgenic crop.[15] Such spontaneous hybridization can lead to the extinction of rare species of plants, animals, or insects, which would have otherwise been left undisturbed.

Given the adaptability that transgenic crops can be bestowed with, planting them in unnatural geographical locations raises the risk of contamination considerably.[16] For instance, introgression of transgenic DNA into natural crop landraces for growing maize in the remote mountains of Oaxaca, Mexico has been reported.[17] In addition, transgenic pollen has been shown to cause considerable harm to rare insect species. For example, pollen from *Bt* corn, which is a genetically modified form of corn with pesticidal qualities, has been found to be harmful to the larvae of the monarch butterfly.[18]

Field trials involving measurement of natural fertilization of wild radish (*Raphanus Sativus*), a weed, with cultivated radish containing the allozyme allele (Lap-6) yielded contamination at considerable distances. This gives rise to the important question of whether engineered crops can find their way into the food chain. As further evidence, the Starlink Cry9C allele was found occurring in natural corn meant for human consumption. This clearly indicates the need for accurate measurements and preventive measures to avoid such mishaps.[19]

The Board on Agriculture and Natural Resources (BANR), under the aegis of National Research Council (NRC), has placed emphasis on research for studying post gene flow effects from transgenic plants resulting in the release of allergens, toxins, development of resistant pests, and the effect on unintended target species. It also acknowledges that while the techniques developed are safe, the hazards posed are worth analyzing.[20]

Transgenic Corn

Among the world's 13 most important crops, maize or corn ranks second in terms of cultivation and consumption.[21] The botanical definition of corn is:[22]

Family:	Poaceae
Genus:	Zea (ZEE-uh)
Species:	mays (maze)
Category:	Vegetables
Seed Type:	Open Pollinated
Days to Maturity:	81 to 90 days
Height:	4-6 ft. (1.2-1.8 m), 6-8 ft. (1.8-2.4 m)
Spacing:	6-9 in. (15-22 cm), 9-12 in. (22-30 cm)
Kernel Color:	Red, Yellow, Blue-Violet
Soil pH requirements:	6.6 to 7.5 (neutral)

One of the most prominent genetically modified crops is *Bt* Corn, which contains genes inserted from *Bacillus Thuringiensis*, a soil bacterium producing crystal protein toxins capable of eliminating pests. While *Bt* Corn reduces the use of pesticides, it also is proving to be harmful for several insect orders.

Due to the high level of cultivation and consumption of corn, and since corn is open pollinated, the potential for genetic pollution is high when compared to other crops.[23] The identification of genetically modified corn transcending over the genetic pool of traditional corn has caused controversy. Research conducted on obtaining molecular evidence for genetic flow in the species has provided proof that gene flow does indeed occur between corn and its wild relative teosinte, which may engulf entire teosinte populations.[24,25] Studies have shown that pollen dispersal and pollen activity between genetically modified and natural corn crops depends upon the amount of pollen released and the distance between them.[26]

Transgenic corn is introduced into the natural species via pollen flow. However, very little is known about the mechanism of pollen movement. Further, the impact of various weather patterns and wind conditions upon pollen flow is not known.[27] It is proposed to simulate pollination dynamics with Computational Fluid Dynamics (CFD) software to determine pollen trajectories and distance traversed. The results of such simulations will provide insight into the mechanism of pollen flow behavior and guidance for estimating safe distances for planting genetically modified corn from the natural species.

Computational Model

The objective of this research was to use CFD software[28] to determine the distance traversed by the genetically modified corn pollen under different environmental conditions. The CFD software solves the governing integral equations for conservation of mass and momentum, and when appropriate, for energy and other scalars such as turbulence and chemical species. A control-volume-based technique is used to obtain solutions to the governing integral equations, and consists of the following steps:

- division of the domain into discrete control volumes using a computational grid
- integration of the governing equations on the individual control volumes to construct algebraic equations for the discrete, unknown dependent variables such as velocities, pressure, temperature, and conserved scalars
- linearization of the discretized equations and solution of the resultant linear system of equations to yield updated values of the dependent variables

Governing Equations

The equation for conservation of mass, or the continuity equation, can be written as follows:

$$\frac{\partial \rho}{\partial t} + \nabla.(\rho\vec{v}) = S_m \qquad (1)$$

where ρ is density, t is time, $\vec{v}$ is velocity and S_m is the mass source term which may include the mass added to the continuous phase from a dispersed second phase, e.g., vaporization of liquid droplets, and/or from any user-defined sources. This equation is the general form of the mass conservation equation and is valid for incompressible as well as compressible flows.

For two-dimensional axisymmetric geometries, Equation (1) one can be written as:

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho v_x) + \frac{\partial}{\partial r}(\rho v_r) + \frac{\rho v_r}{r} = S_m \qquad (2)$$

where x is the axial coordinate, r is the radial coordinate, v_x is the axial velocity, and v_r is the radial velocity.

Conservation of momentum in an inertial, non-accelerating, reference frame is given as:[29]

$$\frac{\partial}{\partial t}(\rho\vec{v}) + \nabla.(\rho\vec{v}\vec{v}) = -\nabla p + \nabla.(\bar{\bar{\tau}}) + \rho\vec{g} + \vec{F} \qquad (3)$$

where p is the static pressure, $\bar{\bar{\tau}}$ is the stress tensor, $\rho\vec{g}$ is the gravitational body force and $\vec{F}$ is the external body force which may contain model-dependent source terms such as porous-media and user-defined sources.

The stress tensor $\bar{\bar{\tau}}$ is given by:

$$\bar{\bar{\tau}} = \mu\left[(\nabla\vec{v} + \nabla\vec{v}_T) - \frac{2}{3}\nabla.\vec{v}I\right] \qquad (4)$$

where μ is the molecular viscosity, I is the unit tensor, and the second term on the right hand side is the effect of volume dilation.

For two-dimensional axisymmetric geometries, the conservation of momentum equation in the axial direction is given as:

$$\frac{\partial}{\partial t}(\rho v_x) + \frac{1}{r}\frac{\partial}{\partial x}(r\rho v_x v_x) + \frac{1}{r}\frac{\partial}{\partial r}(r\rho v_r v_x) = -\frac{\partial p}{\partial x} + \frac{1}{r}\frac{\partial}{\partial x}$$

$$[r\mu(2\frac{\partial v_x}{\partial x} - \frac{2}{3}(\nabla.\vec{v}))] + \frac{1}{r}\frac{\partial}{\partial r}[r\mu(\frac{\partial v_x}{\partial r} + \frac{\partial v_r}{\partial x})] + F_x \qquad (3)$$

while the conservation of momentum equation in radial direction is given as:

$$\frac{\partial}{\partial t}(\rho v_r) + \frac{1}{r}\frac{\partial}{\partial x}(r\rho v_x v_r) + \frac{1}{r}\frac{\partial}{\partial r}(r\rho v_r v_r) = -\frac{\partial p}{\partial r} + \frac{1}{r}\frac{\partial}{\partial x}$$

$$[r\mu(\frac{\partial v_r}{\partial x} + \frac{\partial v_x}{\partial r})] + \frac{1}{r}\frac{\partial}{\partial x}[r\mu(2\frac{\partial v_r}{\partial r} - \frac{2}{3}(\nabla.\vec{v}))] - 2\mu\frac{v_r}{r^2} + \frac{2}{3}\frac{\mu}{r}$$

$$(\nabla.\vec{v}) + \rho\frac{v_z^2}{r} + F_r \qquad (4)$$

where

$$\nabla.\vec{v} = \frac{\partial v_x}{\partial x} + \frac{\partial v_r}{\partial r} + \frac{v_r}{r}$$

and v_z is the swirl velocity.

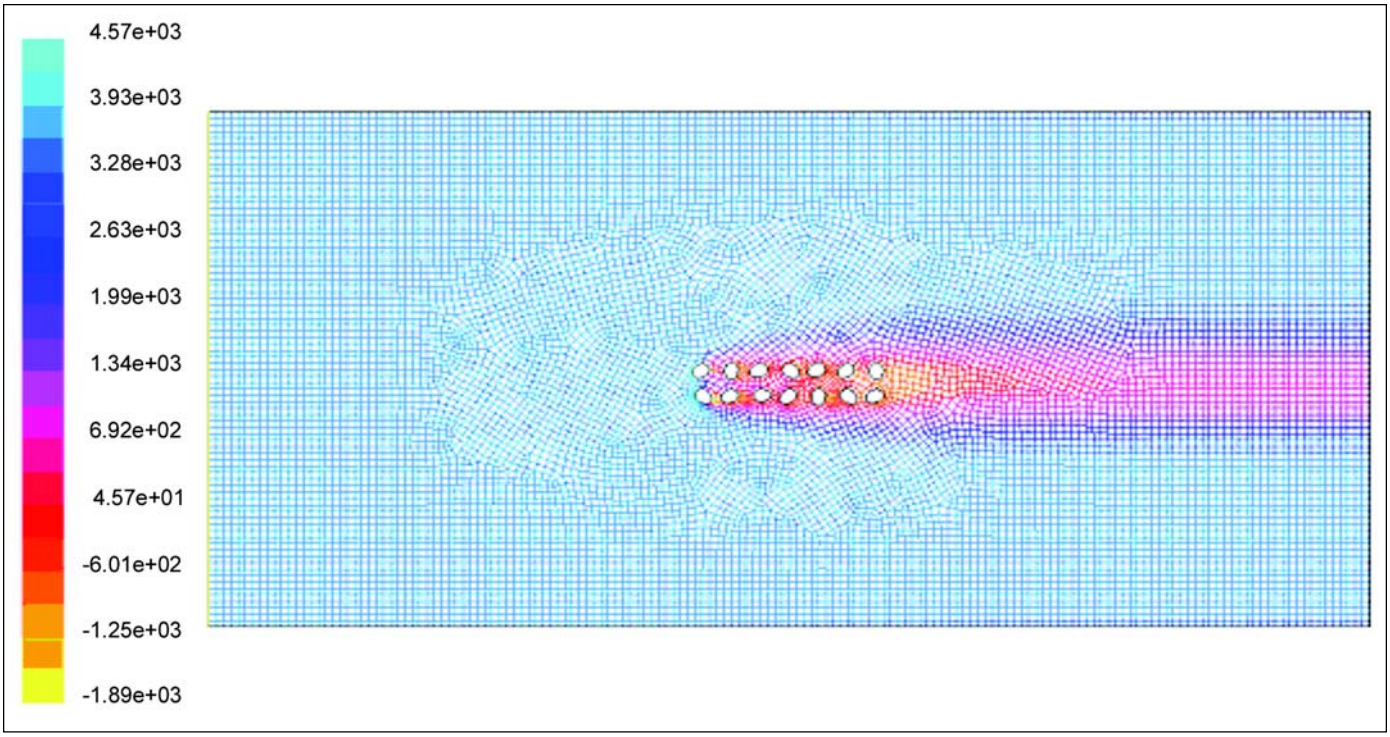

Figure 4. Contour of Total Pressure (Pascal) for a cluster of pollen.

Numerical Model

The concept used in this project consisted of numerically determining the pressure forces exerted on pollen grains by wind, which in turn was then used to determine their trajectories.

The numerical simulations were similar to wind tunnel tests in which air flowed past the model pollen grains. To determine the computational grid, consisting of the pollen grains suspended in air, physical properties of pollen grains were required. Figure 1 shows a genetically modified *Zea mays* pollen grain. Typical pollen grain size ranges from 90 to 125 µm and pollen weight is $247x10^{9}$ grams.[30] Figure 1 also shows the computerized representation of this pollen grain. Both two and three dimensional representations were developed.

The pressure forces exerted on pollen grains were determined for three cases:

1. single pollen in an air stream
2. 11 pollen grains randomly distributed in air stream
3. 14 pollen grains arranged in an orderly cluster in an air stream

A preprocessing tool[31] was used to create the three complete computational models. Each model consists of the computational corn pollen models placed within the computational flow field. The preprocessing tool discretised the model geometries into numerous control volumes. For two-dimensional simulations, the geometries were meshed with uniform quadrilateral elements, and for the three dimensional simulations, the geometries were meshed with uniform hexagonal elements.

Results and Discussion

The computational models developed above were imported into the CFD software.[28] Here, material properties, boundary conditions, and solution parameters were specified. Since maize is diclinous, it is predominantly fertilized via wind pollination, rather than by natural vectors such as insects. The phenomenon of wind gusts was considered in which a gust of wind is defined to be a sudden rise of velocity ranging from 10 m/s (33 ft/s) to 40 m/s (130 ft/s), lasting for a minimum of 2 sec to a maximum of 20 sec.

The air was modeled as a viscous fluid using k-epsilon turbulence model. Pressure distributions around the pollen grains were calculated by the CFD software at wind speeds of 10, 20, 30, and 40 m/s (33, 66, 98, and 130 ft/s). Example results from the CFD software are presented in Figures 2 through 4. These figures show the calculated pressure distribution around pollen grains subjected to an airflow of 20 m/s (66 ft/s). The total pressure on individual pollen grains was then used to calculate the distance traversed by the pollen grains.

Tables A and B show the range of distances traversed by randomly distributed pollens and pollens in a cluster for wind speeds of 10, 20, 30, and 40 m/s (33, 66, 98, and 130 ft/s), and gust periods of 10 sec and 20 sec. By comparing Tables A and B, it can be seen that the distances traversed by randomly distributed pollens are much higher than those of pollens in a cluster. Each of the randomly distributed pollen grains are individually subjected to the pressure forces of the wind gusts, whereas only the leading pollen grains in the cluster are subjected to the pressure forces of wind gust. Thus, each of the randomly distributed pollen grains traverses a greater distance than the pollen grains in a cluster.

Wind Speed m s^{-1} (ft s^{-1})	Distance Traversed m (ft)					
	Time 10 sec			Time 20 sec		
	LOW	MEAN	HIGH	LOW	MEAN	HIGH
10	33	64	87	65	122	164
(33)	(109)	(209)	(284)	(214)	(400)	(540)
20	84	133	194	159	245.24	350
(66)	(274)	(436)	(634)	(520)	(805)	(1147)
30	110	206	320	207	365	555
(98)	(362)	(676)	(1048)	(678)	(1198)	(1819)
40	187	340	489	339	582	815
(130)	(615)	(1115)	(1603)	(1114)	(1910)	(2672)

Table A. Distances traversed by randomly distributed pollen.

Wind Speed m s^{-1} (ft s^{-1})	Distance Traversed m (ft)					
	Time 10 sec			Time 20 sec		
	LOW	MEAN	HIGH	LOW	MEAN	HIGH
10	0.21	24	72	0.42	46	138
(33)	(0.69)	(77)	(237)	(1.39)	(150)	(453)
20	0.076	54	150	0.15	101	276
(66)	(0.25)	(176)	(493)	(0.50)	(332)	(906)
30	10	86	258	21	159	456
(98)	(34)	(282)	(846)	(68)	(521)	(1496)
40	9	121	313	18	219	544
(130)	(30)	(395)	(1026)	(59)	(718)	(1783)

Table B. Distances traversed by pollen in a cluster.

From Table A, it can be seen that the maximum distance traversed by a pollen grain was 815 m (2670 ft), which closely match the results of experimental field trials.[32] In the experimental field trials, it was found that pollen grains, on average, traverse distances on the order of 200 m (656 ft). However, in extreme cases, pollen grains were found to traverse distances exceeding 880 m (2625 ft).

Conclusion

In this article, CFD software was used to estimate the distances traversed by genetically modified or transgenic corn pollen. To ensure the purity of the natural species, transgenic crops must be sufficiently excluded from the natural belts of the parent species. Since the determination of transgenic pollen transport using live field trials could result in cross-pollination, numerical simulations were performed. The results of these numerical simulations indicate that genetically modified corn pollen could travel as much as 815 m (2670 ft), which is in good agreement with experimental results. The numerical results provide insight into the mechanism of pollen flow behavior and guidance for estimating safe distances for planting genetically modified corn from the natural species.

Nomenclature

$\vec{F}$	External body forces
I	Unit tensor
p	Static pressure
r	Radial Coordinate
S_m	Source
t	Time
v_r	Radial Velocity
v_x	Axial Velocity
V_z	Swirl velocity
x	Axial Coordinate
μ	Molecular viscosity
ρ	Density
$\bar{\bar{\tau}}$	Stress tensor

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This article discusses an innovative approach for designing and constructing a modular large-scale bulk pharmaceutical facility.

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An Alternative Approach to the Modular Design and Construction of Large-Scale Bulk Biopharmaceutical Manufacturing Facilities

by Gordon Leichter and Lars Turstam

Introduction

Speed to market is a paramount concern for most biopharmaceutical manufacturers. The commitment of capital is continually faced with increasing pressure to provide returns on investment in the shortest possible amount of time.[1] This increasing pressure has forced engineering disciplines to embrace and refine the concept of modularization for the design and construction of new manufacturing facilities exemplified in a recent study conducted by the Construction Industry Institute.[2] This article is a discussion of an innovative approach that pushes the envelope of respective modular technology for a biopharmaceutical application.

Recently implemented innovations to the concept of modular construction for a large-scale bulk biopharmaceutical manufacturing facility are discussed in this article. The rise in popularity of using modularity in construction, primarily due to the continual field successes of the technology, has put demands on the industry to push the envelope on the existing limitations of the concept. The focus of this article is on the emerging techniques that have evolved to develop modularization further.

This article is organized in four sections to provide the reader with a better understanding of the concepts and applications associated

Figure 1. Typical standard facility module; external dimensions of 44'Lx15'Wx14'H (13.3x4.4x4.2M) with a floor area of 650F^2 (60M) and an average weight of 50 tons (cross-bracing shown for shipping purposes).

Figure 2. Relief panels in a modular facility with a stucco exterior that matches adjacent building.

with modularization. The initial discussion is about modularity in general, comparing and contrasting perceptions of what constitutes a module. This discussion leads into aspects of the benefits and challenges of modular facilities specifically, comparing timelines and cost influences. The third section is a case study of technical innovations recently implemented for a large-scale biopharmaceutical facility, and the conclusion addresses some insights into lessons learned and forward looking concepts in this developing area of engineering.

What is Modularization?

The term "modular" is used synonymously within the pharmaceutical, biotech, and other industries in reference to many different applications. Modularity has been used to describe anything from a software routine within an assembled computer program to the fuselage of a Boeing 767® aircraft. Even as early as 1876, the Statue of Liberty was built in "modules" before being delivered to New York City.[3] Therefore, the concept of modularity is nothing new or innovative in that regard. However, within the pharmaceutical industry, the concept of modularization has gained a significant amount of interest. The term "module" has been used to describe anything from a bank of solenoids to skid mounted processing equipment to entire facilities. For the purpose of this discussion, the term "modular" and "module" will refer to a self-contained assembly manufactured off-site under controlled conditions, then delivered and integrated into the final point of use location with the minimal amount of reassembly.[2]

Process Modules vs. Facility Modules

Process equipment mounted within large steel frames or skids constitutes one of the more common descriptions of a module. This modular approach is an ideal application to defer the fabrication of complex piping and instrumentation to a shop environment where there is close proximity to tools, materials, and expert resources. The extent of the module is not limited to mechanics. Operational testing of both hardware and software can be conducted within a module. Similarly, pre-qualification of the respective systems also can be conducted within the constraints of the module. Pre-qualification alleviates complexities experienced during field start-ups and allows for timely updates to documentation during transport and installation.

In a similar manner, there have been technological advancements in modularity extending past the boundaries of the equipment skid to include the entire facility. However, there are many variations to the concept of modular facilities. These variations range from the trailer park type stackable offices ubiquitous to all construction sites to the more sophisticated versions used for pre-fabricated buildings, to the state-of-the-art versions now being used for pharmaceutical processing facilities. The approach to modular construction has recently evolved significantly to the level that entire facilities can be produced under the same controlled conditions as described for equipment skids.

Facility Modularization

This innovative approach to the modularization of pharmaceutical production facilities allows for the building structure itself, complete with all architectural finishes and process components, to be fabricated off-site under controlled conditions. This approach has been proven to alleviate the logistical complications experienced with conventional construction projects. These structural steel modules come complete with poured concrete floors finished to the most demanding requirements. Walls are insulated and final finishes are applied. Heating Ventilation and Air-Conditioning (HVAC), electrical, plant, and clean utilities are permanently installed within the modules. Process equipment is installed in the module in the final operating location as indicated in Figure 1. All of these functions, normally performed in the field at various levels within the building, are performed in the workshop at an easily accessible ground floor level for increased efficiency and quality.

After all of the internal finishes have been applied in an assembly line environment, the modules are stacked together similar to an enormous Lego® model. With all the modules assembled together, interconnections are completed to allow the facility to become functional while still under the workshop environment. Functional testing, pre-qualification, and operator training can be conducted on the modular facility in parallel to the activities occurring at the construction site.

The modular facility can be accepted by the operating company at the module provider's facility. After acceptance of the facility, the modules are disassembled, protected for shipment, and delivered to the permanent location. The robust structural steel frame of the modules, which serves as the actual building structure, offers exceedingly superior shipping protection compared to traditional crating provided by Original Equipment Manufacturers (OEMs). The equipment installed within the module, which is in its final operating location, will not require reassembly or extensive retesting.

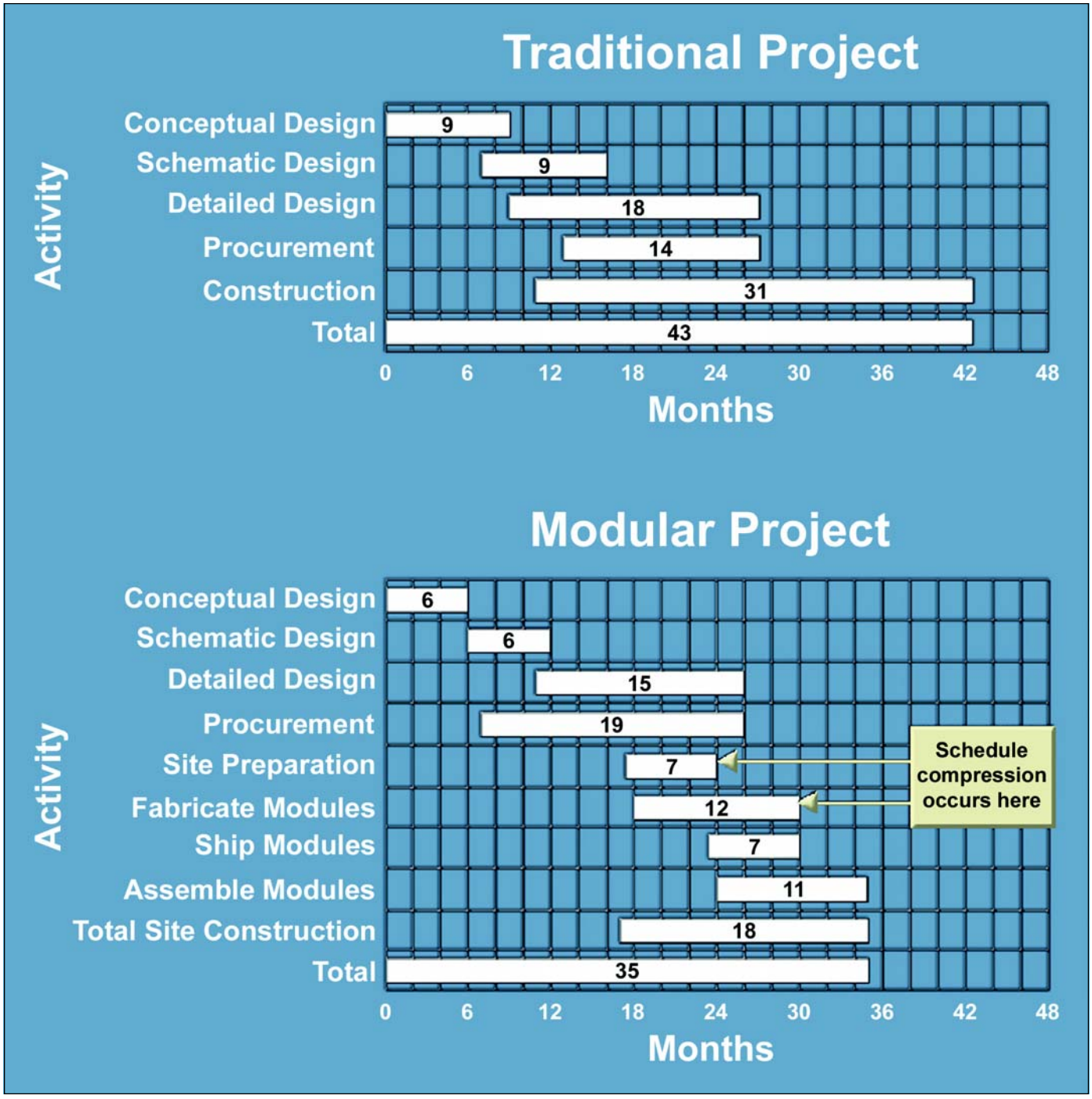

Figure 3. Comparison of a traditional construction project schedule to a modular construction schedule.[6]

The exteriors of the modules are commonly constructed out of epoxy painted steel, insulated to comply with local climatic conditions and fire ratings. Seismic and hurricane zone requirements are incorporated into the design as required. The robust design of the structural steel frame, usually using 25cm x 12mm (10" x 1/2") square tubular column members, provides a stability to the structure exceeding most conventionally built structures. Additionally, any type of architectural façade can be attached to the exterior, allowing for an external finish that is undistinguishable from any conventionally constructed building. Special requirements for hazardous operations are accommodated by the utilization of relief panels and reinforcement of the adjacent module panels as shown in Figure 2.

Benefits and Challenges

Though there are many benefits to the modularization of facilities, it might not be the perfect solution for every project. The following section compares some of the benefits of time to market, predictable and reliable results, and high quality to challenges such as the necessity for a clearly defined scope of work [User Requirement Specification (URS)], a commit-

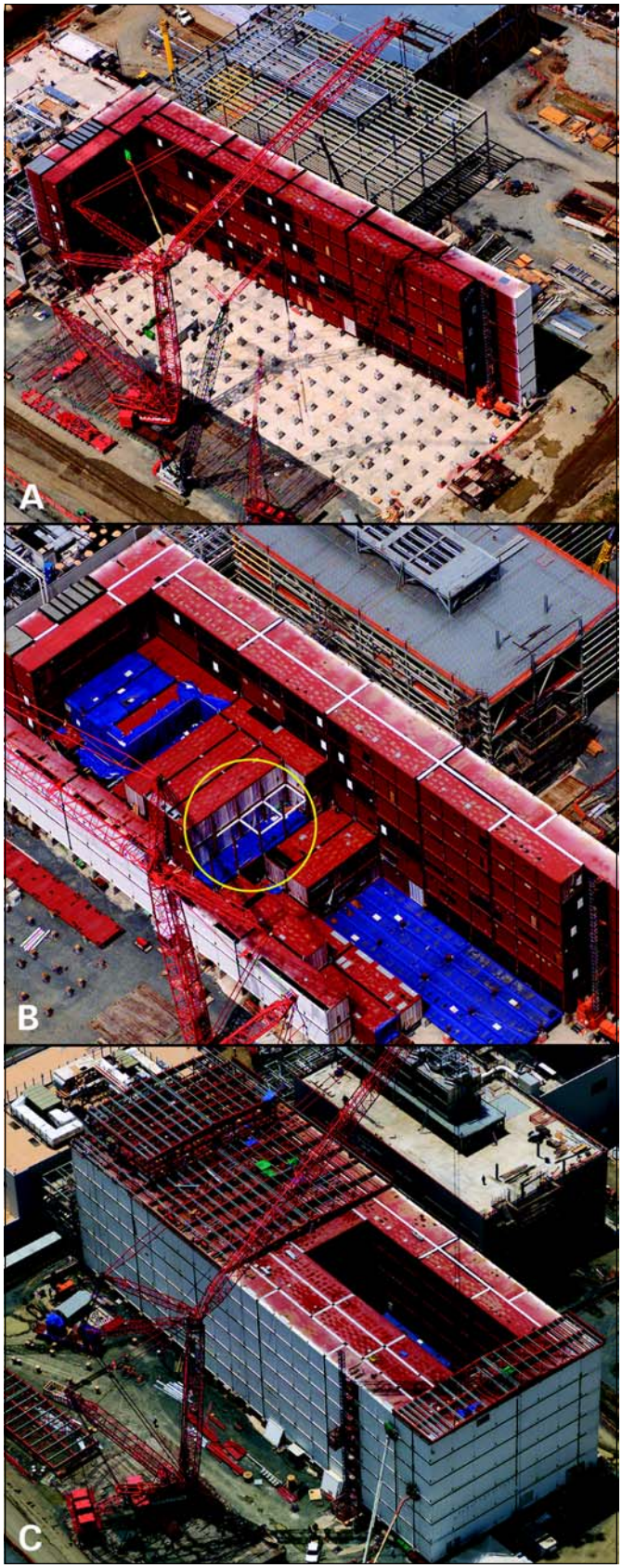

Figure 4. A) Initial facility modules set in place; B) one "Ballroom" is erected for just-in-time arrival for process equipment skids; C) central "Ballroom" on level 6 is configured as the facility is nearing completion.

ment to long-lead equipment, and an ability to balance changes in regard to process and schedule.

Improving Time to Market

One of the main arguments for using modular manufacturing is ultimately in the anticipation of time savings compared to conventional construction and field assembly approaches. Time savings through modular technology on a project is due to the advantages of parallel activities being conducted offsite to relieve the congestion and delays that would have occurred if all the required manpower were to converge onsite. Timeliness and enhanced quality, characteristic to modular technology, are realized through shop floor efficiencies under controlled conditions.[2] These conditions allow for repeatable and consistent results, while eliminating the extraneous effects of weather delays, worker slow downs, and unpredictable site logistics.

For the above reasons, modularity has gained recent popularity as an accepted method for minimizing new facility construction timelines due to the inherent predictability of the project process. Parallel activities between site preparation of foundations and non-critical support structures can be performed while the more sophisticated process intensive equipment is fabricated off-site. Even though the initial price for using modularization may appear to exceed conventional construction, the assurance of a predictable outcome and reduced timeline are clear cost savings incentive for operating companies.[2] Net present value of investments combined with earlier product revenue is an important consideration in construction projects, as larger plants become more capital intensive.[4] The increased demands for earlier return on capital employed are transcending into increased pressure on engineering disciplines to bring facilities on line faster.[5]

Time to market is one of the biggest concerns in regard to employed capital and market opportunities.[1] Considering that some products are worth millions of dollars a day to the producing company, every day a facility is not producing product is a loss on that capital employed. With the increase in demand for large scale manufacturing, the complexity of projects spans across many issues and disciplines. The reality of these large-scale projects is that if built conventionally, it would require an extremely large number of skilled laborers and material coordination at the jobsite. This jobsite coordination would result in a significant effort to provide office housing, parking, and material receiving and storage. These efforts would be prohibitive from a logistical standpoint alone, while adding more expense and time to the project. Just the limitations to personnel access due to the maximum allowable density of people per square foot could make site construction take twice as long for conventional construction compared to modular construction.[2]

The advantage of conducting many activities in parallel allows for significant schedule compression in comparison to traditionally built projects - *Figure 3*.[6] Schedule compression and quality gains are realized through the efficiencies of manufacturing under controlled conditions. These gains can be envisioned through the ease of access for workers to every

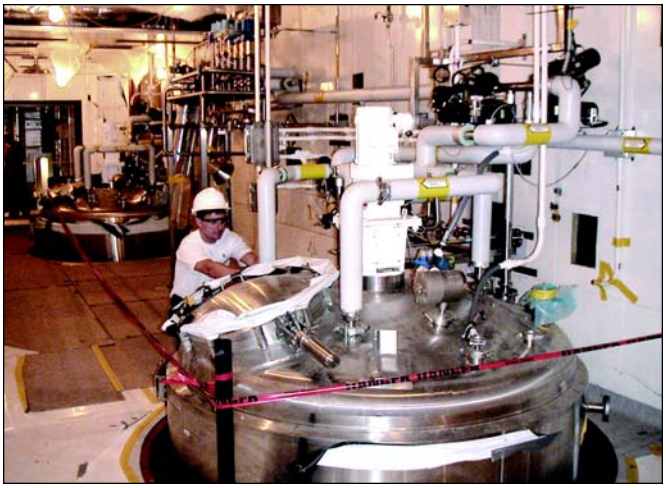

Figure 5. Large processing vessels are set in place within a "Ballroom."

part of the facility while the parts of a multi-story structure are on one level. Workers can move from module to module performing difficult field tasks in a simplified assembly line manner. Secondly, many parts of the building can be worked on simultaneously without having to wait for one floor to be complete before another floor is constructed. Critical areas can be focused on and isolated from non-critical areas regardless of the location in the final building.

Challenges to Project Organization and Implementation

However, there also are challenges associated with the modular facility concept. When considering that the gains realized with the modularization revolve around project delivery, organization is key. The benefits of conducting activities in parallel require a very good understanding and definition of those activities. Sure, there is a lot of talk about well-defined URSs, but the reality is not always clear-cut. The gains anticipated through using a modular approach for a new facility can be quickly diminished if the design criteria are nebular. Often, it is better to expend extra time on the front end of a project to assure a really well defined and stressed URS before moving into detailed design. Because of schedule compression, more activities occur simultaneously compared to a traditional project. Disruption to that process due to unclear definitions can have a ripple effect through the entire project. However, when uncertainty does exist in a certain area or process, and can be identified early on, it can be contained to a specific area. This then can allow the ability to focus on other areas of the building, until the uncertainty is resolved.

Long-Lead Equipment Implications

Long-lead equipment poses a similar challenge to the modular facility project delivery process. With complex processing equipment, such as bioreactors and lyophilizers, having lead-times of up to 18 months, these pieces of equipment can become the critical path for most projects. Characteristic to a well defined URS is to identify and define long-lead equipment early on in a project so it can be procured in a timely manner, which is no different from any other project. Similarly, anticipated gains from schedule compression are quickly lost when fabrication is delayed due to equipment deliveries. Anticipation of the issues arising from long-lead equipment can be contended with by either providing large access panels in sections of the modules, which is normally provided for egress, or the respective module that the equipment will operate in can be sent to the equipment supplier. The fitted out module then provides the OEM the opportunity to assemble the equipment into the actual final installation location, alleviating the need for breakdown, reassembly, and additional packing. There are new techniques and approaches to this issue of long-lead equipment, which are discussed later in this article.

Changes

A final challenge worth discussing in regard to the challenges faced with modular facilities is regarding changes. Changes are an inevitable part of all projects, and are difficult to quantify in respect to this discussion. However, the challenge that changes pose for the modular approach can be considered from two perspectives, anticipated changes and unanticipated changes, which is the reality of most projects. Anticipated changes regarding uncertainty of a process or final equipment configuration can be dealt with in a similar manner as long-lead equipment.

Unanticipated changes can have rippling effects through a project amplified by the schedule compression described earlier. It is quite difficult to propose solutions to unanticipated events, as experience has proven that these types of situations need to be dealt with specifically. The consideration that needs to be kept in mind is if the change can be isolated or will it cause changes throughout the facility. Modules can be added, removed, or even moved, allowing for some additional flexibility compared to traditional construction. The major difference to be aware of is that because of schedule compression, there is less of a window of time to consider changes.

An Alternative Approach to Modular Construction - A Case Study

As biopharmaceutical manufacturing facilities grow in scale, the approach to modularization of these facilities has posed a challenge for engineers and constructors. A recently completed 200,000+ F^2 (20,000 M^2) state-of-the-art, U.S. based biopharmaceutical purification suite, posed such a challenge in this regard.

Schedule Compression

The challenge revolved around finding a way to reduce the proposed construction time of the facility by a minimum of six months. A six-month reduction in the actual construction of the facility was the maximum reduction that was conceivable at the time based upon the shortest possible critical path for long-lead equipment as shown in Figure 3. The focus naturally moved toward devising a solution that allowed the

Figure 6. Final touches are applied after 12 months of field assembly.

building to be a modular facility and the large processing equipment to be modular equipment skids so that as much work as possible could be performed off site and in parallel to the jobsite construction.

In addition to the anticipated reduction in the site construction time, an additional three to four month reduction in the schedule was projected toward the final handover of the building to manufacturing by incorporating pre-testing and pre-commissioning at the respective modular supplier's facilities. Ultimately, the combination of the construction schedule compression and pre-qualification will enable the operating company to begin producing product at a minimum of 10 months sooner compared to a conventionally stick-built project.

Project Scope

This referenced purification suite is a green-field project. The purification suite structure is an 84 F (25.2 M) high six-story building, on a footprint of 1,300 x 3,660 F (33 x 93 M). In total, there are more than 100 process vessels with a total volume exceeding 500,000 liters with the largest vessels at 22,000 liters. Modular equipment skid manufacturers supplied the majority of vessels 3,000 liters and larger.

There is approximately 40,000 feet (12,000 M) of hygienic piping connecting the modular equipment skids within the facility, and an equal amount of plant utility piping within the facility. 130 hygienic piping loops required passivation. There are three HVAC zones, one per each production level with separate make-up air units and in total 34 air handlers installed. Most of the process areas, approximately 45,000 F^2 (4,500 M) or 25 % of the building, are classified (Class D to Class B) with some operations also conducted under Laminar Air Flows (LAFs). A Building Management System (BMS) and a process Distributive Control System (DCS) also were provided.

Design elements included seismic zone 3 and hurricane zone considerations to fulfill code requirements of Unified Building Code (UBC) 97. This was accomplished by providing stiffer exterior walls and using the outer row of facility modules as moment resisting frames. Additionally, due to the use of the flammable solvents in some parts of the process, some of the facility modules had to be designed to Class I Div II explosion proof standards.

The purification process required close to 20 steps inclusive of numerous chromatography steps. Support processes included equipment for Clean-in-Place (CIP), buffer preparation and buffer hold, and large cabinet washers. The process flow is considered a gravity feed design. Most of the production equipment spanned two stories within the building with platforms around the large processing vessels.

Project Challenges

The aggressive timeline of this particular project in combination with the complexity and scale of the processing equipment required innovative thinking by all involved. For the most part, there were two significant issues in regard to modularity faced with this large-scale project. The first and foremost issue was how to physically accommodate the large-scale processing vessels and platforms within the constraints of existing modular facility technology in an effort to minimize or eliminate the need for disassembly of the equipment skids during installation. Secondly, due to the different locations of the modular manufacturers around the world, how to effectively coordinate all of these efforts across multiple companies in multiple countries to assure that everything would fit together during field erection.

Large modular equipment skids are impacted by two general ingress issues on new construction projects, either a large opening in the building needs to be left unfinished, or the skid must be disassembled to fit through the size of the most restrictive opening. Regardless of either approach, reassembly, delayed completion of respective areas, and disrupted validation efforts were considered to constitute a major time constraint for this project. Furthermore, the interconnecting distributed utilities would not have been able to be finalized and terminated until the process equipment was installed.

By using modular facilities for new construction, the advantages are realized by having all of the architectural details, process utilities, and process equipment fabricated and installed within a structural steel frame (module) that fits together with other modules to form the actual building structure. However, due to the shear size of the processing vessels along with the significant number of facility modules

needed for a building of this magnitude, an innovative concept had to be conceived.

The size limitations of the facility modules, usually dictated by roadway transport restrictions, necessitates that very large processing vessels be removed and shipped separately, sometimes creating similar issues of disassembly faced by the equipment skid suppliers. Additionally, because of the significant number of facility modules required, 320 in total, and the long lead time of the equipment skids, 120 in total, it was not conducive to the timeline to assemble the entire facility and conduct pre-commission at the modular facility manufacturer's plant, as done with previous projects.

Integration of Large Process Skids

The ultimate challenge posed was to minimize or eliminate the need to disassemble any part of the modular equipment skids by installing them directly into the building as it was erected. This challenge transcended down to the development of a new approach by the modular facility and modular equipment skid suppliers toward integrating all their actions into a concurrent goal. The approach was not only a challenge technologically, but stressed the paradigms of traditional project collaborations as well.

One of the most important factors that aided the effort of this challenge was that a very well written and clearly defined URS was provided. The modular facility provider was responsible for the building structure, excluding the foundation. The multiple process steps were then divided amongst the process equipment skid suppliers and the modular facility supplier based upon expertise and most sensible logistics. Areas of the building were then assigned to the respective suppliers based upon this process focus.

To tackle the first obstacle of accommodating the large processing equipment skids within the modular facility constraints, an innovative concept emerged from the module facility supplier to create wide open areas, spanning a number of floor levels, which would create an inter-locking fit between the large equipment skids and the structural steel of the facilities modules. This concept, referred to as a "Ballroom" enabled the collaborative team to maximize schedule gains by having respective pieces arrive at the jobsite in almost a Just-In-Time (JIT) fashion and "snap" together like a huge Lego® model.

While the final manufacturing and factory acceptance testing was being conducted on the processing equipment, the "Ballroom" areas were erected in sequence to be ready just prior to the arrival of equipment skids - *Figure 4*. Upon arrival at the jobsite, the large equipment, skids with multiple tanks up to 22,000 liters, were lowered into place in-between structural members - *Figure 5*. On the upper level, the platforms integral to large equipment skids aligned with portions of the facility modules to form a "tank farm" for buffer prep, which was comprised of 23 vessels mounted in 11 multiple-vessel equipment skids. Once the last equipment skid was set, the facility modules that form the ceiling and subsequent upper floors were immediately set in place and the erection of the building proceeded.

Where an area and a respective process responsibility aligned, the equipment skid supplier took responsibility for all internal processing functions within that area, inclusive of all piping, electrical, controls systems, and even fire protection. The equipment skid supplier terminated the respective building connections according to coordinates provided by the modular facility supplier. In areas where there was an overlap of process responsibilities between the equipment skid suppliers and the modular facility supplier, the use of a precision global coordinate system was used to assure proper alignment inside and in between the facility modules.

Use of Global Coordinates

This concept of global coordinates allowed for accuracy and predictability of alignment through 3-D modeling, which enabled many parallel activities to be conducted in different locations. The accuracy and tolerances of global coordinates held throughout the immense building structure would have been difficult or close to impossible to hold in a conventionally built building. The rigidity and structural integrity of the massive steel facility modules allows for a diagonal tolerance within +/- 3/8" (10mm) for each module, which contributed to an overall tolerance of +/- ¾ " (20mm) over the entire building structure. The tight tolerances of the global coordinates allowed for such precise alignment of the skid mounted equipment to the facility modules that the majority of assembles fit together without out any interferes. "It was amazing, these massive equipment skids were lowered into the (facility) modules in the field and the mounting holes actually lined up," exclaimed the Project Manager from one of the modular equipment skid suppliers.

Web Based Project Management and Design

The procedure of sectioning off the respective areas according to process disciplines worked extremely well. This effort was aided by the latest state-of-the-art Web based project management and design software. The Internet based project management software Lotus® Sametime Server was used to coordinate all the respective module providers and allowed design reviews to be conducted simultaneously from all of the respective locations. The client and construction project managers could sit in the southeast U.S. and simultaneously view and approve designs with engineers in the mid-west, Canada, and Sweden. It was simple to bring in additional members from the respective teams, who traditionally would not have been able to participate in design reviews, such as maintenance and operations personnel.

In addition to the Web based project management tools, the design coordination effort was enhanced by the use of 3D modeling software. Designs were exchanged and tracked through the Web based management system. The combination of the ease and timeliness of design reviews and approvals was another significant contributor to the successful project execution and schedule compression.

On Site Erection Schedule

At an average rate of three to four modules being set a day, the

entire building was erected in less than eight months. This unprecedented accomplishment began with site construction starting in mid 2002. The first modules arrived at site in January of 2003, and began to be set in place in February - *Figure 4*. The last facility module was set in place in mid-September of 2003. Interconnections, elevators, and a raw material penthouse were completed over the following five months with a handover to the operating company by the end of March 2004. "The total site construction of this building would have taken close to 36 months if built conventionally," commented the Construction Site Manager.

Lessons Learned and a Look Forward

The large-scale biopharmaceutical project discussed above will be well into the commissioning phase by the time this article is published - *Figure 6*. For the purpose of client confidentiality and process propriety, names and details have been excluded. Though technological strides in regard to the advancements in modular concepts were achieved on this project, there are three lessons that can be shared as a benefit to the industry for future projects of similar scale. These lessons revolve around; first, a true understanding of what should or shouldn't be completed prior to site work as well as what can and cannot be done with modular technology; second, a weakest link situation in regard to all suppliers on the project; and third, the excellent example of coordination efforts for all the logistics.

When considering using modular technology, redundancy of efforts in comparison to return on investment needs to be considered at the initial planning stage of the project. There are redundant efforts such as pre-testing and pre-commissioning of equipment, process loops, HVAC loops, etc.; that will assure a higher rate of return with the avoidance of surprises and unplanned delays during start-up. Conversely, there are efforts to consider such as passivation and extensive disassembly of equipment, where there is little advantage due to the necessity to repeat the process in the field anyway.

Additionally, as much mechanical and electrical work as possible should be carried out under the controlled conditions of the modular supplier's shop environment. However, it was felt that the size of this facility made it necessary to conduct most of the electrical cabling work and HVAC ductwork at the construction site. Specifically, some of the ceiling fixtures, ductwork, and electrical cabling were left to be finished in the field to get the facility modules on site as soon as possible. Due to the accelerated pace of the compressed JIT schedule at the construction site, the unpredictability of deferred field labor caused complications. In hindsight, it would have been better to hold those respective facility modules back in the workshop for some additional time, which turned out to be more than double in the field.

From a weakest link standpoint, where modularization allows for many things to happen in parallel, schedule compression gains can be compromised if critical activities do not happen succinctly. While some delays can be overcome due to the inherent flexibility of being able to juggle some material and equipment delays by working sections of the facility independent of other respective areas, pre-planning and coordination efforts leave little room for mishaps. Extra effort needs to be expended to assure sub-suppliers keep on track, drawings are approved in a timely manner, and utilities are available when needed.

Due to the speed and number of activities occurring simultaneously, delays in a compressed schedule are amplified when things can no longer be worked around. This situation relates to internal and external issues to the project. In the case of the large-scale biopharmaceutical facility, intense focus was given to internal aspects of the purification suite, when it was discovered that the plant utilities, which were conventionally stick built, were behind schedule. Schedule gains could be jeopardized if these utilities are not available in a timely manner.

Future Trends

In conclusion, modularization has evolved over the years as more and more pressure has been put on engineering disciplines to provide innovative ways to provide better returns on capital employed. The efforts that go into modularization need to be considered from a project delivery standpoint in the initial planning phases of a project to maximize the potential for greater returns. Increased efficiencies will be realized as the industry learns more about how to better use the benefits and understand challenges of this emerging technology.

Future developments in this technology will focus more on the point of origin for pre-manufacturing in an effort to perform as much work and pre-qualification as possible offsite. Increased acceptance of the concept will be evidenced in preparing facility modules and delivering them to OEMs where long-lead equipment can be installed directly into the modules and shipped directly to the final location, alleviating as many interim steps as possible.

Additional foresight into the pre-testing of DCS and Supervisory Control and Data Acquisition (SCADA) systems within the modules while in the workshop will bring added benefits to the sometimes unpredictable and hectic start-up issues that plague startups of conventionally built projects. Biopharmaceutical facilities will no longer be thought of as fixed assets because the entire facility will be able to be relocated similar to a piece of equipment. There also will be more modularization of other parts of the facility such as utility packages. These trends indicate that modularization is becoming more mainstream and will provide for increasing innovation in the field of facility design and construction.

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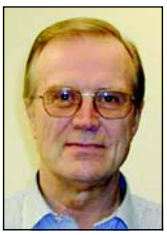

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Plants on Demand

by Donald R. Hall

This article explores the likely timeframes available to add capacity under "high, early" sales scenarios, the measures that need to be taken to achieve these schedules, and the impact such measures will have on the capital approval and facility creation process in the supply chain.

The Business Imperative - High Early Sales Ramp on New Drugs

It is costing more to bring new drugs to market. The estimated average cost per new drug ranges from $500 million[1] to $1.7 billion.[2] It is taking longer to develop the compounds, and FDA approval times have lengthened in recent years with the result that there is less time remaining on the compound's patent life to recoup the investment in R&D and provide a return to the shareholders. Figure 1 shows the large number of molecules that are evaluated before a final compound achieves approval, the time this takes, and the years of patent life remaining after approval. Competition from competitors' drugs and pressure on profit margins from increasingly concentrated purchasing power, e.g., HMOs, the Federal Government, etc., add to the stress on the industry's profitability and risk profile. Drug companies are therefore adopting a strategy that will ramp sales up as quickly as possible after receiving approval by the FDA or other regional authority having jurisdiction. This "high, early" sales strategy demands a different response from the supply chain than the more gradual increase in need for drug product experienced in the past. The manufacturing capacity of the inventing and/or prime marketing pharmaceutical company as well as its suppliers must be able to respond to the new situation. Firms providing equipment and services for the creation of new capacity also must adjust accordingly.

Research and Development Response

Advances in genomics, rapid throughput screening, combinatorial chemistry, etc. are producing greater numbers of new candidates with

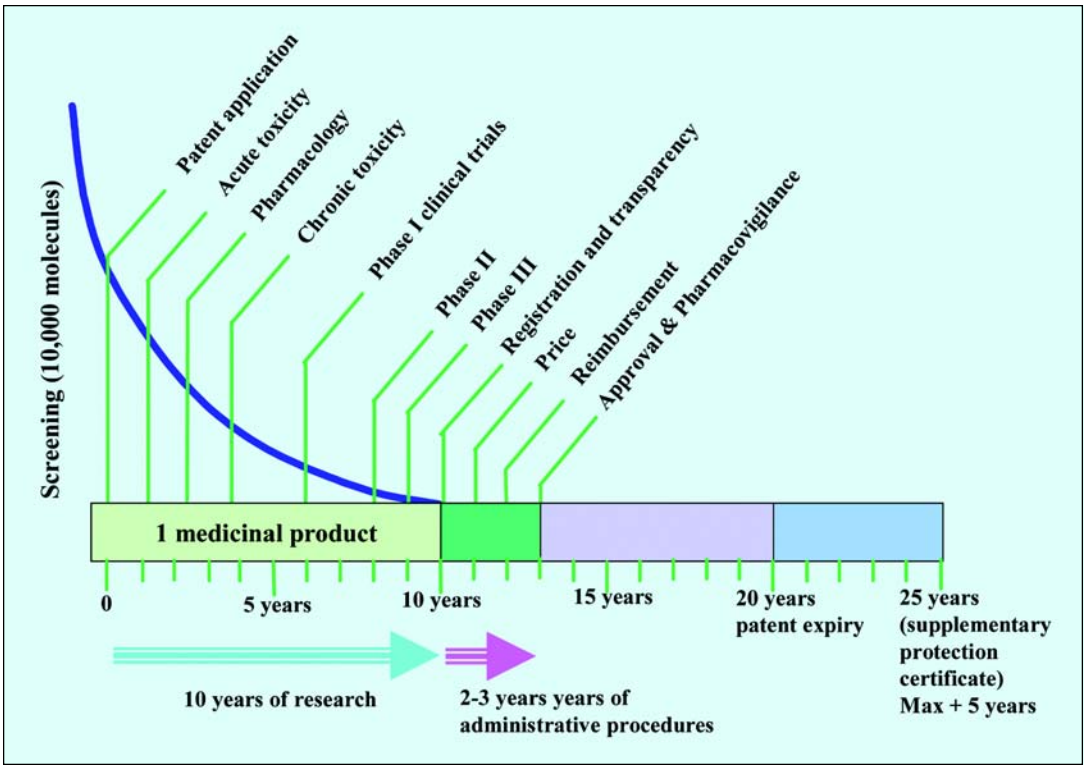

Figure 1. Phases of the Research and Development Process.[3]

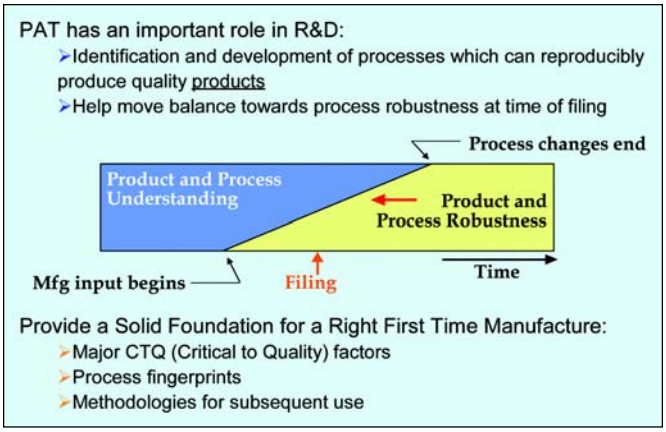

Figure 2. The use of Process Analytical Technologies (PAT).[3]

higher specificity of action per researcher than ever before. Reorganization of personnel from single discipline "silos" to multi-discipline, global teams is helping to move compounds down the development path more rapidly and securely.

To decrease development timelines, companies cannot take the time necessary to develop the perfect manufacturing process before requesting approval. This means the processes to produce the Active Pharmaceutical Ingredient (API), while capable of producing pure product, may be less than fully robust and have to undergo significant improvements over time. Figure 2 shows that to minimize and mitigate the effects of process changes, manufacturing viewpoints need to be incorporated earlier in the development cycle, and new facilities to produce new drugs must be inherently adaptable to accommodate inevitable process improvements.

Supply Chain Response

Forecasting the demand for a new drug is difficult. To underestimate it and not have the production capacity available means profits and returns to shareholders are lost forever; to overestimate it and have large excess capacity and an underutilized asset is wasteful and damages profitability and return on capital employed. In the past, the increase in demand for a new product was usually gradual and the time available to add capacity generous compared to the case of the current "high early" sales and marketing strategies - *Figures 3 and 4.*

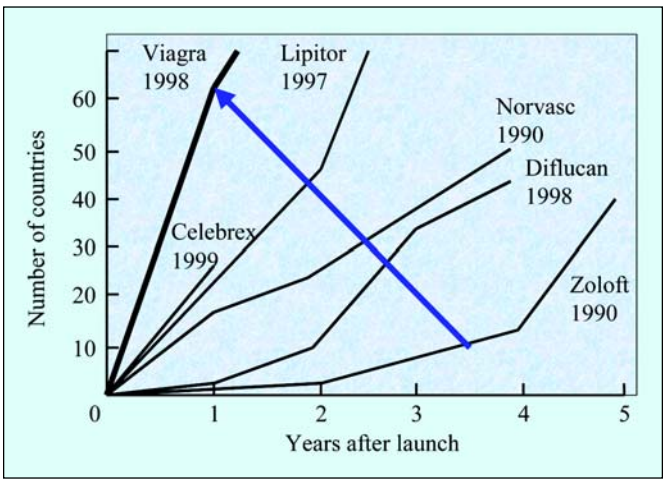

Figure 3. Product Launches - Supply Chain. Accelerated launches to achieve faster sales ramp-up.[3,8,9]

To support the "high early" sales strategy, significant capacity must be in place before approval. The most conservative strategy would be to have a plant built before approval that matches the highest sales forecast. Alternatives are to use an existing pilot plant or build a product launch facility for use by new products and then add purpose built units within the timeframes "bought" by the previous increment's market satisfying ability.

To have a top of forecast plant in place before approval guarantees sales demand will be met and associated profits earned. However, if the drug fails or actual sales fall short of top forecast or are much more gradual, the investment will prove uneconomic and inefficient in the use of personnel and other resources such as utilities. The consequences of such a shortfall can be mitigated somewhat if the plant is designed for multi-product use and other products are made in it during the shortfall period, but this requirement adds time, cost, and complexity that may offset its benefit. The number of steps or processes to be done in the plant also can be limited with more steps being done by suppliers. This pushes more of the capital investment risk down the supply chain to suppliers, but perhaps increases the risk of later supply chain failure as less well capitalized suppliers fail to invest in facilities soon enough in advance of new orders. Further, the know-how associated with the outsourced steps and the cost savings from foreseeable process improvements accrue to the supplier and not the inventing company.

An incremental capacity creation scenario is shown in Figure 5. The initial increment is followed by four more increments over seven years with the last unit designed for maximum efficiency with an optimized or even new process to be able to compete with generic manufacturers when the drug's patent expires. The second increment comes on line 20 months after the initial increment is on line, the third, 16 months after the second, the fourth 16 months after the third and the fifth, 36 months after the fourth. Note that work on each increment must begin before the preceding increment is on line since the total time required per increment, after the initial increment, from start of engineering through validation is likely to be in the two to three year time frame. This overlapping of capital projects in fact becomes a continuous capital program, which is also shown schematically on the right side of Figure 4.

To add capacity incrementally carries risk of production shortfall if building and other permits are not obtained in the required time; if design, construction, and qualification schedules are not met; or if product variability and other processing anomalies occur in the new units. To achieve the shortened timeframes demanded of the incremental strategy requires the embracing of advanced facility creation methods. Advanced methods can save as much as a year in the creation of an increment of capacity. In the context of this article, "conventional" means the traditional serial approach of design-permit-bid-build-bid-commission and validate. "Advanced," means minimizing dependency on permits, maxi-

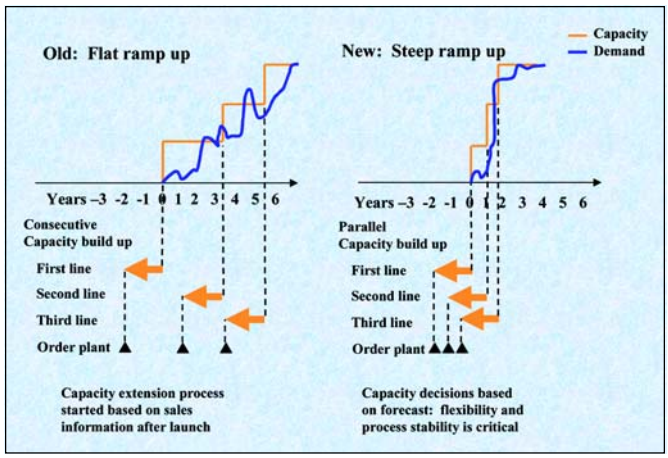

Figure 4. Product Launches - Supply Chain. Decision on capacity extension even before launch.[3,9]

mizing parallel activities, showing flexibility in purchasing policies, and constructing and testing both building and process elements offsite to the maximum practical extent. Figure 5 shows that by using advanced methods the start of the project to build the initial capacity can be delayed from mid Phase II to mid Phase III clinical trials. This gives an additional crucial year of process development to make the process more robust, product quality variations narrower, validation thus faster and smoother, and the predictions for drug approval, market size, and rate of sales growth more accurate. Capital also is conserved since outlays are delayed for a year.

Placing a Value on Saving a Year

One of the biggest values the one year delay buys for pipeline products is there is more known about the product and the probability of technical success can make a significant jump in this time frame. Decision science uses the term "expected value" or "eNPV" to provide a single value for a family of potential outcomes. As an oversimplified example, let's assume a unique process where there is not likely a second use for the facility to be built in the foreseeable future. Then say the NPV of the facility without the product is (-) $100 million. Now lets say that average NPV for all the scenarios where the product is successful is $1 billion. If the project starts before the end of Phase II trials, there might only be a 40% chance of technical success. Depending where in Phase III trials the project outlays begin and how these trials are constructed, the odds may have improved to an 80% chance of technical success. The expected value improves from 0.6 x (-100)+0.4 x 1000=$340 million eNPV to 0.2 x (-100)+0.8(1000)=$780 million eNPV. If one is getting ready to make a $100 million capital gamble, gambling later with an average "win" of $780

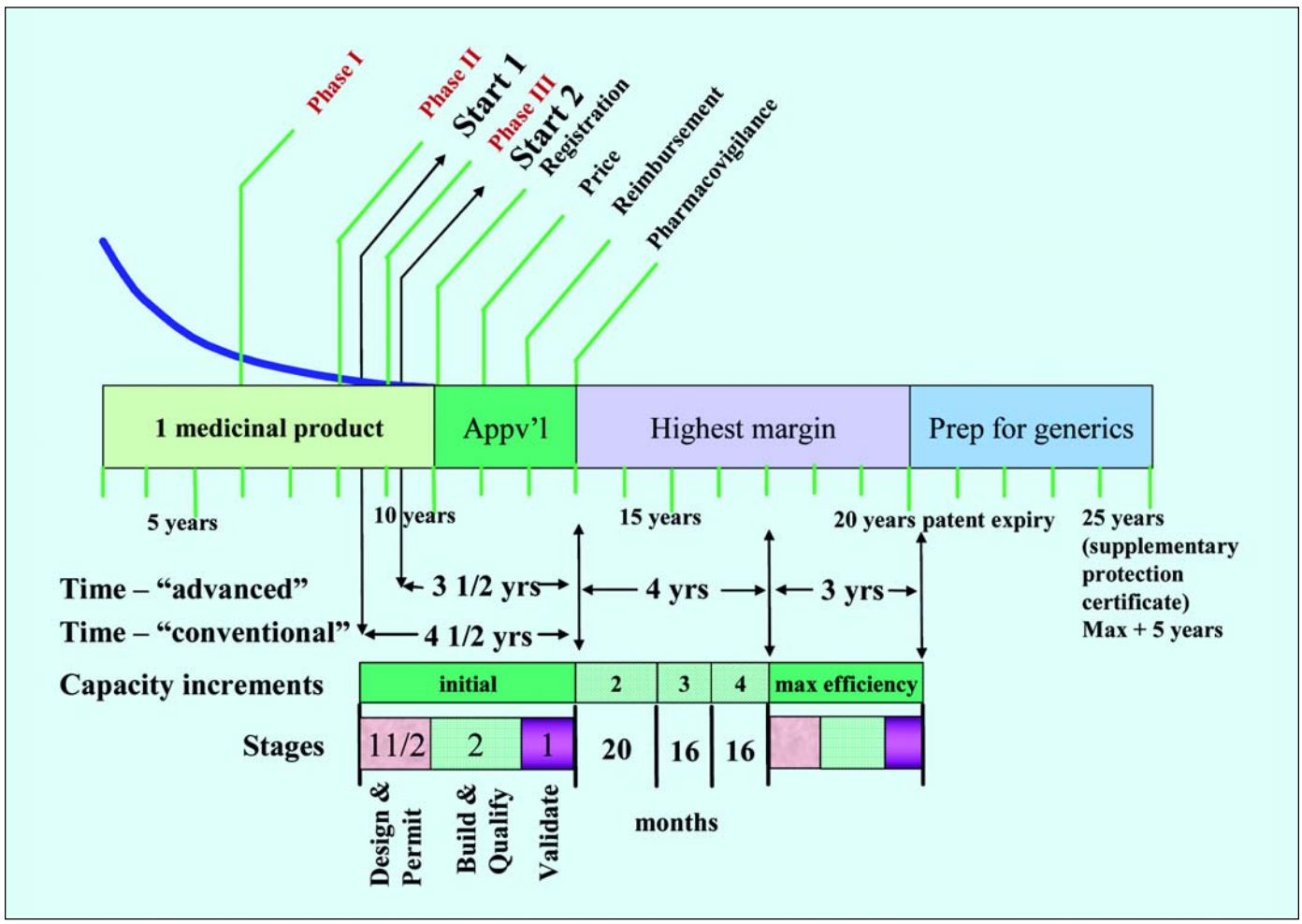

Figure 5. Capacity creation scenario.[10]

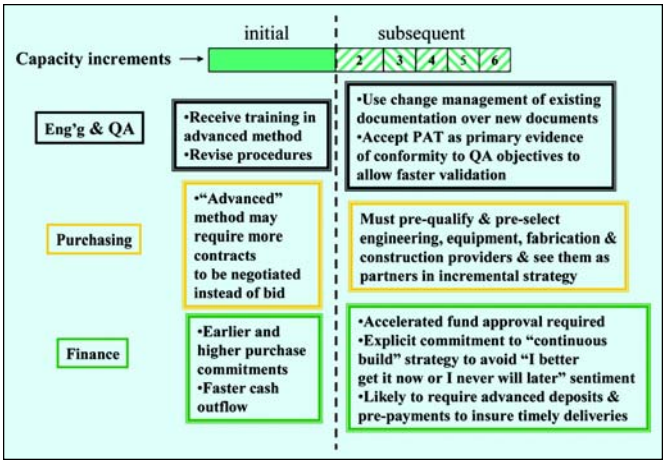

Figure 6. Key policy and procedure adjustments by corporate groups.[10]

million eNPV is much better than gambling earlier with an average "win" of $340 million eNPV.[4]

Adjusting the Corporate Culture

For the incremental strategy to be successful and the advanced methodology adopted, key corporate policies and procedures must be adjusted - *Figure 6*. Machinery must be put in place to support a continuous capital expenditure program lasting the life of the product. The operating company and its suppliers must organize to ensure best past practice and knowledge is applied in each subsequent increment. Documentation must be preserved, controlled, and easily retrieved for re-enactment. Alliances need to be formed with key service and key equipment providers.

Conventional and Advanced Capacity Creation Methods

Figure 7 shows the sequence of events and durations for the "build and qualify" stages for conventional and advanced approaches for the initial plant to produce a new API. Engineering and validation stages and times are not included. Durations used are estimates based on recent experience. It is assumed permitting and construction activities are starting from a "frozen" design. In the advanced method, work can begin on the building and process modules without first having to obtain a building permit. In fact, the final site may

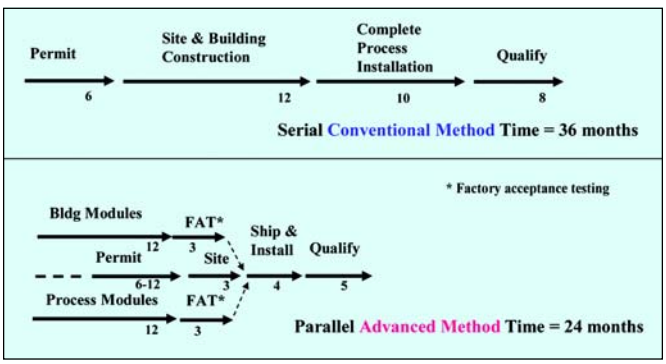

Figure 7. Comparison of conventional and advanced methods during build and qualify stages.[10]

not yet be selected. Work on process systems need not wait for the building modules to be completed if the design is conceived with the goal of maximizing the separation of concerns between the building and process systems. The ability to do factory acceptance testing (Figure 8) means most of the Installation Qualification (IQ) and portions of the Operational Qualification (OQ) can be done before installation on site. This shortens the onsite qualification time. The possible time savings during the "build and qualify" stages provided by the advanced methodology over the conventional approach is approximately 12 months.

Published benchmarking data for bulk pharmaceutical plants producing APIs by organic synthesis show an average total time of 54 months for an initial increment when project formulation and funding approval, engineering, and validation stages are included.[5] The advanced method also may offer time savings during these stages. Modular plant suppliers are likely to know their cost better because of more controlled shop conditions. They can therefore supply more accurate cost estimates earlier on to give greater confidence to the decision makers to help speed the project formulation and fund approval stage. Many system designs and fabrication details also are pre-done by this class of builder which can save engineering time. And, as mentioned earlier, validation should be quicker because process development has had an additional year to improve the process and make it more reliable and repeatable.

To maximize the benefits of using an advanced capacity creation strategy, the decision to use the advance methodology must be made early during the project formulation stage, before significant engineering decisions are made. This is because the time saving advantages available from the advanced methodology substantially diminishes if designs are allowed to progress in a manner that provides only prefabricated skids and assemblies instead of complete modular operational process units and fully modular buildings. Further, the desired "modularity" of a plant influences the format and make up of PFDs, P&Ids, and in fact, the sequence, timing, and content of the engineering and qualification documentation, and the ability to reuse same for subsequent increments. The decision for advanced or conventional is therefore fundamental and must be made at the very outset of the capacity creation process.

The advanced method has certain higher costs than the conventional method such as the added cost for structural steel to support the units for shipment, the cost to ship the units to the site, and the cost to disassemble and re-assemble them. These higher costs are offset by factory over field efficiencies and savings in construction management fees and general conditions expenses associated with the more protracted site construction period for the conventional approach. When all costs are considered through validation, the advanced and conventional methodologies will produce about the same total project cost.

Besides saving time, module builders have a higher probability of applying best past practices and knowledge to their designs and implementation and commissioning strategies.

Figure 8. Modular Potent API unit undergoing Factory Acceptance Testing.[10]

This is because of greater constancy of both professional and trade staff and greater specialization in certain types of plants. This tends to make their project cost, schedule, and performance outcomes more predictable and assured.

Issues with Smaller Increments

The idea of a continuing construction program surrounding a GMP manufacturing operation is abhorrent to most experienced manufacturing and quality assurance professionals unless a reliable means to isolate these activities can be demonstrated. Building designs must incorporate this requirement into the design of HVAC systems and personnel and material flow paths to ensure that GMP envelopes of the operating spaces are not violated as new units are added. Designs for utility and process systems must preclude disruption to on-going operations as new systems are added or existing systems modified. On site construction activities and crew sizes must be minimized to ensure security and keep the manufacturing teams focused on their primary mission of reliable production of quality product.

The concept of many units to do the job that could be done by a single unit feels intuitively inefficient, especially to an engineer or financial person. One larger scale, dedicated unit would provide efficiencies of scale and be more economical to build. However, if to ensure continuous product supply, redundancy in utility systems and key process equipment trains is added to the large scale unit's scope, the cost savings diminish substantially. This makes multiple smaller scale units of equivalent total capacity, and having inherent redundancy, become more comparable in cost to one large unit. In all likelihood, for an important product, another unit at another site will be required to ensure continuity of supply in the event of a natural or manmade disaster. This unit can be the second increment of capacity.

Multiple units offer greater production flexibility for cleaning, maintenance, and trial modifications for process improvements.

Smaller scale units present less scale up risk, which is particularly important to the early capacity increments when the process is still being developed and less than fully robust.

Adding new increments means actual operating and maintenance experience can be reflected in each new increment's designs and equipment selections to eliminate problems and amplify positive results. With each new unit, the possibility exists to incorporate the latest technology, especially in the areas of process controls and on line analytical instruments where technology moves swiftly.

When the possibility for significant process improvements reaches an end and the process is most robust and cost effective, a "lights out," highly efficient, automated plant can be built and incorporate the best techniques of process intensification to maximize space/time yields. This also readies the company for competition from generics. The previously built units can be put to other uses such as development, new product production, or market launch coverage. If these units are modular, they can be moved to new company owned sites to spread production to more tax advantaged areas or for other strategic reasons. As an alternative way to harvest the remaining value of the drug product in its waning years, the units, if modular, can be easily sold and moved along with the product technology to another operating company's site, such as a generic producer. Technology transfer in these two examples is greatly enhanced by the ability to move the modular, fully qualified, and documented plant to the new production location.

Requirements for a Plant That Satisfies a "High Early" Sales Strategy

In an ideal world, a plant to match the "high early" sales strategy would be timely (modular), adaptable,[6] aesthetically pleasing, efficient, capital cost effective, and meet all corporate safety standards, insurer requirements, and the applicable ISPE Baseline® Guide.

The building housing the production systems needs to provide for environmentally controlled and segregated pro-

Figure 9. Modular unit installed and in operation.[11]

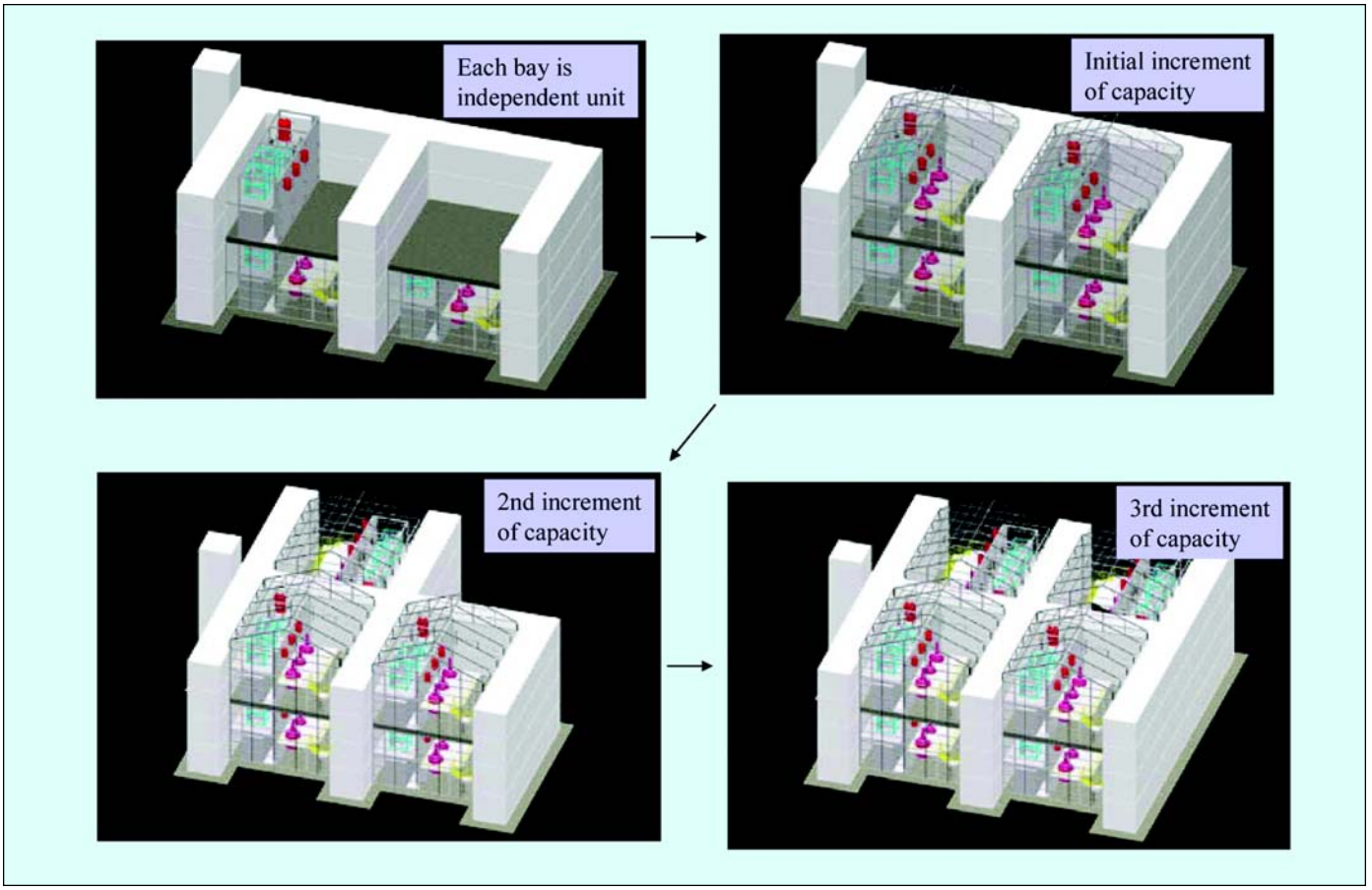

Figure 10. Modular Building & Modular Process Units – add without disruption.[11]

duction spaces, meet the local and international building codes appropriate to its use, accept additions of production spaces and other supporting spaces without disrupting the GMP envelopes of existing production units in operation, and be easily modified and adapted to different environmental and use classifications.

The process systems must have minimal interaction with the building systems to minimize coordination and the possibility for physical interferences, and thereby facilitate parallel construction with confidence. The systems must be master planned for the "maximum" case. That is, they must be designed for the maximum number of features apropos to the class of system at hand to allow one to start with a less than maximum case and add features as required over time with the least cost, downtime, and damage to the aesthetics and operability of the unit in which the system exists. An important feature is a good turn-up/turndown capability. This provides for increasing capacity by increasing batch size in the same equipment.

Utility systems should be associated to a production unit and sized to support that unit over its turn-up/turn down range. This avoids over investing in central utility plants and related infrastructure that can so burden the initial increment as to slow and inhibit approval of funds for the project. Figure 9 combined with Figure 10 show a design approach that attempts to satisfy many of the above requirements.

Project Planning, Team Make Up, and Document Reuse

Qualification and validation requirements must be embedded in the initial project planning. These activities represent a significant percentage of the total time to create capacity, e.g., 20 to 40 % of total project time depending on the complexity and type of product/process. Designs and construction sequences that optimize qualification and validation can be dramatically different from the designs and construction sequence traditionally pursued. Quality Assurance must therefore be a key project contributor right from the beginning along with finance, development, manufacturing, purchasing, health-safety-environmental, and engineering. Key outside service and plant providers also should be brought onboard as soon as possible for the benefit of their experience and perspectives.

Plant documentation requirements are now better defined by the ISPE Baseline® Guide for Commissioning and Qualification. This definition and the rigor it imposes will facilitate and support the case for reuse of certain documentation on subsequent increments of expansion to save time and insure equivalent results. Documents amenable to reuse per Quality Assurance agreed change management procedures instead of recreation are:

- User Requirements Brief
- Requirement Specifications

- Functional Design Specifications
- Validation Master Plan
- Detailed Design Specifications
- P&IDs
- Major Equipment Specs
- Equipment Layouts
- Site and Building Designs
- Environmental and Building Permit Documents
- Commissioning Plan
- Control Estimate
- Building Shop Drawings
- Specialty Item Drawings
- Mechanical Catalogs
- As Built Drawings
- Commissioning and Validation protocols
- Spare Parts List
- Training Materials
- SOPs
- PAT Data Reports

Conclusions

Speed in capacity creation is a competitive necessity in today's pharmaceutical industry environment. Speed allows one to wait longer until information to size, locate and justify the investment becomes better. Speed provides the ability to match a steep ramp up in demand. Under the "high, early" sales strategy, the entire supply chain is affected since each sub-supplier has to respond and add capacity in the same timeframe the inventing and/or prime marketing pharmaceutical company will take to add capacity. The attitude and policies toward facility creation to support a product's production has to move from a single event, one project at a time orientation, to accepting more of a continuum of capital outlay. Contracts with suppliers and plant providers need to be supportive of this view. Besides using modular techniques to shorten schedules, plant documentation needs to be organized and controlled for reuse using QA approved change management techniques.

Some readers may interpret the term conventional approach as the most conservative approach and advanced approach as the risky approach. In fact, it is just the opposite. The Construction Industry Institute[7] has verified this view through independent studies. Other capital intensive, price competitive, technology based industries such as chip making have adopted more advanced capacity creation methods and information reuse out of necessity. With the goal to maximize profitability and return on capital employed in an ever more competitive pharmaceutical industry, the advanced method of capacity creation, as described herein, has become the least risky, less costly, and most assured choice.

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3. Figures 1, 2, 3, and 4 are excerpted with Permission form Dr. Peter Green, Vice President Pharmaceutical Sciences – Michigan, Pfizer, from a paper entitled, "From a New Chemical Entity to a Marketed Product – The Development Process as Part of the Value Chain," presented at the October 9, 2003 meeting of the Chemist Club, Marketing and Economics Section, New York City.

4. Example provided by William Fox, Sr. Engineering Consultant, Project Development, Indianapolis, IN.

5. Paper presented by Stan Newberger, Principal, CE&IC at winter meeting of ISPE in Tampa, Feb 10-12, 2004 in the Bulk Pharmaceutical Guide Conference.

6. The term "adaptable" instead of flexible is used by William Fox, Sr. Engineering Consultant, Project Development, to describe the inherent ability to add capability, ultimately to the limits of a system or space's masterplan, without compromising functionality or operability. The term flexible, when stated as a project requirement, seems to encourage the inclusion into the initial scope many elements that may not, in the end, be used very frequently and which add cost, clutter and complexity.

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11. Hovione Corp.

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This article evaluates the merits of using modular cleanroom technology for the construction of pharmaceutical and biopharmaceutical facilities.

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Determining When to Use Modular Construction

by Declan Greally and Rodger Edwards

Introduction

Modular construction is a term that is used to describe 'factory production of pre-engineered building units that are delivered to site and assembled as large volumetric components or as substantial elements of a building.'[1] The modular units may be room-sized or parts of larger spaces which are combined together to form complete buildings. The structural frame of modules can vary, depending on the application. This article is concerned only with light steel frames generally used for the pharmaceutical industry.

It is important to put construction activities within the pharmaceutical industry into a wider context. To date, examples of buildings that have been constructed using steel frame modular technology include student residences, hotels, and fast-food restaurants as well as pharmaceutical facilities.

The main reasons offered for this increase in use both within and outside the pharmaceutical industry are as follows:[2-4]

- improved quality and reduced waste
- compressed construction time
- increased safety
- reduced weight
- to overcome local skill shortages

Impediments to using modular construction as an option include:[5]

- increased engineering costs
- early design freeze which may reduce the scope for flexibility
- absence of a robust economic advantage
- higher project risk due to unfamiliarity of some project participants with specific requirements
- complicated interface issues

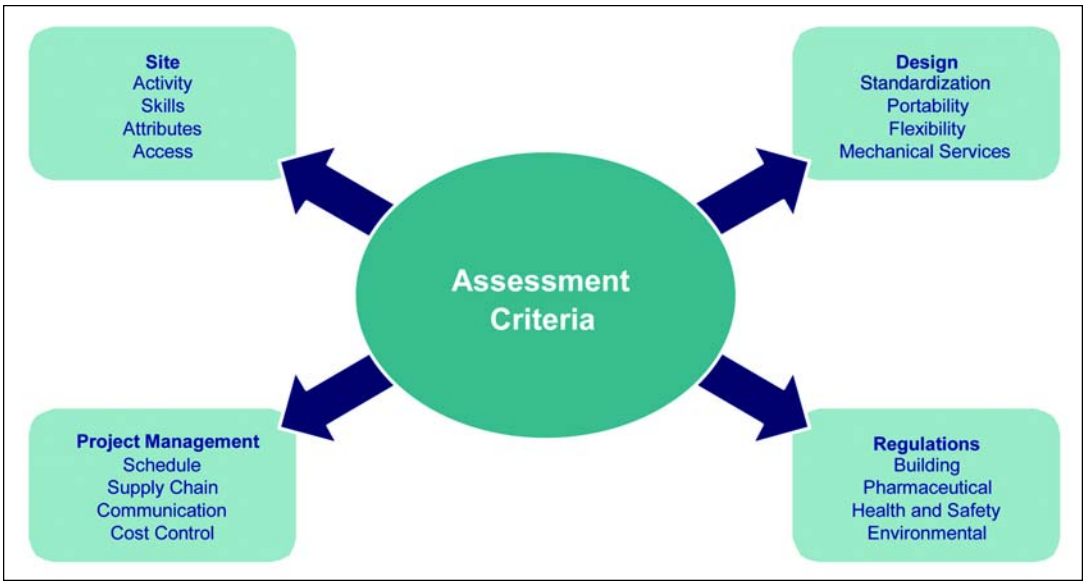

Figure 1. Selected criteria for the assessment of different construction methodologies.

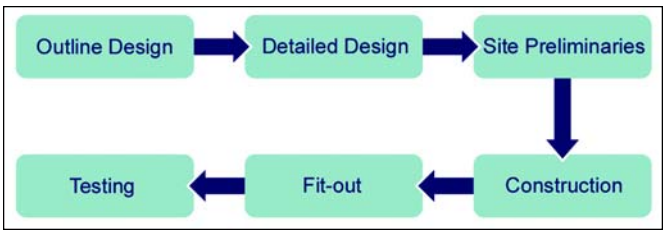

Figure 2. A typical construction program.

Historically, pharmaceutical manufacturing facilities have been constructed using traditional building methods. Although steel frame modular technology has been available for at least 25 years, it is only in the last 5 to 10 years that modular construction technology has been employed for major pharmaceutical manufacturing facility projects.

It is becoming apparent that modular construction may, in some instances, be a suitable alternative to traditional construction methods; however, a detailed cost-benefit analysis needs to be performed for every project to select the most appropriate construction option. Benefits that modular construction can offer hotel and restaurant construction projects may not easily transfer to the pharmaceutical industry.

The aim of this article is to evaluate the merits of using modular technology for the construction of pharmaceutical manufacturing facilities. An evaluation methodology, based on analysis tools proposed by the Construction Industry Institute,[6] has been developed and this will enable the reader to assess the applicability of modular construction for specific projects.

Comparison Criteria

Whether to use modular construction or traditional building techniques is a question that is becoming more common within the pharmaceutical industry and one that may have a different answer depending on the project. The Construction Industry Institute has developed an assessment methodology to evaluate the benefits of prefabrication, preassembly, modularization, and offsite fabrication.[6] A variation of these has been used by the authors and discussed in this article to evaluate the merits of modular construction for pharmaceutical projects. Figure 1 presents the headings and sub-headings under which modular construction for the pharmaceutical industry will be discussed.

Site

Site Activity

Construction activities invariably result in disruption to areas surrounding the construction site due to:

- dust generation
- increased density of personnel
- noise and vibration
- access restrictions
- accidental damage

Most pharmaceutical organizations are very sensitive to disruption of this nature. Dust, for example, arising from construction activities can be drawn into the ventilation inlets and result in unexpected challenges to air filtration systems, or be carried into adjacent buildings by people or wind. In addition, these organizations may not have the space, infrastructure, or finances to house a design and construction team. Any reduction in site-based activities would therefore be advantageous.

Companies involved in the modular construction industry claim that site activity can be reduced by 30-40% if modular technology is used.[2] In particular, because it is inherently a dry construction, dust generation also can be minimized. This has the potential to limit disruption and subsequently any adverse impact on ongoing production activities. On the negative side, depending on the site, movement and lifting of large volumetric units may cause significant, but intermittent disruption to adjacent facilities.

Construction Skills

The recent trend to locate pharmaceutical manufacturing facilities in more remote global locations has meant that it is not always easy to get access to skilled labor at the right price. Off-site factory-based construction of the facility and subsequent transportation to site is a potential solution that modular construction offers to this lack of local resource.

However, the modular construction route could, however, result in a number of disadvantages. First, in some instances, pre-fabrication will preclude monetary benefits from local labor incentives, and second, preparation of the site by local contractors may be sub-optimal because of inherent unfamiliarity with modular construction.

Site Attributes

Adherence to construction program and budget can be greatly affected by adverse local conditions such as:

- extremes of weather
- economic and political instability
- labor instability
- poor availability of building materials

It is the goal of every pharmaceutical construction project to achieve a wind and watertight envelope in as short a timeframe as possible. Early attainment of this goal not only reduces program sensitivity to adverse weather conditions, but also facilitates a clean-build.

Pre-fabrication of building components can reduce the time to reach an enclosed shell and this route is used extensively by construction firms.[5] Prefabrication of the entire building in modular format and in a factory-based setting enables facilities to become wind and watertight in a very short timeframe. Indeed, the entire construction of modules can take place under cover. Each module is constructed and enclosed as a separate entity, and exposure to the elements is minimized. Before leaving the factory, modules are wrapped in protective waterproof covering until they are ready for site installation.

Moving construction activities away from areas of politi-

cal, economic, or labor instability can reduce project risk. There is a potential for modular construction to facilitate this. However, it should be remembered that modules need to get from the country of origin to site; and costs and delays associated with local permitting and security arrangements must be factored in.

The location of pharmaceutical manufacturing facilities in remote global locations may mean that buildings are exposed to wide temperature variations. A high building mass may be required to ensure that the building's interior is not affected by such fluctuations. This is easily achieved when using traditional construction methods; however, for modular construction, increased building mass may reduce mobility and maneuverability due to increased weight. It may be feasible to enclose the modular building in an outer brick shell to overcome such difficulties.

Site Access

Sites with constrained lay-down areas, poor access, and heavy-lift restrictions can greatly hamper 'buildability' or the ability to construct a building in a cost effective and timely manner. Restricted vehicular access (for example, narrow roads and low bridges), lack of storage space, noise constraints, and poor access for cranes all serve to potentially delay the build process and impose additional costs.

All construction methodologies need to find innovative ways to overcome such difficulties and each site will need to be evaluated against the construction method of choice. Pre-fabricated modules, for example, generally require:

- good infrastructure to enable transportation to site
- large laydown areas prior to final assembly
- heavy and large-volume lifts

Poor roads, costly permitting, and schedule constraints for shipping may force the modular construction team to use lengthy transportation routes. Constrained site access can adversely impact traditional construction methods in a similar fashion. However, the ability to reduce loads may result in more options, but perhaps with associated cost implications, for transportation and lifting.

Project Management

Schedule Control

Speed to market with new products (or new product extensions) is critical for most manufacturing companies. Where new product introduction also requires a new purpose-built facility, construction must be carried out as rapidly as possible. This is particularly true for the pharmaceutical and biopharmaceutical industries, which need to maximize the patent protection period after what is usually a long and expensive product development cycle.[7]

A typical construction program follows the sequence of activities as shown in Figure 2.

One way to reduce construction time is to perform as many construction activities in parallel as possible. Strategies which traditional construction companies employ to achieve this include:

- use of well-developed supply chains to take long lead items off the critical path
- pre-fabrication of building components[5]
- phasing detailed design so that it overlaps with construction
- phasing construction so that it overlaps with fit-out and testing
- design to enable simultaneous working in several construction areas on the same site

With the pre-fabrication of modules, it may be feasible to achieve parallel programming of the following major activities:

- site preparation, planning, and construction
- construction, fit-out, and testing
- Co-construction of a number of modules by different modular construction companies.

For less complicated non-pharmaceutical projects, it has been shown that modular construction can reduce construction time by 30-60% through parallel programming.[2]

In many cases, traditional building methods can facilitate a late design freeze; however, this may not be readily achievable for pre-fabricated modules with a high level of interface requirements.

Economics

The economic assessment of construction technologies can be divided into two parts for comparison:[4]

1. Cost assessment - focuses on the costs of construction as determined by the Bill of Materials.

2. Financial assessment - which takes a more holistic view of commercial benefits that can be derived from the speed of construction and improved cash flow.

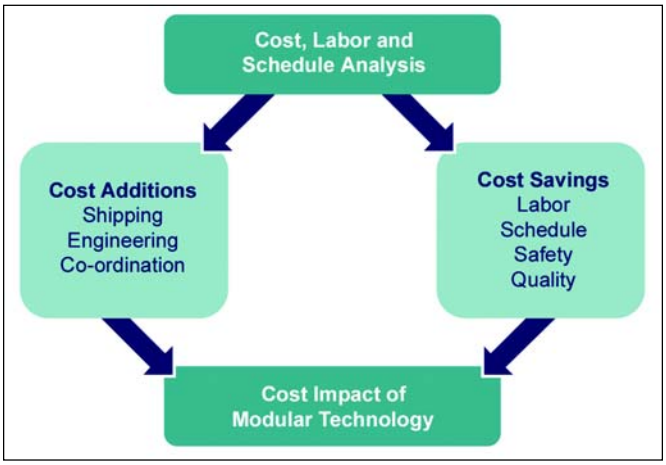

Figure 3. Bill of Materials Cost analysis to evaluate modular construction.

The manufacture and transport of construction materials releases about 10% of UK CO_2 emissions.
Some estimates indicate that waste generated using traditional building methods reduces profits by some 25%.
The construction industry caused 16% of all water pollution incidents in 1997
Construction work on-site is responsible for 4.7% of all noise complaints

Table A. Environmental statistics taken from a report prepared by the Centre for Sustainable Construction (UK).[10]

Each project needs to be evaluated on its own merits. Figure 3 indicates where modular construction can impact costs in relation to traditional build.

In general, building materials used for modular construction are more expensive when compared to traditional construction. Additional costs also are incurred for design coordination and module shipment.

To offset these costs, savings can be achieved through greater productivity and increased safety. Other benefits include savings on preliminaries, scaffolding, and wastage. Modular construction technology results in less construction material wastage,[2] because of greater reliance on (a) standard construction sizes, (b) pre-fabrication of components, and (c) sub assembly, rather than delivery of sheet materials. This also will reduce incidences of material theft and improve stock control.

To reduce the cost impact of using modular construction, such that it is cost neutral (when compared to traditional build), documented assessments for non-pharmaceutical projects have shown that a high level of standardization within a construction project is required.[4] It should be borne in mind that shorter production runs would result in reduced cost efficiencies and potentially less favorable comparisons with traditional construction.

Functionality
Multi-product, biopharmaceutical cGMP pilot plant with associated Process Development and Quality Control Laboratories
Fully contained with respect to clean utilities, wash, preparation and storage areas
Biocontainment required for Genetically Modified Organisms
Main Issues
High levels of construction activities on site in surrounding areas, worker density, site access and on-site storage are major problems
Difficult to access skilled and non-skilled labor. However financial incentives to use local labor are available
Early design freeze is not feasible due to a large number of unknowns with respect to the production processes that will be carried out in the facility
Early occupancy of the facility is required to initiate batch production of clinical trial material.
Due to a high level of financial commitment on existing construction projects, the budget for this facility is constrained.
Economic, labor and climatic conditions are stable however the area receives a large amount of rainfall

Table B. Main characteristics of the biopharma project used to demonstrate the evaluation models.

Rogan et al[4] demonstrated that the most significant commercial benefit that modular construction offers is a faster return on investment brought about by a reduction in construction time. Construction time, in this case, was reduced by 33%, which resulted in a 43% increase in the internal rate of return.

Regulations

Pharmaceutical Regulations (QA and cGMP)

Very few industries are as highly regulated as the pharmaceutical industry. Wherever possible, quality should be designed into production equipment and facilities to avoid any adverse impact on the product itself. The following construction attributes may help achieve facilities to meet the User Requirement Specifications efficiently:

- 'proceduralized' construction methods
- single point-of-contact project management
- minimal number of different trades
- on-going testing and defect correction
- clean build[8]

Traditional construction methods typically require a significant number of trades whose activities overlap in many instances. This can make it very difficult to supervise and test each element of the building. This difficulty is compounded by different working methods that individual trades may employ.

Modular construction companies have more opportunities to use factory-controlled procedures and high levels of automation.[2] Testing and in-built quality assurance may be easier to achieve; however, this will depend on the quality systems of the modular construction company. Maximum benefits can be derived when the modules are fitted-out at the factory as internal components and installed equipment can be fully commissioned in the form of Factory Acceptance Testing (FAT) prior to delivery. It is vital that the construction company has a good quality system so that these benefits can be realized.

The construction materials used in modular technology also are inherently cleaner than those used for traditional buildings, which greatly enhances facility clean up.[2] The ability to 'Clean-build' is very important for pharmaceutical facilities as it makes the post construction clean-up activities far less onerous.[8]

Segregation of production activities is very important for many pharmaceutical and biopharmaceutical companies. A traditional construction method achieves this by allocating specific processes or process steps to designated rooms. With modular construction, different processes can be allocated to individual modules (or groups of modules) which can reduce the potential for cross contamination.

Building Regulations

Irrespective of construction methodology, the overall objective of a building project must be the same. In other words, the facility must be fit for purpose and must satisfy local and national building regulations such as:

Key Driver	Question	Case for MC?: Yes/Maybe/No
Program	Are there significant constraints for the project schedules? MC may help to meet schedule constraints.	*Yes*
Site attributes	Are there significant site attributes such as extreme weather or lack of infrastructure that may impact project performance? MC can potentially relocate work to more favorable conditions.	*No*
Site access	Do available routes and lifting paths allow using modules with the dimensions set by truck, rail or barge shipment? Using the largest possible modules increases the benefits of MC.	*Yes*
Skill base	Is there a lack of good local labor available in the project area? MC may help by moving work to areas with adequate labor.	*Yes*
Build regulations	Are there significant environmental, legal, and/or regulatory considerations that may constrain the project? MC may help to alleviate constraints by allowing parallel work while such issues are handled.	*No*
HSE	Is there an opportunity to decrease safety risks by using MC? MC may be able to relocate work to less hazardous environments such as ground level or controlled climates.	*Yes*
Quality Assurance	Is there an opportunity to decrease the overall quality testing timeline by using MC? It may be possible to carry out a significant number of tests in parallel prior to final assembly.	*Yes*
(MC = Modular Construction)		

Table C. Level I evaluation.

- fire regulations
- foundations
- access for disabled people
- ventilation

Where lengthy permitting is required, it may be feasible to commence the fabrication of modules prior to receiving the necessary planning permission. This is a risk that must be carefully managed to avoid significant monetary loss should the planning application be refused.

Environmental Regulations

Environmental requirements vary from country to country but in general the following need to be considered:

- energy conservation including energy consumed in material production and transportation
- waste generation during the build process including CO_2 emissions during the production of build materials
- air leakage[9]
- aesthetics
- materials of construction especially use of re-cycled waste
- water pollution incidents

Statistics taken from a report prepared by the Centre for Sustainable Construction (UK)[10] are shown in Table A.

As with other industries, the construction industry is under growing pressure to reduce its impact on the environment. Modular construction could potentially help this cause in the following ways:

- reduced wastage due to standardized components and a greater use of standard operating procedures
- effluent streams which are easier to control
- reduced site-based noise

Health and Safety Regulations

Health and safety statistics for the UK (2001/2002) show that 29% of fatal accidents and 14% of non-fatal accidents occurred in the construction industry.[11] This has remained relatively unchanged over the past five years.

Aspects of modular construction can mitigate some of the health and safety risks associated with traditional build by reducing (a) site-based worker density, (b) hazardous area working, and (c) exposure to extremes to weather. Construction using factory controlled procedures and with closer supervision can also reduce the level of injuries.[5]

Design

Mechanical Services

The density of mechanical services required for a facility depends on functionality. Warehouses, for example, generally require a very low density of services. The opposite is true for pharmaceutical production suites where HVAC ducting and pipework for clean utilities can result in very congested technical spaces.

Cost effective use of modular construction requires a high value per unit volume[1] to offset higher construction and transportation costs. It may not be suitable for warehouses, and potentially has greater application for more highly serviced facilities.

In general, pharmaceutical production facilities require warehousing facilities. Therefore, if modular construction is being considered as a construction option, it may be appropriate to construct the warehouse element using traditional methods and the process areas using modular construction. Often the most highly serviced elements of the building are constructed from modular units and the remainder of the structure is constructed conventionally.[1]

Where pipework runs through a number of modules, difficulties with interfacing can arise, especially when modules are being supplied by more than one module manufacturer. Great care needs to be taken such that (a) modules can be integrated properly when they arrive on site and (b) pipework can easily be maintained when incorporated into a modular format.

Flexibility

If buildings have expandability and flexibility designed-in, the cost of future change can be reduced. Increasingly, the pharmaceutical and biopharmaceutical industries are looking for greater flexibility with respect to batch size, segregation, and re-fitting with new technologies. To achieve such features using a traditional construction approach, the design phase may need to be extended so that potential future requirements can be considered.

With modular construction, modules of different capacities can be added at a later date with minimal disruption. There is no reason, of course, why the capacity of traditional buildings cannot be expanded at a future date by adding pre-engineered modules.

Scoring Key:

-5: Strongly pro traditional ◄——— 0: Neutral ———► +5: Strongly pro modular

Driver	Project Objective	Score for Modular Construction
	SITE	
Activity	More options to reduce on-site labor density requirements Maximize security and protection of proprietary technology Reduce the risk of equipment damage	*5* *0* *0*
Skills	Maximize access to skilled labor and licensed crafts Maximize labor-related grant schemes and tax incentives	*5* *-2*
Attributes	Reduce the impact of adverse weather conditions Reduce impact of poor labor/political/economic conditions Improve labor productivity and increase labor cost stability	*2* *0* *2*
Access	Reduce the impact of poor infrastructure Reduce impact of small laydown areas & difficult site boundaries Minimize the costs associated with site preparation	*-2* *-5* *0*
	PROJECT MANAGEMENT	
Schedule	Maximize ability to get product to market early/reduce downtime Reduce impact of long lead items of equipment Minimize equipment installation and commissioning timelines	*5* *N/A* *5*
Cost	Improve overall project cost control Reduce project capital cost Enhance future reuse/salvage value Maximize site-related grant schemes and tax incentives	*2* *-2* *N/A* *-5*
Supply Chain and Communications	Minimize delays due to supplier availability and delivery Maximize integration of all design team members Minimize the impact of poor communication and coordination	*-2* *0* *-2*
	REGULATIONS	
Pharmaceutical	Minimize start-up time by early detection/elimination of defects 'Proceduralize' special assemblies/activities wherever possible	*5* *2*
Building and Environmental	Reduce the impact of lengthy permitting Enhance future ability to reuse/salvage Reduce the impact of stringent environmental restrictions	*N/A* *N/A* *2*
Health and Safety	Minimize necessary work in hazardous areas Reduce impact on any ongoing operations Maximize monetary safety-associated incentives Reduce insurance costs Reduce the requirement for larger (heavy) lifts	*5* *5* *N/A* *0* *-2*
	DESIGN	
Mechanical Services	Design-in facility maintainability Maximize efficiencies from high-density installations and routings Maximize efficiencies from the use of design tools Maximize opportunities arising from design innovation Maximize project efficiencies by modularizing mechanical systems	*0* *-2* *N/A* *N/A* *0*
Flexibility	Facilitate late business decisions and late design freeze Maximize opportunities to design-in future flexibility	*-5* *0*
Portability	Maximize the potential to relocate facilities	*N/A*
Standardization	Maximize efficiencies from standardization across projects	*-2*

Table D. Level II analysis.

Future internal modification of modular facilities will be constrained by the inherent structural requirements of each individual unit. This is not the case for traditional facilities where a supporting column can be removed by spanning columns on either side of it.

Portability

Modular buildings can be disassembled and modules can be relocated to create new buildings quickly and economically. This is not feasible for traditional buildings. However, it is unclear at this stage whether 'portability' will be a major factor within the pharmaceutical industry, although flexibility and adaptability in asset terms can be extremely important.

Standardization

In 1999, CIRIA predicted that standardization and prefabrication will become significant across all market segments within the next 10 years. The biggest economic savings will come from the ability to use standard components and systems.[12] With modular construction, there is an opportunity to (a) standardize individual components and (b) use standard operating procedures thereby decreasing design costs and increasing construction predictability.

Standardization of modules may be very difficult to achieve for pharmaceutical manufacturing facilities because of (a) the wide variety of equipment and plant requirements and (b) the different types of activities that are performed ranging from cGMP production to QC testing, administration, and warehousing.

Project Specific Analysis of Modular Construction

To evaluate the potential advantages and disadvantages of using modular construction, project managers who are considering this approach need a systematic method for analysis prior to making a final decision. This analysis should be performed as early as possible in the project: since modularization, shipping envelopes and interfaces typically dictate many constraints of detailed design, early decisions are generally more successful.[5] The approach to analysis described in this article has been adapted from a software-based model put forward by the Construction Industry Institute (CII). The reader is advised to review this model to determine its suitability for their specific project. The analysis as described by the CII and illustrated below must be performed out by the project team and all major stakeholders. Team member should be aware of the advantages and disadvantages associated with the different construction methodologies prior to carrying out the exercise.

To demonstrate how the model works, an analysis has been carried out for a typical biopharmaceutical project that has specific constructability issues - *Table B*. Assessment scores for this project have been entered in italics throughout the model presented.

The analysis is divided into two sections known as Strategic Levels. The Strategic Level I analysis is designed to serve as a business planning tool to identify the potential overarching drivers, or otherwise, for using modular construction. Table C shows some examples of typical project drivers. The Strategic Level II analysis is a more thorough assessment tool and lists project specific objectives, as shown in Table D for each key driver listed in Table B.

The response to each objective is scored according to the scoring key associated with Table D. Negative scores for specific objectives indicate that modular construction would not be suitable to achieve this objective. The scores are added and averaged for each project objective and taken forward to Table E for further evaluation.

Using this table, a weight factor is applied to each of the raw scores and the end result (which will be between -5 and +5) will help to determine the appropriateness of modular construction. A score of less than zero for a given project would indicate that modular construction is not a suitable construction option. However, if the result is positive, as for the example project demonstrated, a decision can be taken to perform a cost analysis described under the Project Management section (Figure 3) to fully evaluate the financial impact of modular construction.

Category	Average Raw Score	Weight Factor (0 to 5)	Weight Factor Percent	Weighted Score
	A	B	C = B/ΣB	D = A*C
SITE				
Activity	*1.67*	*4*	*0.11*	*0.18*
Skills	*1.5*	*3*	*0.08*	*0.12*
Attributes	*1.33*	*1*	*0.03*	*0.04*
Access	*-2.33*	*2*	*0.05*	*-0.12*
PROJECT MANAGEMENT				
Schedule	*5*	*4*	*0.11*	*0.55*
Cost	*-1.67*	*4*	*0.11*	*-0.18*
Supply Chain and Comms.	*-1.33*	*5*	*0.13*	*-0.17*
REGULATIONS				
Pharmaceutical	*3.5*	*5*	*0.13*	*0.46*
Building and Environmental	*2*	*2*	*0.05*	*0.1*
Health and Safety	*2*	*5*	*0.13*	*0.26*
DESIGN				
Mech. Services	*-0.67*	*4*	*0.11*	*-0.07*
Flexibility	*-2.5*	*0*	*0*	*0*
Portability	*N/A*	*0*	*0*	*0*
Standardization	*-2*	*2*	*0.05*	*-0.1*
		38	**C * 100 = 100%**	**Final Score ΣD = *1.07***

Table E. Summary of Level II analysis.

Summary

For many types of buildings, modular construction technology is becoming a recognized alternative to traditional construction. The reasons for this include: shorter construction period, increased opportunities to improve quality, increased opportunities to increase safety, and advances in construction technology, communication, and design tools

Many factors need to be carefully analyzed before making a decision to use modular construction for pharmaceutical facilities. A number of key drivers need to converge so that the net benefits of modular construction can be realized. In general, a high level of module standardization is required to ensure that this approach is cost effective. For many pharmaceutical projects, this may be difficult to achieve.

Finally, to achieve the full benefits of modular construction for pharmaceutical manufacturing facilities, it must be evaluated as a build option alongside traditional prior to facility design.

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Rodger Edwards graduated with a BSc (Honors) in metallurgy and materials science from the joint UMIST/University of Manchester Department of Metallurgy in 1979 and then spent three years as a research student in the same department, researching thermophysical properties of liquid metals. He joined the Department of Building Engineering at UMIST as a research assistant in 1983 with his main research areas being the measurement of ventilation rates using tracer gases and the computer simulation of hot water systems. He finally obtained his PhD from UMIST in 1986. In 1987, he was appointed as a lecturer in the Department of Building Engineering at UMIST, and in 1997 was promoted to Senior Lecturer. He was elected to membership of the Chartered Institution of Building Services Engineers (CIBSE) in the same year. Edwards has been the Director of the Pharmaceutical Engineering Advanced Training (PEAT) program since December 1996, and has supervised more than 40 successful MSc graduates through their dissertations. He is also a Faculty Tutor at UMIST, and is Chairman of the Merseyside and North Wales Region of CIBSE. He has been an ISPE member since 1996.

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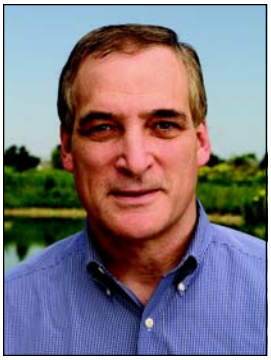
PHARMACEUTICAL ENGINEERING Interviews George Fotiades, President and Chief Operating Officer, Cardinal Health



George Fotiades is President and Chief Operating Officer of Cardinal Health. In this role, he oversees the day-to-day operations for all Cardinal Health businesses.

Cardinal Health, Inc. (www.cardinal.com) is the 17th largest corporation in the U.S., generating annual revenues in excess of $56 billion. Headquartered in Dublin, Ohio, Cardinal Health employs approximately 55,000 people; 42% of those outside the U.S.

Background Brief

Q Please tell us about your career. What is your educational background? Can you provide us your career history in the pharmaceutical industry?

A My career spans 27 years with a major portion of it in consumer packaged goods, consumer medicines, and prescription pharmaceuticals.

I graduated from Amherst College with a degree in economics, and then received my MBA from Kellogg School of Management, Northwestern University.

I began my career working at Proctor and Gamble. During the 11 years I was there, I went from Brand Assistant to Vice President of Marketing for a range of personal products. From there, I worked for three pharmaceutical companies – which are, in chronological order: American Home Products, Bristol Meyers Squibb, and Warner Lambert.

At American Home Products, I was responsible for sales and marketing for what was then their household products group when they were a diversified pharmaceutical company. At Bristol Meyers Squibb, I was responsible for the Clairol group in the U.S., and then I later became president of the consumer medicine business in Japan. After this, I became President of Warner Lambert's US consumer medicine business which included Benadryl, Sudafed, Zantac, Listerine, etc., and a range of other beauty care products in addition to the healthcare products.

Then in 1996, I left the world of diversified pharmaceutical companies to become president of R.P. Scherer. R.P. Scherer was a global supplier to Warner Lambert for soft gelatin encapsulation technology that was used in a range of over the counter products that Warner Lambert produced. It was an independent global public company that included drug delivery and soft shell capsules products.

Cardinal Health acquired R.P. Scherer, about 18 months after I joined, so in August 1998, I joined Cardinal Health with responsibility for R.P. Scherer. Then as Cardinal Health developed its strategy of providing a broad range of services to the pharmaceutical manufacturing and biotechnology companies, I became President of Cardinal Health's Pharmaceutical Technology and Services segment. We ultimately expanded this group and I became President and CEO of Cardinal Health Life Sciences and Products segment which includes pharmaceutical manufacturing, product development, packaging, product manufacturing, logistics, and marketing services. In February of 2004, I became President and Chief Operating Officer of Cardinal Health.

Additionally, I also serve on the board of a company called ProLogis, which is a Real Estate Investment Trust (REIT), and the largest provider of distribution services worldwide for global customers.

Q Do you think your experience in big pharma benefited you in your current position with Cardinal Health?

Cardinal Health History Timeline as of 04/15/2004 www.cardinal.com	
1971	Robert Walter founds Cardinal Foods, Inc. - a food wholesaler.
1979-1980	Cardinal Foods moves into drug wholesaling with the purchase of the Bailey Drug Company. With this addition, Cardinal Foods is renamed Cardinal Distribution, Inc.
1983	Cardinal Distribution becomes a publicly held company with common stock trading on the NASDAQ at $1.03 a share. Cardinal Distribution operates four Midwest distribution centers.
1984	Cardinal Distribution purchases Ellicott Drug Company, expanding its drug distribution business into new markets. The purchase places Cardinal Distribution in the top 12 publicly held distribution companies.
1986	Cardinal Distribution acquires wholesalers James W. Daly, Inc. and John L. Thompson Sons and Co.
1987	Leader Drug Stores, a cooperative of independent retail pharmacies, becomes a part of Cardinal Distribution. National PharmPak is formed.
1988	Cardinal Distribution's food operations are sold to Roundy's Inc. Marmac Distributors, Inc. is acquired. Cardinal is recognized as the #1 or #2 wholesaler in each of its regional markets, serving 17 percent of the customer population in the United States.
1989	Cardinal's management commits to increasing the company's earnings per share (EPS) more than 20 percent - a commitment to shareholders that is a hallmark of Cardinal Health's performance today.
1990-1991	Ohio Valley - Clarksburg, Inc. joins Cardinal Distribution. Cardinal Distribution is the nation's sixth largest distributor of pharmaceuticals and health care products. Cardinal Distribution expands into the southern market with the purchase of Chapman Drug Company.
1992-1993	Cardinal Distribution expands with the formation of National Specialty Services, Inc. Solomons Company joins Cardinal Distribution, bringing a broad-based presence in Southeastern markets. Distribution centers are opened in Mississippi and Florida.
1994	Cardinal Distribution, Inc. becomes Cardinal Health, Inc., reflecting our commitment to the health care industry. Cardinal Health commences trading on the NYSE under the symbol CAH.Whitmire Distribution Corporation, Huminston-Keeling, Inc. and Behrens Inc. are acquired, making Cardinal Health the third largest pharmaceutical wholesaler in the United States. Cardinal Health grows from its status as a regional East Coast distributor to a national health care provider.
1995	Medicine Shoppe International, the country's largest franchiser of retail pharmacies, is acquired—Cardinal Health's first non-distribution acquisition.
1996	Pyxis Corporation is acquired. PCI Services, Inc. joins Cardinal Health. PCI operates in the United States, Puerto Rico, United Kingdom and Germany. CORD Logistics, Inc. is formed to offer drug manufacturers warehousing, information systems, customer service and financial support systems.
1997	Cardinal Health acquires Owen Healthcare.
1998	R.P. Scherer Corporation is acquired. This marks Cardinal Health's first major venture into serving health care manufacturers. Cardinal MarketFORCE is formed to recruit skilled sales and marketing teams for drug manufacturers. MediQual is acquired and Cardinal Information Corporation (CIC) is established.
1999	Cardinal Health merges with Allegiance Corporation - a manufacturer and distributor of med-surg and laboratory products and services. The Enright Group, PHARMACISTS:prn and Automatic Liquid Packaging Inc. also join the Cardinal Health family of companies.
2000	Customers begin ordering on cardinal.com, the most extensive online catalog of health care products. Cardinal Health unveils plans for the Product Development Center, capable of delivering a drug from lab to commercialization. Cardinal Health forms Vistant Corporation to apply Pyxis' dispensing and logistic technologies beyond the health care market.
2001	Bindley Western Industries, a wholesale pharmaceutical distributor and provider of nuclear pharmacy services, merges with Cardinal Health. SP Pharmaceuticals joins the company.
2002	Cardinal Health acquires Magellan Laboratories Inc. (Raleigh), a leading full-service contract pharmaceutical development organization and Boron, LePore & Associates, Inc. a full-service provider of strategic medical education solutions.Today, Cardinal Health is the largest provider of health care products and services in the world. The company has 50,000 employees in 22 countries on five continents. Fortune magazine ranks Cardinal Health the 23rd largest corporation in America. Our worldwide brand is launched, uniting all employees under a single name - Cardinal Health.

A Yes, most of my career has been focused in marketing. In marketing, you learn to understand the needs and trends that affect your customers. Certainly, having worked on the customer side has given me additional insight into the industry, including how decisions are made by customers, how companies work to get things done, and how you can best work with customers to help them solve problems.

The other aspect of my industry experience is the relationships that I've developed over time, which as a supplier in the business-to-business world is a significant benefit.

Cardinal Health Background

Q Please describe the businesses of Cardinal Health.

A I would like to begin by describing a history of Cardinal Health, and then I will progress with a description of the different organizations within Cardinal Health.

Cardinal Health has been in business for 33 years, it's a young company, in fact the CEO, Bob Walter, is the founder of the company. For the first 10 years of its life, when it was a young fledgling company, Cardinal Health was focused on food distribution.

In 1982, Walter looked at the drug distribution industry and saw an opportunity to move into what was then a very fragmented industry with significant opportunity for efficiency and consolidation. From 1982 to 1993, Walter built a U.S. national distribution company, operating four Midwest distribution centers. By time the mid 1990s rolled around, the industry had consolidated to where there were essentially three major players – the same players who currently own 93% of the distribution business. These companies are Cardinal Health, McKesson, and AmerisourceBergen. The distribution business is a great business for Cardinal Health representing more than 40% of our operating earnings. More important, we have delivered tremendous cost savings to customers through our efficiency, while increasing service levels. Today we offer unprecedented access to pharmaceuticals, while lowering costs and ensuring the safety of the U.S. drug supply.

From 1993 to today, Cardinal Health diversified its healthcare offerings so drug distribution is just one of our businesses. In the 1993-1994 timeframe, the company looked at ways that it could add value to the two major components of their business in drug distribution. That is, we were buying products from pharmaceutical companies, and it was then distributing thousands of SKUs to tens of thousands of different points of patient care or patient purchase. Cardinal Health then looked at how they could provide services at the healthcare provider end.

As a result, we acquired several businesses including, for example, a business called Pyxis Corporation, which had a very innovative means of providing secure dispensing of pharmaceuticals within the hospital setting. You can think of it like an ATM machine, where the nurse would input their password or card swipe, which would allow them to access individual compartments that housed the patients' medicine. The medicine would then be given directly to the patients in

their hospital room. The machine would later be replenished from central pharmacy. Today, we own the dispensing business in the hospital with Pyxis.

Next, Cardinal Health acquired Owen Healthcare, which was a franchise pharmacy service for hospitals. Today, Owen is the largest of its kind in the hospital pharmacy business. Owen can be found in about 2000 hospitals and pharmacies that we manage in the U.S. In fact, we are one of the leading employers of pharmacists in the U.S., not only with Owen, but also with another business that we acquired called Medicine Shoppe™, which is a franchise retail pharmacy that is more like the neighborhood apothecary, as opposed to a drugstore chain.

In 1996, we made our first acquisition at the other end of the healthcare chain by acquiring PCI Services, Inc. (Packaging Coordinators Inc). PCI was the leading provider of contract packaging services for pharmaceuticals. PCI manufactures blister packs and bottles as well as printed components. When we acquired them, they had a fairly broad based business with a number of large pharmaceutical companies.

Then in 1998, we acquired R.P. Scherer Corporation, which was the company's largest acquisition to date, and its first acquisition that had a broad-based manufacturing platform with a number of plant operations around the world. R.P. Scherer was focused on soft gel encapsulation technology, which was a fairly proprietary form of manufacturing, very complex, very difficult, for hard to solubilize pharmaceuticals as well as health and nutritional products. Zydis, the fast disperse drug delivery technology from R.P. Scherer, was first used in Claritin ready tabs. This technology is used today in the manufacture of **Zyprexa** one of the fastest-growing schizophrenia drugs.

Following R.P Scherer, in 1999, we made the acquisition of Automatic Liquid Packaging Inc., which is the leading provider of what is called the 'blow-fill-seal' technology. This gave us our first platform in sterile manufacturing.

At around the same time that Cardinal Health acquired Automatic Liquid Packaging and R.P. Scherer, it also acquired Allegiance, the leading manufacturer and distributor of medical surgical instruments to the hospital and acute care centers.

So combined with our pharmaceutical distribution business, we had quite a presence between both Allegiance and Pyxis at the hospital. Cardinal Health created four operating segments that are publicly reported: Pharmaceutical Distribution, Medical Products and Services, Automation and Information Services, and Pharmaceutical Technologies and Services, which is the business I formerly represented. The company's four platforms cover most of the entire healthcare chain. With each of the acquisitions, our strategy was to acquire businesses that were leaders in their field. In fact, everything that we've acquired was sought after for being best-in-class, and for being a leader in their field, whether it was medical surgical instruments, soft gelatin capsules, or packaging. *Our strategy was to become a broad based healthcare service provider. It also was important to us to retain the management as part of Cardinal Health, and that has been key to our success in these acquisitions.* As you can see, our strategy was to acquire and build scale in our specialties. We are not in this business for a hobby. We have global capabilities with incredible flexibility that enables us to deal with a wide range of customers at any given point in time.

We supply the most broad-based healthcare provider services to the industry. Our leadership position, scale, and breadth enable us to work with customers in many different ways that creates value for our customers. These are the principles behind our acquisition strategy in our past and now.

Q What are the businesses under Life Sciences Products and Services?

A The Life Sciences Products and Services Group provides services for difficult to manufacture products or specialty products that require proprietary or unique expertise. That is why our attention has been on soft gelatin technology; fast disperse freeze dried technology of **Zydis** the sustained release technologies for oral dosage forms, and blow-fill-seal, a more complex technology than conventional pharmaceutical manufacturing.

Of course, we also have incorporated other technologies into our portfolio such as lyophilization, which is for parenteral or sterile dosage forms of biotech products. This is a huge growth area today in biologics. *We have focused on difficult – to- manufacture specialty dosage forms for which our customers would find either impractical or inefficient to build the scale internally, and where if they could rely on someone with a high level of competency, financial resources, and partnership capabilities on the outside, would make far more financial and business sense for them to use our capabilities than to build the capability internally.*

I mentioned previously, that we acquired PCI Services, R.P. Scherer and Automatic Liquid Packaging. We also acquired SP Pharmaceuticals for its sterile manufacturing platform, or sterile lyophilization, then made a subsequent investment in Raleigh, North Carolina for additional capacity for the growing lyophization field. As we added capabilities at Cardinal Health, another important part to our strategy was not just to increase our commercial manufacturing capability, but to build complementary capabilities further upstream in the pharmaceutical development area. This way, early on, when people are working with their drug to try to put it in the best dosage form, we could help them with the dosage form. This allows us to create relationships as far upstream as possible. We decided that for some companies, it was important to have development capability further upstream to support their R&D work, especially on dosage forms where they may have less experience. This also allows us to be able to work with them downstream when they are looking for commercial manufacturing. As a result, in the oral dosage area, we needed to create capabilities that would be on the scale and execution of what a big pharmaceutical company would be used to.

In order to provide this kind of upstream support, we built a development center in New Jersey capable of oral dosage forms in Phase I, Phase II, and Phase III clinical manufacturing as well as formulation support. Similarly in San Diego, we

Cardinal Health Acquisition History as of 04/15/2004

www.cardinal.com

Acquisition Date	Company Name	Operating Segment
05/12/80	The Bailey Drug Company	Rx Distribution
09/14/84	Ellicott Drug Company	Rx Distribution
01/20/86	John L. Thompson Sons & Company	Rx Distribution
04/30/86	James W. Daly, Inc.	Rx Distribution
01/20/88	Marmac Distributors, Inc.	Rx Distribution
06/18/90	Ohio Valley-Clarksburg, Inc.	Rx Distribution
10/15/91	Chapman Drug Company	Rx Distribution
04/01/92	Medical Strategies, Inc.	Rx Distribution
05/04/93	Solomons Company	Rx Distribution
12/17/93	PRN Services, Inc.	Rx Distribution
02/07/94	Whitmire Distribution Corp.	Rx Distribution
07/01/94	Humiston-Keeling, Inc.	Rx Distribution
07/18/94	Behrens Inc.	Rx Distribution
11/13/95	Medicine Shoppe International, Inc.	Rx Distribution
05/07/96	Pyxis Corporation	Automation
10/11/96	PCI Services, Inc.	PTS
03/18/97	Owen Healthcare, Inc.	Rx Distribution
02/18/98	MediQual Systems, Inc.	Automation
05/15/98	Comprehensive Reimbursement Consultants, Inc.	PTS
08/07/98	R.P. Scherer Corporation	PTS
02/03/99	Allegiance Corporation	Medical-Surgical
04/01/99	Surgical Instrument Repair Services, Inc.	Medical-Surgical
05/20/99	PHARMACISTS: prn, Inc.	Rx Distribution
05/21/99	Pacific Surgical Innovations, Inc.	Medical-Surgical
06/04/99	The Enright Group, Inc.	Medical-Surgical
06/25/99	Pharmaceutical Packaging Specialties, Inc.	PTS
06/30/99	AutoValet Systems Intl - Product line purchase	Automation
07/12/99	MedSurg Industries, Inc.	Medical-Surgical
08/25/99	Herd Mundy Richardson Holdings Limited	PTS
09/10/99	Automatic Liquid Packaging, Inc.	PTS
11/18/99	Trimaras Printing Company, Inc.	PTS
12/30/99	HelpMate Robotics, Inc.	Automation
01/21/00	Contract Health Professionals and Pharmacists - Ance, Inc.	Rx Distribution
07/19/00	Rexam Cartons, Inc.	PTS
07/26/00	Dermatology division from Advanced Polymer Systerms, Inc. (Enhanced Derm Technologies, Inc)	PTS
08/16/00	Bergen Brunswig Medical Corporation	Medical-Surgical
09/01/00	ENDOlap, Inc.	Medical-Surgical
11/01/00	Ni-Med kit manufacturing (from Oak Medical Industries LLC)	Medical-Surgical
11/01/00	CurranCare, LLC	Medical-Surgical
12/15/00	Manufacturing Facility in Humacao, Puerto Rico from from Alcon (Puerto Rico), Inc.	PTS
12/22/00	VegiCaps Division from American Home Products Corporation	PTS
01/02/01	International Processing Corporation	PTS
02/14/01	Bindley Western Industries, Inc.	Rx Distribution
02/26/01	Astra-Zeneca Plant in Corby, UK	PTS
03/16/01	Critical Care Concepts	Medical-Surgical
03/23/01	American Threshold	Medical-Surgical
03/28/01	FutureCare	Medical-Surgical
06/29/01	SP Pharmaceuticals, LLC.	PTS
10/23/01	Purchase of Manufacturing facilityin Raleigh, NC from Schering-Plough animal Health Corporation.	PTS
11/15/01	Professional Health-Care Resources, Inc.	Medical-Surgical
01/07/02	Eon Media, Inc.	Automation
04/15/02	Magellan Laboratories, Inc.	PTS
06/26/02	Boron, LePore & Associates, Inc.	PTS
08/15/02	Atlantes Services	Automation
11/05/02	KVM Technologies	Automation
01/01/03	Syncor International Corporation	PTS
10/01/03	Gala Biotech	PTS
10/29/03	The Intercare Group	PTS
12/02/03	Medicap Pharmaces	Rx Distribution

have a facility capable of manufacturing sterile or parenteral dosage forms in support of Phase I, Phase II, and Phase III trials- so these facilities serve as places where pharmaceutical manufacturers or biotech firms can go at the early stage of development, and also for the commercial scale.

In addition to these facilities, we have a pharmaceutical development operation in Raleigh, North Carolina, which came to us from the acquisition of Magellan in 2002. Magellan was a private company that had built a great business in analytical and formulation chemistry. We acquired them to provide us with additional expertise in contract product development services, so that we could harmonize our SOPs across all of our pharmaceutical development operations including Somerset, New Jersey, San Diego, California and Raleigh, North Carolina.

The most recent acquisition that we've made, which was a couple of months ago, was a company in Europe called The Intercare Group. They are a miniature version of Cardinal Health with a distribution business in the United Kingdom. They own a fairly large brand called Martindale, which is their own brand of hospital-based sterile generic products. They also have a contract manufacturing division, which represents a significant part of their future growth for sterile manufacturing supporting biotech products in Europe. Our driving reason for this acquisition was for the contract manufacturing platform, but in addition, we were obviously attracted to the generic hospital market as well as the Martindale brand.

This last acquisition gives us a broader scale and enables us to support global pharmaceutical customers who want European capability.

Q How does your Nuclear Pharmacy Services business fit with the company strategy?

A On the surface you might say, what does Nuclear Pharmacy Services have to do with a pharmaceutical company or biotech company? Isn't the Nuclear Pharmacy Services business geared to a hospital? The service they provide and the biggest business is around cardiac imaging agents, where the pharmaceutical product is shipped directly to the hospital pharmacy which formulates on demand for the hospital. They are compounded at the hospital pharmacy because the imaging agent has to be delivered in a matter of hours to be used by the radiologist. The customer in this case is Bristol-Myers Squibb or Amersham, who we support, but of course the customer is also the hospital in the clinical setting where we are delivering the end product. This is a form of customized pharmaceutical medicine, which if you look forward, the newer medicines particularly oncology drugs have to be compounded at a nuclear pharmacy before being administered to the patient. For example, Biogen Idec's ZEVALIN, Coulter's Bexxar – these are oncology drugs that use a nuclear pharmaceutical capability to essentially enhance these cancer drugs.

As more oncology drugs use nuclear medicine as a means of enhancing the drug, it allows these nuclear pharmacies to deliver a more valuable service directly to the customer. For

ZEVALIN, the material is delivered to our nuclear pharmacy, and then the drug is compounded into its final form where it is then administered to the patient. Likewise for Coulter's Bexxar. The nuclear pharmacy has value in situations where medicines need to be to be customized at the patient level before administering and/or has characteristics which require unique logistics. For example, if the half-life of the product is incredibly short, which is the case with the products just described, a nuclear pharmacy is valuable because it has the ability to do the final formulation work and it has the logistics to support delivery to thousands of locations or points of care in a matter of hours.

Q Describe the growth within Cardinal Health's Life Sciences business.

A The Life Sciences and Products segment represents 20% of Cardinal Health's earnings, $3 billion revenue, and supports about 20 to 25 pharmaceutical products at the manufacturing pricing level. We have about 40 plant operations around the world today, 25 of them are FDA approved facilities, and a larger number than that are approved by the local authorities in their specific locations.

We've created the broadest offering in the marketplace for these kinds of services to pharma and biotech people. We see the company's growth in a couple of ways. Big pharma companies are going through a large transformation in how they do business particularly in terms of productivity - gaining more productivity in product development and also looking at ways at managing costs differently, particularly with price pressures. The other growth driver focus is biotech companies. There is no shortage of biotech companies, nor will there be. There are a growing number of products in the biotech pipeline. And many of these companies are wisely choosing not to invest in infrastructure that is unrelated to drug development, because if they can go out and find a partner like ourselves to develop, manufacture, and distribute the products, they can keep their precious dollars focused on getting the drug approved. We can support them from end to end.

Q What do you see as the opportunities for Cardinal Health in contract manufacturing?

A Within Cardinal Health, we operate in neat operating groups, *we see the greatest opportunity for the company in continuing to integrate the capabilities we have across all of Cardinal Health. The power of that integration becomes very evident the more we focus around the different business segments that are in the market place and the kind of needs they have.*

For example, our nuclear pharmacy business can work with the product of a big pharmaceutical company or a biotech company that requires work at the nuclear pharmacy to add a nuclear isotope to make it a better drug and then use us for the logistics to get it to the hospital. At the hospital level, our presence in having a strong hospital franchise through our medical products and services group and our distribution group can have large benefits to our nuclear pharmacy services group in terms of influencing market share for products that are made in our nuclear pharmacy services business.

If you look at the oncology segment, we can work on oncology products as a pharmaceutical development company or we can help manufacture them, but we also can help distribute these products to the oncologist's office, which is something that occurs on the other "side" of Cardinal Health. The point is that when we take a look from the outside in, the real power of our organization in the future is in its ability to have multiple touch points in healthcare. That visibility allows us to identify the needs of individual segments like a biotech company, or a company focused on oncology products, or the ability to deliver in the hospital segment or the physician's office. These are ways we can create value - by combining different segments of Cardinal Health. That is really where we see some great opportunities for us going forward. These opportunities are significant for us because we are a young company. With everything that is happening in healthcare today, there is still a need for more efficiency and the need for more effectiveness. A company that has all these touch points in healthcare can do an awful lot to create value for people. We are very much focused on how we can integrate our company, work with customers at senior levels within organizations, with people who have a view of the entire spectrum of what they are trying to accomplish as a company, but we also recognize where we need to be successful is at the working level for each individual project, where you are only as good as what you've accomplished yesterday, so that's an important component too. Obviously we are looking to build on the strength we are starting to create by having all these touch points in a specialty where there is an insatiable demand for figuring out ways to be more efficient or to create better drugs.

Q Do you now, or will you in the future, develop, manufacture, and market your own products?

A No, by and large we are predominantly focused on enabling other people's pharmaceutical products.

Q Where are your development and manufacturing facilities located?

A Our facilities are located in 11 countries as follows:

- 28 medical/surgical manufacturing plants and 47 medical/surgical distribution centers
- 24 pharmaceutical distribution centers in the U.S.
- 38 pharmaceutical manufacturing, laboratory, and packaging facilities

Q What is driving expansion within the CMO or CPO business?

A The use of outsource providers are driven by different needs for big pharma and the biotech industry.

Big pharma is working to dramatically change their cost structure and focus on improving the productivity of their R&D pipeline. One of the ways they are looking to manage costs is by streamlining the supply chain, which up to now has been managed internally. They also are looking for support and services for difficult to manufacture products or for specialty manufacturing processes that require proprietary or unique expertise. As the pressure on healthcare costs accelerates, big pharma will look at outsource providers as strategic partners who can reliably deliver better service at reduced cost.

Because biotech companies are choosing not to invest in infrastructure unrelated to drug development, they are looking to outsource providers with expertise in manufacturing and support services. Bioprocesses typically include lyophilization and aseptic processing. Cardinal Health has expanded their sterile manufacturing capabilities in the U.S. and Europe, providing a platform and scale to support global pharmaceutical customers. The logistics of producing targeted drugs and delivering to the clinic, hospital, or patient bedside also creates a distribution opportunity for an outsource provider who has these services.

Q What are the biggest risks in contract manufacturing?

A A general risk we might face is one where an investment is required on our part. We then must understand what the return on that investment will be. This requires us to be closer to the client or the market to understand the products we work on, to understand the market place, and to understand the regulatory issues. Obviously, we have to manage this much like a portfolio; we don't want 100% of what we do to be high risk business because there is tremendous economic return in just the fee for service business, which has far less risk.

Q What is the main concern your clients have in using contract manufacturers?

A I think most people would like to say it is cost, but by far the most important concern is quality and reliability. *The demand for quality from industry, from customers, and from regulatory authorities has increased substantially. Not only is it incredibly important to be a compliant manufacturer/provider, you must be a highly reliable one; you do what you say and you deliver what you promise.* Cost comes after this.

Q How do you address the variations in product packaging, formulation, or manufacturing processes with multiple clients?

A In contrast to captive manufacturing facilities, our operations are designed to be highly flexible. We have made a huge investment in scale to have that flexibility. We spend a lot of time optimizing the utilization of our assets. This means we focus a great deal on changeover time and how to reduce the time it takes for changes. We focus on cleaning validation and how to do that efficiently.

Q What current or pending regulations will have the biggest effect on the contract manufacturing business?

A I think the biggest focus today is the systems based regulatory approach the FDA adopted not long ago. Previously, they had a specific product focus, now they are focused on the integrity of the key systems within the plant. For a contract manufacturer the size of Cardinal Health, we have to have consistency in our practices across a wide range of plants. This is both for the benefit of the authorities and for our customers. From a contract manufacturer's point of view, we can't afford any mistakes because our livelihood is built around being able to persuade our customers that they can rely on us without supply interruption. If you get into trouble, you disappoint the FDA, yourself, the client, and the patient. It can taint your reputation, which can impact your business. For us, regulatory has to be a core competency.

The focus on perfect quality is going to continue to accelerate, requiring improved manufacturing systems and processes. The challenge will be the implementation of improvements without regulatory obstruction.

Q How will Medicare reform and cost containment measures imposed by governments and private insurers around the world affect the CMO business?

A If there is going to be an effect, it will be a positive one. Medicare reform will to some degree increase pharmaceutical consumption, resulting in increased manufacturing and distribution. So I think greater access is good for everybody, including the patient.

Cost containment measures are going to increase the focus on how to get more efficiency out of the supply chain. This may mean that industry will look to outsource even more so that they can reduce their own cost and the infrastructure dedicated to manufacturing and increase their investments in drug development or sales and marketing. I don't believe we have seen the full brunt of this effect in industry, but the trend is there.

Q How is Cardinal Health addressing the security issues of product distribution?

A Cardinal Health has done a considerable amount to protect the integrity of the supply chain. The big trend now underway is Just-In-Time (JIT) manufacturing for pharmaceutical products. In the past, pharmaceutical manufacturers have encouraged a buy and hold mentality, which has resulted in a large amount of inventory in the supply chain. This has created a large secondary market for arbitrage, selling drugs to smaller organizations whose sole purpose is to resell the drug at a profit. As the industry moves to JIT manufacturing, the inventory in the supply chain will be reduced, minimizing the opportunity for illegal diversion of products.

This case study presents the issues addressed when designing and constructing a pharmaceutical production facility in Eastern Europe.

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Developing a New Pharmaceutical Facility in Eastern Europe

by Prakash Davda

Introduction

This article presents a case study of the issues to be addressed when designing and constructing a new pharmaceutical production facility in Eastern Europe. Solutions to the expected difficulties were developed which overcame the differences between Eastern and Western European methods and standards. This applied particularly to cGMP, regulatory issues, construction time, cost, quality, available materials, codes, culture, contractual ethos, and language.

The Brief

The requirement was to design and build a new tablet production plant on an existing pharmaceutical site in Bulgaria to produce approximately three billion tablets per year for large volume generic formulations of plain or coated types with possible addition of hard gelatine capsules and effervescent tablets at a later date.

Key criteria were to:

- have the facility in production as soon as practically possible
- create flexible space with a capability for expansion
- provide cost effective construction with low maintenance and energy costs
- provide an efficient and pleasant professional working environment
- provide visible confirmation of the operating company's commitment to activities in Bulgaria
- comply with cGMPs binding on Bulgarian pharmaceutical manufacturers from April 2003 and subsequent MCA requirements
- ensure all local authority requirements with respect to planning, en-

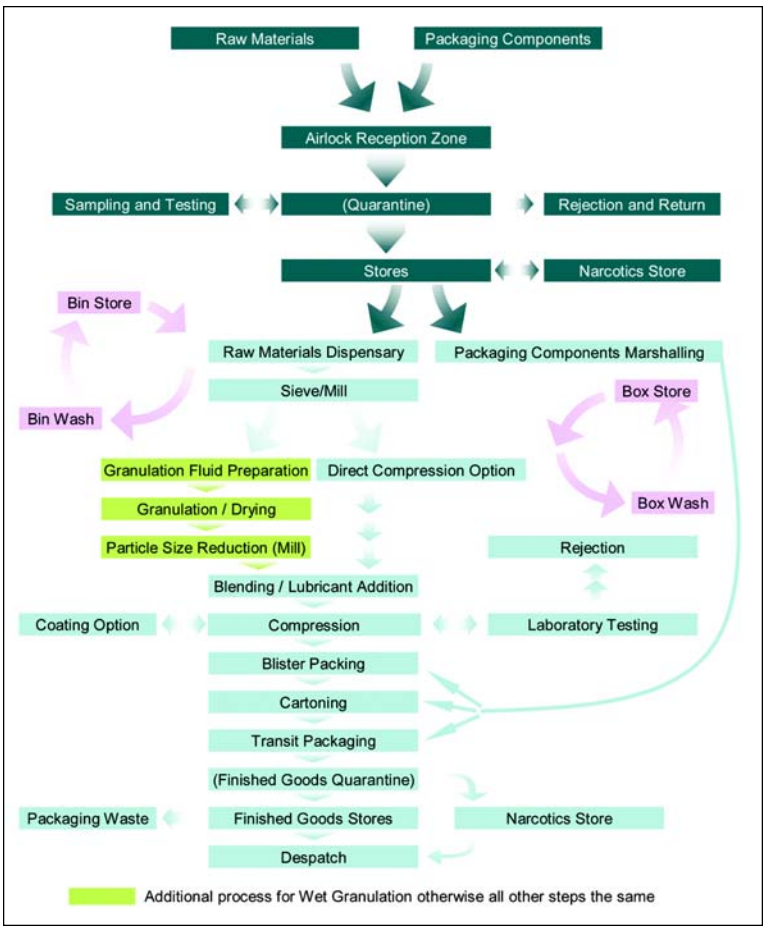

Figure 1. Production of coated or non coated tablets by direct compression and wet granulation.

vironment, approvals, health and safety, etc. are understood and aim to comply

The Strategy

Owing to their limited in-house resource, the operating company (based in Iceland) chose to employ an international company, specializing in pharmaceuticals (based in London), which could both design and support the construction of the project. Expertise in pharmaceutical projects was the key ingredient and the single source would ease and minimize lines of communication and reduce the possible conflicts of split responsibilities.

It was agreed that the management language would be English, and that at site level, the language would, of necessity, be Bulgarian.

The concept proposals, preliminary drawings, and specifications would be designed to meet UK standards and would be in English. The detailed engineering drawings also would be produced as for the UK, but a Bulgarian consultant would modify them to meet local requirements.

Similarly, to gain the operating company's board approval and to move the project ahead quickly, cost and time targets were to be set as though it were a UK project, but it was acknowledged that Bulgarian costs may be less and the time requirement may be longer than in the UK. These targets would be adjusted when more information became available.

The implementation of the work was based around tendering 45 individual sub-contract packages to allow sequential progress and reduce the time period required for a single contractor tender. It also was considered that the risks involved in using one contractor would be mitigated.

The Concept

Optional design layouts were developed to produce combinations of possible process and packaging options for an initial output of two billion 500 mg tablets. Initially, products were

Figure 2. Concept layouts.

to be solvent based followed subsequently with aqueous based.

The variances developed were based on the following:

- Two billion 13 mm (500 mg) tablets by direct compression - uncoated
- Four billion 7-9 mm (250 mg) tablets by direct compression - uncoated
- 1.5 billion 10 mm (250mg) tablets by wet granulation
- One billion coated tablets
- 1.5 billion tablets in blister packs - minimum of 10 tablets per carton

The above figures were dependent on achieving good Overall Equipment Efficiencies (OEE) and this was difficult to determine in Bulgaria. In practice, during start-up, the learning curve involved would influence the OEE.

The capacity of the plant was to be doubled with the introduction of additional process equipment. However, it was initially based on two shifts: seven hour days x five days over 250 working days per year.

To develop the processes, generic production procedures as depicted in Figure 1 were used to establish the outline requirements.

An optimum layout as indicated in Figure 2 was agreed based on the operating and design company's experience of the needs in Iceland and the UK while ensuring full compliance to regulatory requirements. The Bulgarian operators and engineers agreed with the layout and flow arrangements. Nevertheless, based on their experiences in Eastern Europe, they believed the facility should be 20% larger than the planned 4,600 sq.m. (49,725 sq.ft.) solution. This was their view on most elements of the design – large 'built in' factors of safety.

The agreed scheme allowed for a sampling booth, two dispensing booths, two granulation and fluid bed dryer suites, blending, six tablet press suites, two coating suites, one capsule filling suite, automatic IBC wash station, four blister packaging, cartoning and over-wrapping suites, and generous work in progress areas with design for future expansion.

The Preliminary Design

To keep the project moving quickly, a decision was made to undertake preliminary engineering using UK design standards, but modified to take into account the known Bulgarian standards at that time.

A review was made of Bulgarian methods, capabilities, and their ability to meet known Western standards. Although masonry was the normal form of construction for the building envelope, steel and metal cladding were available at reasonable cost, although not commonly used. This was considered desirable for speed and flexibility for the future. Internal finishes were available to meet the required cGMPs. However, application techniques were yet to be explored.

Basic Bulgarian design codes were incorporated into the preliminary design, such as seismic codes, floor, roof and wind loadings, summer and winter dry and wet bulb conditions.

The concept design was developed using the information obtained, but maintaining the operational and cGMP features.

All production areas were designated to Class 100,000. However the design was to consider achieving Class 10,000 in the future without involving any major modification to the construction, fabric, or finishes.

Pressure regimes were established whereby movement of air through the various areas satisfied the requirements for containment of powders and elimination of risk of cross contamination. At the same time, all designated clean areas for dispensing, production, and packaging were maintained at positive pressure (10Pa) relative to external atmospheric pressure, thereby preventing ingress of unclean air from outside.

The possibility of manufacturing effervescent tablets meant certain production areas required a low humidity environment. This was achieved by incorporating regenerative chemical dehumidifiers on systems serving the specified areas.

The cleanroom pressures, temperatures, and humidities were designed to be monitored by a Validated Building Management System which would have the capacity to monitor and record all room data for a year's operation. The system was designed to provide a separate "back up" facility.

The central pure water system was designed to provide pure water to USP24 standard to serve clean-in-place systems, IBC automatic wash station, laboratories, and small parts wash areas.

To minimize operational cost of the air conditioning systems, the ratio of fresh air to re-circulated air was selected at 20% to 80%. To avoid any cross contamination with this high percentage of re-circulated air, filters were installed on the return air systems in addition to the main EU 11-HEPA filters on the supply systems.

Estimating the cost of the building, services, and process equipment was based on UK costs although it was recognized that the cost of the building should be less than the equivalent in the UK so a comfort factor was built in.

All new production and packaging equipment was sourced and costed from Western Europe suppliers.

Similarly, a design and construction program was produced as though the facility were to be designed and constructed in the UK, which would give a challenging target for Bulgarian sub-contractors.

Based on the 30 preliminary drawings, the cost plan and program produced, the board members of the operating company were able to confidently make an informed decision that the proposed solution would meet their business plan requirements for the Bulgarian facility.

Local Authority Requirements

In order for the UK staff to understand the local authority approval process, considerable time and effort was devoted to the subject as some of the materials, methods, and techniques used in Western Europe were not generally available in Eastern Europe. Importing material was not an easy option as it would take time for them to be accepted by local authorities. This caused several difficulties throughout the project, requiring very careful discussion and negotiations

with local and national authorities. Some examples are listed later in this article under Observations and Recommendations.

In Bulgaria, there are explicit approval stages known as Protocol 1 to 17. Each Protocol needs to be completed sequentially and the authorities will not accept parallel execution. Whereas in the UK, once planning permission is granted, construction work can progress awaiting building regulation approval - although at risk. In Bulgaria, one would be penalized with a fine if this process was followed. However, with some careful tactics and negotiations, the UK company was able to move quicker than the normal process.

The process is very complicated, and one should not rely purely on reading material.

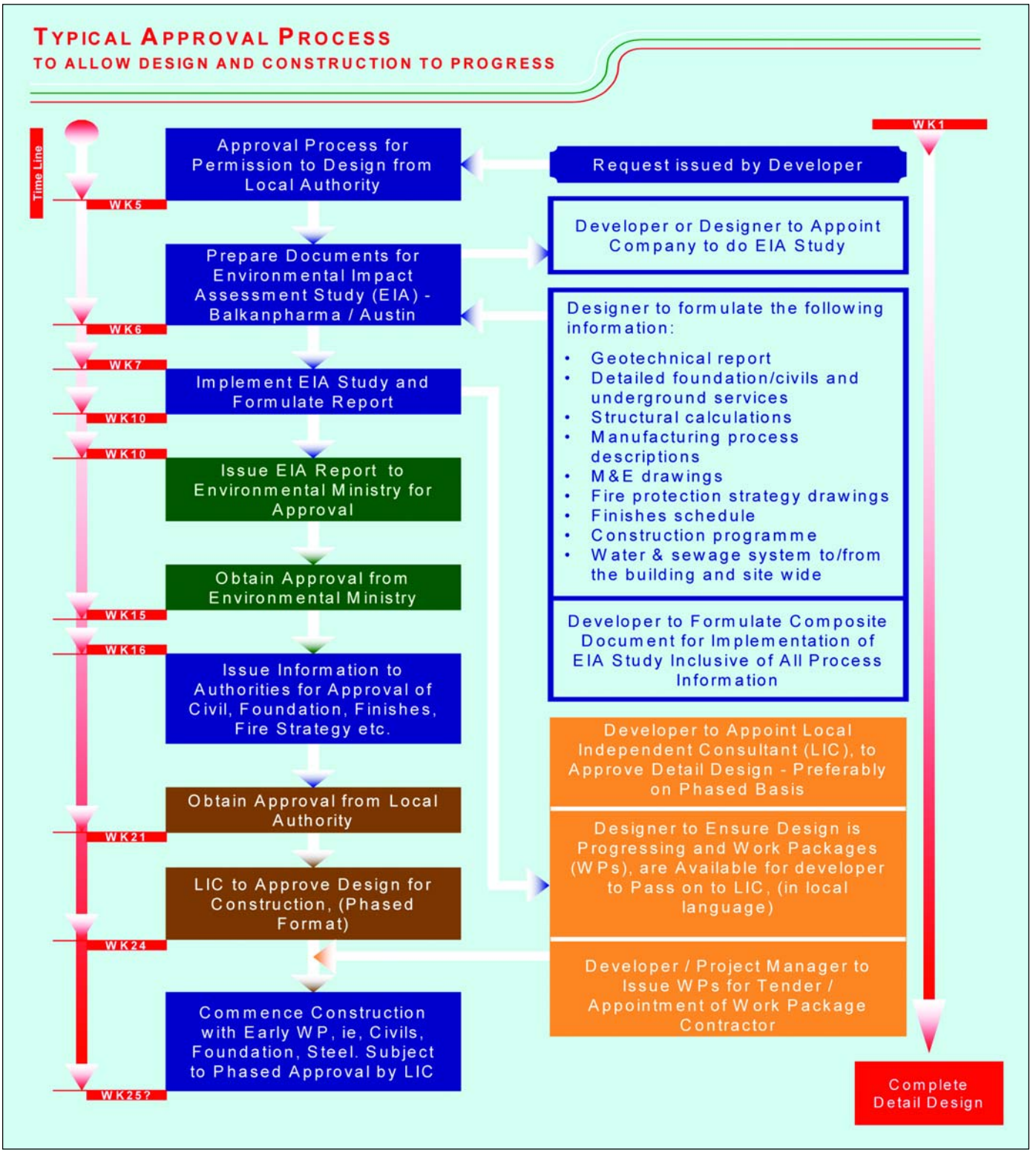

Figure 3. Typical approval process.

Before one considers all protocols in detail, Protocol 1 is the most significant - ***"Permission to Design"*** and ***"Permission to Build"*** is required from the local authority. This process is described in Figure 3 and is usually initiated by the developer.

Preconstruction Stage Approval Process

Once Protocol 1 has been obtained, which could take up to six months, the construction process begins. This is where the requirements must be understood in detail.

Scheduled below is each protocol with information needed. This has been extracted from their National Regulation No 7 -22.05.2001 - statements and protocols issued during the building period.

Protocol No 1 - the site is handed over and accepted by the Contractor and the design is approved for execution. Formal permission is granted from the Mayor's office issued by the Chief Architect.

Protocol No 2 - building site is allowed to formally open to allow building lines and levels to be agreed.

Protocol No 3 - the site book/diary certified from the National Building Supervision Directorate is issued for recording all future activities.

Protocol No 4 - formal hand over/acceptance of all technical documentation.

Protocol No 5 - statement for the building terrain certifying and complying with the detail drawings setting out base building coordinates.

Protocol No 6 - statement certifying soil category and actual excavating working levels.

Protocol No 7 - statement for acceptance of the actual building/assembling works by levels and details.

Protocol No 8 - statement for acceptance of the foundation works for construction.

Protocol No 9 - statement for acceptance of the shuttering, reinforcement and welded works.

Protocol No 10 - deviations from the design dimensions according to Regulation No 3 for the acceptance of the concrete works.

Protocol No 11 - statement for the acceptance and transfer of equipment.

Protocol No 12 - statement for determining the building condition in case of stopping.

Protocol No 13 - acceptance of the completed metal construction corrosion protection.

Protocol No 14 - determine status of all hidden works: concrete foundations, back fill, lintels, masonry, cavity insulation, heat insulation, vapor barriers, internal/external doors, windows, etc. Statement for the building construction acceptance.

Protocol No 15 - statement to confirm the building is ready to be accepted for use. This includes:

- completing 72 hours running test on all systems including mechanical, electrical, drainage, process and production equipment, lifts, etc. and certificate of conformance of any specialist material
- written permission to use imported materials not in accordance with relevant Bulgarian standards and protocol from the licensed Bulgarian laboratory for the imported materials approved by the Ministry of Building
- approved detail drawings and statement of compliance with the design parameters
- Results from 72 hours test on all services. Acceptance Certificate for completion of all works from the relevant authorities including the incoming services supply company, the Regional Inspectorate for Environment and Waters etc.
- statements of completion from the Main Contractor
- proof of ownership and permission to build on territory of someone else's property – if applicable
- environmental impact assessment
- card for assessment of influence on site environment in comparison with the original samples taken at the start
- certificate for achieving the set design parameters within the whole facility
- statement from Occupational Health and Safety Authorities allowing the building to go into operation
- statement from the Fire Fighting Emergency Regional Service
- document issued by the Cadastre Agency (Local County) for building survey, underground technical systems, and equipment survey in attendance with the Cadastre Agency

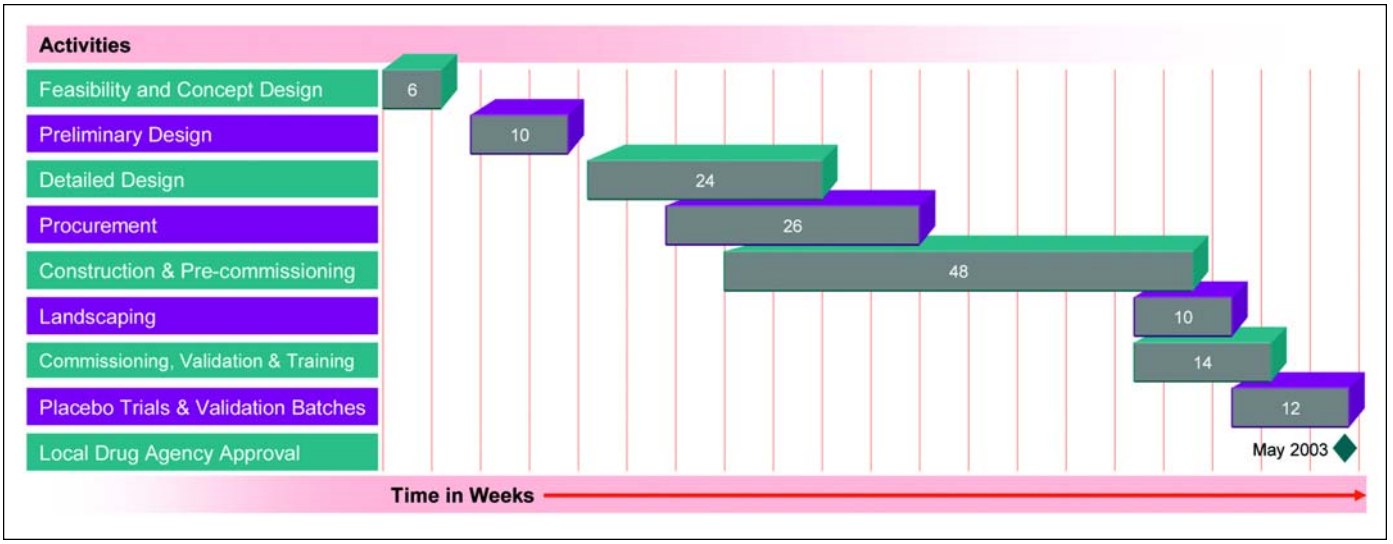

Figure 4. Time schedule for key activities.

- letter of appointment from the employer confirming the staff employed, inclusive of log for health and safety induction for all staff

- statement from the Chief Architect of the municipality for law conformity, validity of issued construction documents, and conformity of performance with the above documents, and for compliance with the requirements of Article 68, Article 178, Paragraph 3 of the Law of Territory Management

- statement from the designers confirming compliance of their respective design to the finished works

Protocol No 16 - (where applicable) Certificate for establishing the suitability of the building for use. This certificate is drawn up by the employees assigned by the chief of National Construction Control Directorate or authorized by him/her employee whose name is included in the Letter of Appointment for State Acceptance Commission in line with Ordinance No 6 of 2001 for issuing Permission to Use the Building in Republic of Bulgaria.

Protocol No 17 - (where applicable) Certificate of completing any non compliances/defects based on the decisions of State Acceptance Commission under Protocol 16.

The operating company's in-house engineering resources assisted with this complete process.

Detail Design and Construction

The detailed design drawings and specifications were produced in the UK with support from two Bulgarian architectural technicians to assist translation of codes into English.

The authorities stipulate that all designs by foreigners must be certified by local designers and a local independent supervisor must ensure correct implementation of work on site in compliance with local codes and maintain a fully itemized site diary of all events.

A local consultant in Bulgaria was employed through the detail design process to assist in converting the necessary information into Bulgarian for local authority approvals, and assist with interpretation where necessary to ensure the designs met with the local codes and standards.

The operating company and UK design company agreed that no compromises should be made on material and equipment selection, and that they would be in line with what would be used in Western Europe. However, the operating company requested that every effort must be made to source as much material locally as possible.

The complete project was overseen by the UK company's project manager on a visiting basis throughout the detail design, procurement, construction, commissioning, and validation with a "very hands on" approach with the operating company's project manager supervising the 'day to day' issues on site.

The detail design was prepared in 45 packages to allow early start on site and provide better control of subcontractors although this caused difficulties with local authority approvals. However, the situation was managed.

To assist the project with professional procurement services, a quantity surveyor was needed. In Bulgaria, quantity surveying is not a recognized profession. However, an expatriate quantity surveyor was sourced and hired to assist with the procurement, cost reporting, and administer the tender process.

Each work package was tendered individually. The companies were selected by placing several advertisements in local and national newspapers inviting them to formally show their interest. Short lists of six companies were selected for each package by interviewing up to eight companies. The selection criteria included review of their past experience, management capability, engineering and technical expertise, labor skills, resources availability, responsiveness, ability to work with English drawings and specifications, quality of past work and documentation, demonstration of team working, financial status, cost etc.

The final selection was undertaken by the operating company with assistance from the UK company's project manager.

Each sub-contract package was managed in the same manner as in the UK. The process for tendering, procurement, cost control and monitoring, valuations etc. was accomplished using the UK company's standard procedures extending to changes, variations, and settlement of final account with each individual contractor.

An expatriate construction manager and a building services engineer were assigned full time on site to assist the progress and coordination of the work to the proper quality standards and program. In addition, each discipline designer from the UK attended the site regularly to assist with monitoring quality, coordination, checking specifications of installation, providing training where necessary on construction methods to be employed, and liaising with authorities when allowed.

It was found that the Bulgarian operatives can produce good quality work if properly supervised, but productivity was low. This was overcome by increasing the labor force and maintaining a high level of management on site. Toward the end of the construction period, a few key tradesmen, in particular electricians, ductwork, and pipe work installers, were sent from the UK to protect the program.

Installation work of mechanical, electrical, and process works was organized by the UK company with final commissioning of the mechanical systems being undertaken by a UK company, overseen by a local commissioning company because commissioning engineers must be certified by the local authorities.

The UK company was involved in the validation process from the onset by assisting with writing the User Requirement Specification, Validation Master Plan, chairing Design Qualification reviews, and preparing all Installation and Operational Qualification - Validation Protocols. The on-site activities were supported by the operating company's personnel to ensure cGMP compliance in association with their quality department.

The operating company's Quality Department was involved in the complete process from the start as this was their first facility that would go through the full validation process. This proved to be vital training for them. Although they had good theoretical knowledge of the requirements, they appeared to lack experience in the actual process.

On completion of the facility, the UK company supported the operating company in planning all key activities required in attaining a functional facility including local drug agency approval, management of training, placebo and validation batches, variation licenses, and planning for a MCA inspection.

Observations and Recommendations

1. There are excellent engineering skills in Eastern Europe, but their normal design standards are generally quite conservative. Western European skills can bring more finesse and higher technical inputs to the design

Figure 5. Granulation and fluid dryer suite.

2. It is important that good relationships are developed with the relevant authorities and encouragement of their input will strengthen the project team.

3. The approval process is complicated and extensive. Any one considering a project in Eastern Europe must understand the requirements for each stage.

4. Language can cause misunderstandings. Therefore, it is important that the team is appropriately strengthened with bilingual personnel.

5. Prepare well defined engineering drawings and specifications. Do not leave anything to interpretation.

6. The need for a good strong project and construction manager is a key requisite and everything must be closely followed – checked and double checked. Do not leave anything to chance.

7. Productivity is lower in Eastern Europe, but this can be overcome by increasing the number of operatives. Strong supervision on site is essential.

8. The professional team must be open minded and proactive to deal with issues and perceived barriers as they arise and not get frustrated. Local companies have a set way of working in their country which has not been challenged by western society in the past.

9. Some locals were initially apprehensive about working with western organizations, and particularly about being supervised by UK employees. However, experience demonstrated that with a careful tactical approach and sensi-

Figure 6. Completed facility.

tivity about remuneration differentials, this could be overcome.

10. Daily and weekly monitoring of short and long term program was a mandatory task as reliance could not be placed purely on reported progress by contractors.

11. Working to a budget, program and ensuring quality was a new concept for the locals and required constant reminding from the management team.

12. Local materials are worth investigating if time is available as they are cost effective. However, quality is questionable.

13. The site was purported to be a clear brown field site, yet more than 100 hundred barrels of contaminated waste and a nuclear fall out shelter were found in the ground. These were not identified in the topographic and geotechnical investigations by local companies.

14. The Fire Authority would not accept boarded structural columns to obtain the fire resistance. Hence, they had to be concrete encased. In some areas, solutions offered for fire protection were not acceptable. However, after considerable negotiations and justification, some were finally accepted.

15. The local consultant let the process down in some aspects of approvals due to their lack of experience and knowledge of their own regulations.

16. The water supply quality was found to be inconsistent and unreliable. Therefore, a 50 micron "back wash" prefilter was installed, although original samples did not highlight any issues.

17. The actual management of quality on site was a major issue. The following are simple examples of this:

    (a) Two courses of blue bricks were specified; these were not available in the format required with the setting out of the building and in the finish required. They were subsequently ordered from the UK to avoid delays to the project. On arrival, it was found the contractors had limited brick laying skill.

    (b) Blocks for walls are of different construction and sizes; fair-face block work was not an option because the mortar joint detail could not be achieved to the quality required. Hence walls had to be rendered. This had considerable impact on the setting out.

    (c) Concrete mixing plant was not efficient and the floor slabs had to be laid in several small sections and took considerable amount of coordination, engineering, and time.

    (d) The steel work grade specified was European. However, the contractor did not order the specified quality and quantity. This caused some delay.

    (e) Items such as safety wear, door seals, and ceiling clips were all difficult to obtain locally.

    (f) The contractors were not used to complying exactly with specifications, e.g., all external doors had to be changed twice as they were delivered to the wrong specification and color. All ceiling tiles had to be replaced for the same reason.

    (g) Local pipe/ductwork fabrication and quality of material inclusive of insulation appeared dubious. The quality of installation was also not to a good standard.

    (h) The wall finishes took more than four attempts to get to an acceptable level of quality.

    (i) All antistatic floors had to be re-laid by using a British contractor as the specification could not be achieved.

    (j) The welding on the medium temperature hot water and chilled water pipe work was poor such that a high level of resistance was encountered on the system and the pumps had to be increased in duties to avoid delay to the program.

Results

Despite the inherent difficulties of designing and constructing a facility of this type in Eastern Europe, with a positive

attitude by the team, the problems were overcome to produce an excellent facility.

Speed was a key factor and the critical time schedules met are seen in Figure 4. The overall budget cost was not exceeded. Savings were made on local contracts such as ground works, civils, steelwork, cladding, and finishes. There was an overspending on process equipment such as granulation, tablet machines, blender, blister lines, pure water plant etc. Site supervision was overspent, primarily because of the extensive checks required.

The overall cost of completion was 7.5% below the agreed budget, i.e., just more than $1 million under the $15 million budget. This was achieved by preparing good quality engineering documentation for tendering, pre-selection of companies to be invited to tender, post tender interviews to ensure compliance – technically, financially, and availability of resources; good negotiating and buying skills on the packages and a pro-active client to allow the UK company to effectively design and assist them in management of the project, yet making themselves available to respond efficiently and make decisions when required.

The quality goals were in most cases accomplished and have met cGMP standards.

However, anyone considering a similar project in the future must employ more on-site dedicated supervisors to monitor day to day installation and material quality.

The granulation/fluid bed dryer suite and external view of the facility are shown in Figures 5 and 6 respectively to demonstrate the quality achieved.

The facility has obtained its operating license from the Bulgarian Drug Agency and is in the process of being prepared for an MCA inspection for products made for the European market.

Safety standards imposed on site were in accordance with UK's Construction Design and Management regulations. These were stipulated as part of the appointment of contractors. In reality, they were difficult to impose as the correct form of Personal Protective Equipment was not readily available and there was no motivation by subcontractors to obtain them. However, the safety record on site was better than the average UK site.

Highlights of the Project

- first cGMP compliant facility design in Bulgaria
- first facility to be inspected by the MCA in Bulgaria
- first substantial pharmaceutical project in Bulgaria over the last 12 to 15 years
- facility complete within 12 months from starting on site
- facility ready for manufacturing within six months of completion of construction
- first facility validated to EU standards in Bulgaria
- probably the best pharmaceutical facility in Bulgaria if not in Eastern Europe
- quality of the finished project was generally very good and comparable to the best in the UK
- completed project cost $1 million below the $15 budget
- several cultural problems overcome successfully
- several political problems with approvals addressed successfully
- facility - available for PQ/production 18 months from the first operation on site
- formal opening ceremony achieved 12 months from the first ground breaking
- benchmark set for future pharmaceutical facilities in Eastern Europe
- pro-activeness by the operating company gave the UK company better control and management of the overall project
- the operating company managed very professionally
- safety statistics on site better than a comparable project in UK

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About the Author

Prakash Davda is the Deputy Managing Director of The Austin Company of UK Limited based in London, UK. Davda has more than 20 years of experience in the design and construction of high tech facilities throughout the UK. Throughout the last 10 years, he has been heavily involved in project activities for laboratories, pilot plants, production units, and warehousing for the pharmaceutical industry within the UK. He held the post of Principle in Charge for the Bulgarian project and managed the design, construction, commissioning, validation, and start-up teams. Davda is a member of the Institute of Electrical Engineers, The Chartered Institution of Building Services Engineers, and obtained his Masters in economics and management from The Bartlett School of Graduate (University College London) in 1995. He can be contacted by tel: +44-208-371-9000 or by email: prakash.davda@austin.co.uk.

The Austin Company of UK Limited, 35 Ballards Lane, Finchley, London, N3 1XW, United Kingdom.

This article explores current trends in process piping technology including orbital welding SOPs, fabrication techniques, weld documentation, and passivation of stainless steel tubing systems.

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Installation of Pharmaceutical Process Piping - A Case Study

Part 2 - Orbital Welding, Weld Inspection, Weld Documentation, Passivation

by Barbara K. Henon, PhD, Stephan E. Muehlberger, and Gene DePierro

Installation

During the installation of process piping systems, it is critical for orbital welding personnel to work closely with Quality Assurance inspectors. The inspectors must be on site at the time of welding and inspect the welds as they are completed. Otherwise, the system would be welded together and it would not be possible to reach all of the welds with the fiberscope for inspection.

Figure 4. Orbital field welding of clean steam line to supply panel with a weld head. Welding operator is wearing gloves in compliance with contractor's SOP. The I.D. purge to this weld was twice the usual rate to compensate for a branch in the piping system. Photo courtesy of Sicor Inc.

Welds on product contact surfaces must meet the visual weld criteria of the Materials Joining part of ASME BPE-2000 Standards figure MJ-1 shown in Figure 5. The ASME BPE visual criteria for orbital welds were developed to assure that welded joints do not provide a surface which would favor the growth of microorganisms that would contaminate the system. For example, an unpenetrated weld is a crevice where bacteria can grow and escape the cleaning process. ID concavity or misalignment of weld components could interfere with drainability and make cleaning problematic. Owners and contractors must decide prior to the job on an acceptance level for discoloration of orbital welds from the color chart shown in AWS D18.1/D18.2.[8] Discoloration of the weld and heat-affected zone from oxidation resulting from poor purging during the weld sequence would reduce the corrosion resistance of the system.[9] Any undetected weld failures that lead to system contamination would violate 21 CFR 211(a) and be very costly to correct.

When a certified welder begins work at the start of his shift he connects his orbital welding power supply to a dedicated circuit. He will determine the size of tubing and/or fittings or other components to be welded. The welder selects the appropriate weld head, installs the proper size tube clamp inserts (collets), and a tungsten electrode of

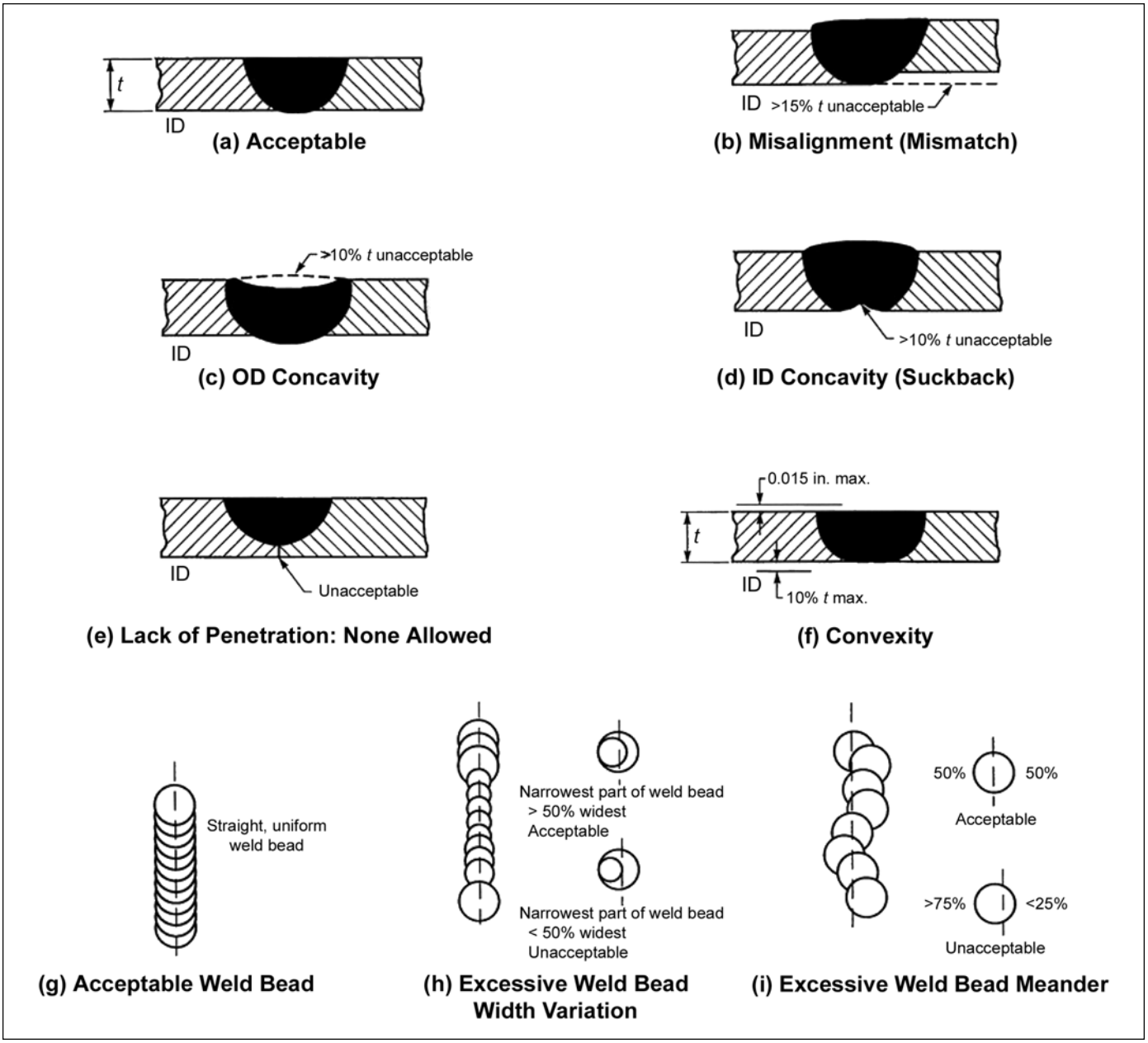

Figure 5. ASME BPE-2002 Figure MJ-1. Acceptance criteria for orbital tube welds. These visual weld criteria are intended to minimize the growth of microorganisms in biopharmaceutical tubing systems. *Reprinted with permission from the ASME.*

the correct length. He then calibrates the weld head for rotational speed to the power supply. A certified argon source is used for the weld head purge which protects the outside (OD) of the weld as well as for purging the ID of the part to be welded.

Opening Coupon

Before he can begin production welding, the welder must "coupon in" or perform a sample weld on the exact same material heat which is to be installed. Even with the restricted BPE sulfur range for 316L stainless steel, there is still some variability in weld penetration from heat-to-heat and schedules for different heats may vary by several amperes. A successful coupon demonstrates to the inspector that the machine is set up properly, the purge is adequate, and the welding operator knows how to operate the equipment.

The first coupon of the day is referred to as the "opening coupon" and welders refer to this as "burning a coupon." Coupon welds must be done on an actual weld joint, not just a "bead on pipe" (which is a weld made directly on a tube without a joint) to assure that the equipment and the operator can properly align the components. When the weld is completed, the welder brushes the outside (OD) with a stainless steel brush to remove weld oxidation, removes any burrs or sharp edges from the ends of the coupon, and gives it to the inspector. A flow chart showing the sequence of welding, weld inspection, and weld documentation is shown in Figure 6.

Coupon Log

Every coupon, good or bad, must be recorded in a coupon log. The weld is identified by the machine used, in this case labelled A or B, with a sample weld number, for example SWA 001, the date, and the welder's ID number. The time of day, date, and material heat number, argon certification, orbital weld head, and power supply serial numbers also are recorded, and the entry is initialled by the inspector. All of this is cross-referenced to the installing contractor's weld procedure documentation. Test coupons are performed routinely if there is a change in power source, a loss of power, a change in purge set-up, or a change of welding operator. Test welds also are performed 100% of the time after a weld has been rejected before proceeding with production welding.

Bench Welding

Once the coupon has been approved, the welder prepares for production welding. He decides whether he will be doing bench welds or field welds and connects the ID purge to the system or components to be welded. Bench welding is done in a protected area where spool pieces up to 20 feet long can be prefabricated prior to installation in the field. Spool pieces can include up to three bends totalling 180° or two bends of 90° each to allow for borescopic inspection. The BPE Standard requires 100% visual inspection of the outside of the weld and a minimum of 20% visual inspection of the inside or product contact side of the weld. The type of borescope used for weld inspection is flexible and more properly referred to as a fiberscope.

The installing contractor is responsible for knowing what length to cut tubing so that the finished spool piece will fit into the exact location in the field shown on the isometric (iso) drawing. The weld ends are cut and prepared in a square butt joint for welding. The components are held in a vise and a pipe stand to achieve the required slope of 0.6° according to the iso diagram. They are manually tack-welded together prior to welding. An ID purge must be used during tack-welding to prevent oxidation since an oxidized tack may prevent full joint penetration of the orbital weld. Unconsumed tack welds are a major source of weld rejection.

All of the welds in a spool piece may be performed before handing the assembly over to the inspector providing all of the welds are accessible to the fiberscope. Water-cooled weld heads used on this site permit high duty cycle welding and improved productivity. Welds were brushed on the OD prior to inspection. As an SOP, the ID purge remains connected to the spool piece until it is cool to the touch.

On a given spool piece, only one or two of the welds may be selected for inspection. On this job, 20% of the accessible welds had to be inspected, but in the process of getting the fiberscope to a particular weld, the QA inspector would see welds that were not scheduled for inspection. The weld inspectors estimated that they looked at about 90% of the welds although only 20% inspection was recorded. If the inspector saw a defect in a weld that was not listed for inspection, the defect would be reported and cut out. At that point, the inspection contractor would work with welding personnel to try to find the cause of the defect, eliminate the cause, and the welder would reweld the joint. All rewelded joints are borescope-inspected and the results indicated on the iso drawing as shown in Figure 7. In making rewelds, the welds must be kept far enough apart to avoid a second weld in the HAZ of the first since any detrimental changes to the metal from welding would be additive. A "pup piece" of the appropriate length may be used to keep the spool piece in conformance with the original dimensions.

Field Welding

Much of the field or "position" welding involves welding together the spool pieces or connecting spool pieces to longer piping runs. Purging is critical for all welds, but particularly for field welds since purge gas of the required purity must be present at the weld joint to avoid oxidation, while the ID purge pressure must be adequate to deliver the gas to the joint without creating excessive pressurization. Excessive pressure on the liquid weld pool results in ID concavity or can even blow out the weld. The flowrate required to achieve the correct ID pressure varies in the field with the tube diameter with the distance from the source and with any restrictions upstream. It also changes if the system has branches such as the weld on the steam line shown in Figure 4. In that case, the flow rate was doubled from what it would have been without a branch in the system. One of the branches was capped off while the other had a restrictor on the exit orifice to help in achieving the correct ID pressure. An oxygen meter was used to monitor the ID purge gas to determine when it was safe to weld.

Field welds must be planned for inspection. Some of the field welds in the mezzanine were inspected with the fiberscope from the floor below. The slope was checked for every change of direction. For this job, the required slope was 0.6° or 1% which is approximately 1/8 inch per foot. The amount of slope varies with the job and the length of the piping run, but the system must be drainable.

Weld numbers are assigned by QA and are recorded in the weld log, on the iso drawing, and etched on the pipe. The weld log and information on the pipe contain the same type of information as was recorded on the coupon log. All of the bench and field welds were recorded in the weld log whether or not they had been inspected. Only inspected welds are recorded in the borescope log.

Weld quality cannot be inspected into the system, but is only as good as the welding equipment, weld procedures (SOPs), materials and surface finish, gas quality, cutting, cleaning, fit-up, and operator experience allow. Third-party QA assures that the welding equipment is functioning properly and that the installing contractor follows his own SOPs. A quality standard such as BPE-2002 fosters understanding between the owner, the installing contractor, and the inspection contractor as to the quality level to be expected in a finished system. Orbital welding has made it possible to achieve high quality welds on a repeatable basis resulting in more cleanable piping systems. This is essential for the successful production of biopharmaceutical products.

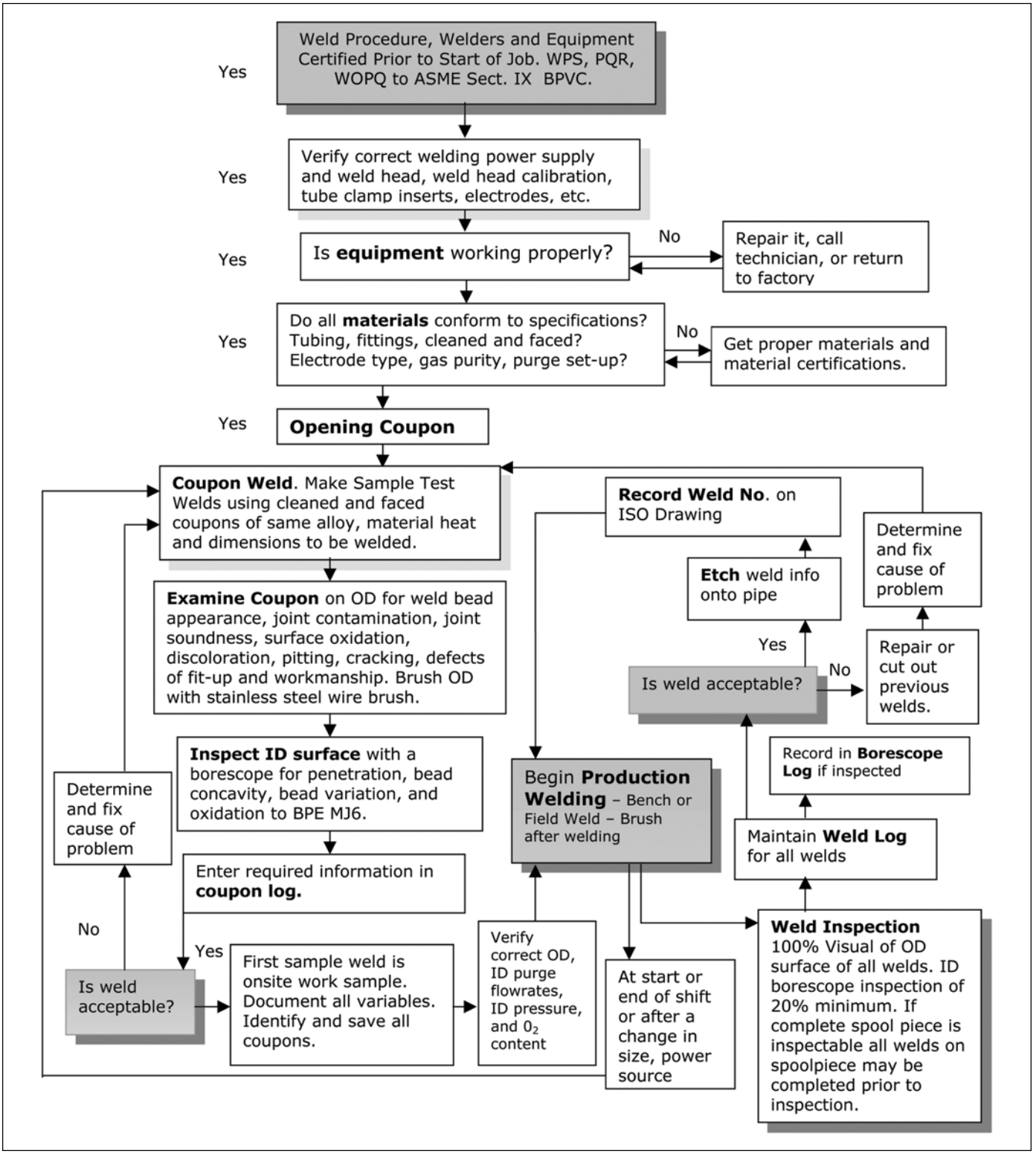

Figure 6. Flow chart for orbital welding/inspection/documentation of stainless steel welds.

Orbital Welding of Skids

Orbital welding is used extensively in the manufacture of equipment skids such as CIP skids or skids with stills for producing WFI. A considerable amount of stainless steel tubing is used to connect the various components on the skids. The skids are assembled by orbital welding at the vendor and brought to the pharmaceutical plant for installation. All of these welds and the field welds done when installing the skid on site must meet the same welding QA requirements. Welds done during skid manufacture are inspected at the vendor.

Isometric Drawings put on CAD

At the end of the job, all of the iso drawings are entered on a computer. Using "plant North," the separate iso drawings can be "clicked" together to combine them in a single document which is then stored on CD as a permanent record.

Pressure Testing

After installation and before passivation, the piping systems are pressure tested. The pressure testing operation is overseen by the Inspection Contractor. This consists of filling the piping system with clean air, nitrogen, or argon at 150% of the design pressure or 150 psi, whichever is greater, and then monitoring the pressure decay for four hours. If there is zero drop in pressure, the system passes. This must be done with a calibrated gauge with certifications.

Passivation

The annealing portion of the stainless steel production process results in a chromium oxide surface film that is enriched with chromium and reduced in iron when compared to the base metal. During the welding process, the passive or unreactive layer is disrupted so that in the weld and in the HAZ, the distribution of elements that comprise the surface may no longer be considered as being passive. During the welding process, the iron concentration at the surface of the weld becomes elevated while the amount of chromium is sharply reduced.[9] Unless a chemical passivation process is conducted before operating the system, the corrosion resistance of the system will be compromised and rouging will occur, especially at welded sites. The purpose of a chemical passivation is to remove free iron or other anodic contaminants from the surfaces of the stainless steel such that a more uniform formation of the passive surface is obtained.

Heat tint-containing oxides of both chromium and iron are formed on the stainless steel surface during welding and must be removed or prevented. Passivation cannot completely remove even relatively light heat tint because, while passivation affects only the outer 50 Å of surface, heat tint can extend to a depth of 400 Å or more.[10] Although the pitting potential of a weld with heat tint may be raised by passivation, suggesting that passivation restores the corrosion resistance lost by welding, when corrosion does occur on a heat-tinted passivated sample it is likely to occur preferentially in the HAZ.[10]

Mechanical grinding and pickling with a solution or paste containing a combination of nitric and hydrofluoric acid may be used to remove heat tint from the welds and HAZs. This treatment removes metal including the area beneath the heat tint which may be reduced in chromium.[11] This treatment, while effective in restoring corrosion resistance, roughens the stainless steel surface and is only suitable for use on surfaces that will be polished and passivated after treatment. Hand-held electrocleaning devices may accomplish the heat tint removal without roughening, but removes metal so dimensional tolerances may be compromised.

The most effective and practical way of retaining the corrosion resistance of a piping system during installation is to be very careful with the purging during the orbital welding operation so as to prevent the formation of visible heat tint to avoid contaminating the system especially with carbon steel tools or any other type of iron contamination, and then complete the process with chemical passivation.

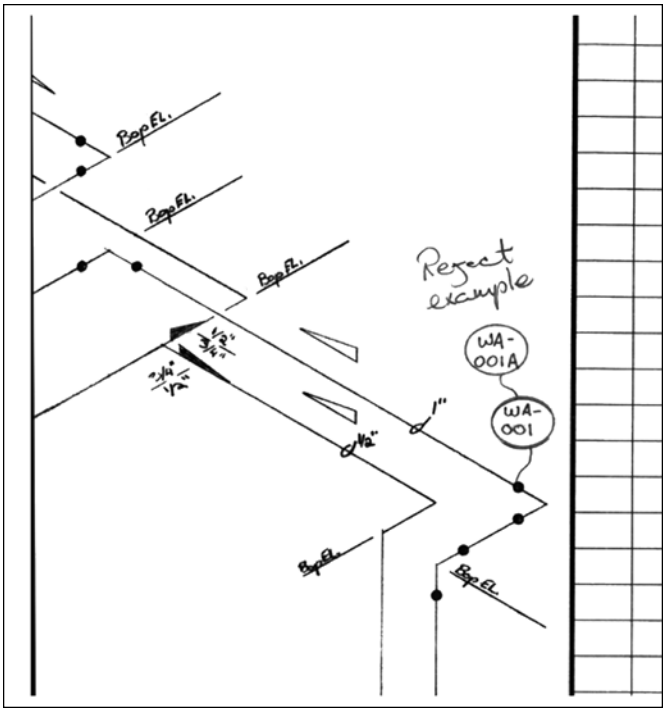

Figure 7. Example of how a rejected weld would be documented on an "iso" drawing. The first weld "window" shows the weld number which is recorded for every weld and the second window indicates that the first weld was cut out, replaced, and the number changed. *Courtesy of Pro-Tech Process, Inc.*

Preoperational passivation is an essential step in bringing a system on line. This is especially important for preventing corrosion of stainless steel systems operating at higher temperatures, subjected to service environments where harsh chemicals such as chlorides are used, or ultrapure water. At the Sicor site, a phosphate based alkaline cleaning solution was used to remove construction debris, organic films, and surface inclusions, i.e., aluminum, sulfides, and others. Citric acid, with a reducing agent and EDTA chelant system, was used for passivating the systems that had been installed with orbital welding. In addition to removing free iron (as with nitric or other mineral acids), citric based chelant systems dissolve surface contaminants and most types of inclusions that contribute to pitting corrosion. Chelants prevent the iron from adhering to the surface so it can be readily flushed from the system. The use of citric acid chelant systems results in an excellent chrome to iron (Cr/Fe) ratio on the surface[12] and is much less problematic from an environmental and safety standpoint than nitric or other mineral acids. However, passivation cannot overcome damage done by improper purging during the welding process.

Validation

Sicor Inc. has its own validation group which has a master

plan for validation. There is a separate validation protocol for each system such as WFI, CIP, clean steam, etc. The validation group does a spot check during the installation and they hire third-party QA who works directly for Sicor. The owner is responsible for working with the FDA to assure them that everything is being done according to current Good Manufacturing Practices (cGMP) and that they have the documentation to prove it.

Risk of Change

When the facility is done, the user starts using it. Once he begins using the system, an operator may find a better way to do his job. This may involve moving piping. Such changes are typical. In the four to five years that it takes to make the vision a reality, the requirements for the facility may change. FDA approval for the drug for which the system at Sicor was built is expected in 2004, but there is always the risk that it won't be approved; then the facility would have to be modified to produce a different drug. They may need to switch a system for the production of a new drug or, if the current drug becomes a big seller, they may need to increase the system capacity to make larger quantities. This might require an adjustment of the flow rate of a water system or a change in the operating temperature. Unexpected changes put a strain on all utilities, water, and infrastructure. Steve Muehlberger likes to make his systems "robust" so they can change directions as demands on the system evolve.

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This article presents lyophilizer and loading operations, and isolator integration.

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Design Considerations For Aseptic Liquid Vial Filling and Lyophilization Operations Within High Containment Isolators - Part 2

by Michael P. DeBellis

Lyophilizer Loading/Unloading

Present technologies used to load and unload vials in a lyophilizer can vary from completely manual operations to completely automated operations. Manual loading is typical of lab or pilot scale lyophilizer units where the quantity of vials is small and easy to handle manually. Manual operations from within an isolator would typically require a half suit operation in order for an operator to be close enough to properly interface with the shelves of the lyophilizer. Trays of vials would be placed on the shelves, one at a time, and pushed into position loading from back to the front of each shelf. This would require tools to be able to push and retrieve the trays during loading and unloading. The loading and unloading areas of the lyophilizer also must be in a laminar flow Class 100 area. Manual operations need to be concerned about particle shedding and generation above the partially stoppered vials during loading. Glove tears are a major concern when dealing with stainless steel or metal trays because many of the corners are sharp and prone to tear gloves. However, manually loading larger pilot scale to production sized units, the lyophilizer loading and unloading of thousands of glass vials would become much more time consuming, strenuous, and typically uses some additional equipment such as accumulator tables or tray loaders for arranging vials onto a tray which will assist the operator in properly configuring vials into trays, and manually loading and unloading them. Vial positioning on trays can be crucial to some lyophilization processes and tray loaders provide a repeatable vial orientation on the trays for each vial size used.

The traying operation extends to how the vials will be handled and physically placed onto the shelves. Whether vials trays are bottomless, have bottoms, or are constructed of stainless steel or plastic, is a process related issue that should be evaluated from a material handling concern as well as a heat transfer concern. Plastic trays do not significantly impede heat

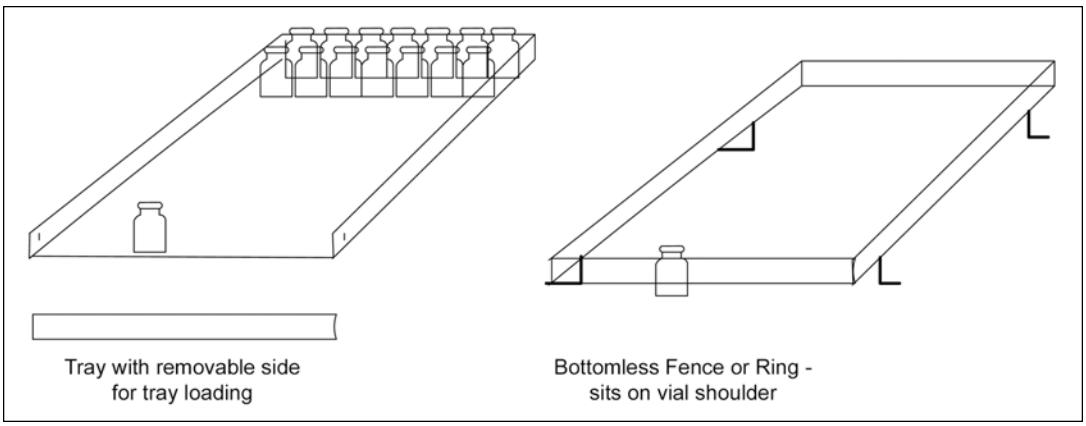

Figure 9. Types of vial trays used in manually loaded lyophilizer operations.

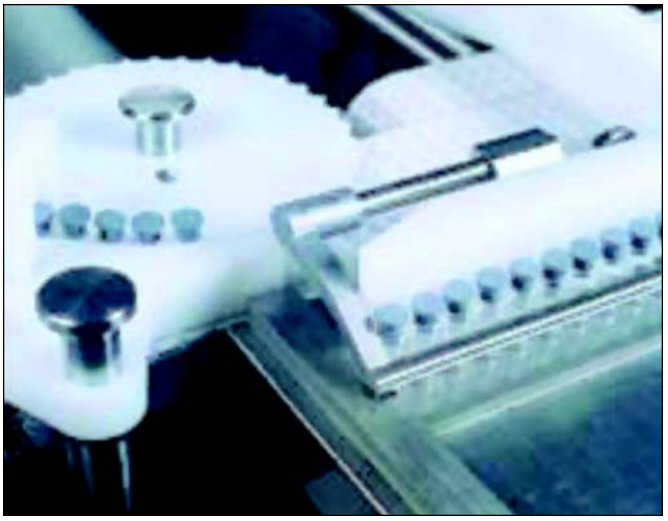

Figure 10. Lyophilizer autoloader system.

transfer between the cooled shelves and the glass vial; however, they are flimsy and may not be able to firmly support some of the larger vial sizes satisfactorily. Typically, the trays with bottoms are used for processing bulk liquids. It is important to use trays that lay flat on the shelves of the lyophilizer. Otherwise, with warped trays, the heat transfer between shelf and product will be unevenly distributed across the tray. This situation will cause varied freezing and drying rates across each tray and the product. Bottomless trays are best for processing product contained in vials as they allow for the vials to sit directly on the shelf for the most efficient heat transfer between shelf and product. The trend in processing liquid products in vials is toward use of the bottomless trays or fences, as they are also referred to. Fences sit on the shoulder of the vials and keep the vials in a tight pack for sliding onto and off of the chamber shelves. The type of tray to be used should be evaluated along with other scale-up considerations when developing the process.

During the unloading of the vials, the same procedures are used and vials are disciplined into a single row presentation into a capping machine. As you may have realized by now, the manual loading of a lyophilizer requires a high degree of operator interfacing and handling of the vials and trays; so much that it becomes extremely cumbersome to perform these functions through isolator glove ports. The idea is to maintain the integrity of the glass vials and minimize breakage throughout the filling line, in and out of the lyophilizer, capping, and including external vial washing - *Figure 9*.

Figure 11. Flexible lyophilizer autoloader system.

Any tray operation being considered also will need to consider the washing, sterilizing, storage, and handling of the trays/fences. Aseptic storage areas are required. Warping of the trays and particle accumulation may become problems as well. A better approach would be to go with trayless loading and unloading. This can be accomplished by pushing vials from an accumulation table directly onto a shelf of a cart. Vials are fenced in on this surface to prevent them from falling over. Fences would sit on the shoulder of each vial and have one removable side to load through when removed and locked into position to hold all the vials in place on the cart shelf. The cart is brought to the lyophilizer load door, docked to a shelf, and the fenced vial can be pushed onto the lyophilizer shelves. For unloading the fences, vials are pulled off the lyophilizer shelves onto the cart shelf until the entire chamber is empty. The vials are then re-disciplined again in single file and conveyed to the capping machine for the final seal to be placed over the stopper. This is the basic manual tray loading/unloading method.

Performing manual loading and unloading operations within a half suit or glove ports of an isolator, if you have ever tried this, is no easy endeavor. Personal hygiene becomes very important when operators share a half suit. Less than 20% of all isolated filling lines in 2002 incorporate half suits in their operations and the remainder used gloves. It would appear that an automated loading and unloading system would be the most desirable of loading methods, especially when it becomes necessary to interface the lyophilizer through a high containment isolator. Automated systems are trayless operations. This eliminates the concerns regarding the materials of construction, storing, handling, cleaning, and sterilizing of the lyo trays.

Automated systems will load and unload lyophilizer shelves in one of two methods:

Row by Row Loading/Unloading: Vials are staged in a single file the entire length of a shelf just outside the lyophilizer loading door area and pushed by a hydraulic push bar device into the chamber. Vials are pushed in one row at a time until the entire shelf is loaded. This procedure is repeated for each shelf until all shelves are loaded. Unloading using a row-by-row loader would be performed in a similar manner with a rear pusher located in the rear of the unit (opposite the load side). These systems are generally fixed, perform dedicated tasks, and are relatively lower in costs - *Figure 10*.

Shelf Loading/Unloading: For this method of loading, the system will accumulate and configure an entire shelves' worth of vials and push the entire pack of vials into the chamber and onto each shelf one at a time. Unloading can be done from the same mechanism as the vial pack is pulled out from each shelf one at a time. The movement and docking up to each lyophilizer unit is automated. These systems take up less space and are generally very flexible systems. They can be used to load multiple lyophilizers when mounted on a rail

system. They are significantly higher in costs as compared to the fixed loading systems - *Figure 11*.

The loading operation speed is dependant upon the filling line speeds. Filling lines in excess of 600 vials per minute would exceed today's auto loading capabilities. The maximum operating speeds for both types of loading system types is approximately 600 vials per minute. However, at this speed line interruptions due to vial mishaps are generally higher than at slower speeds. Generally, most pharmaceutical production type lyophilizer loading/unloading operations are in the neighborhood of 300 – 400 vials per minute depending on the vial sizes. When loading and unloading a lyophilizer from within an isolator, in general, the speeds of the entire line are reduced greatly.

In both types of loading systems, the lyo shelf movement system, which also provides the stoppering action, moves shelves upward and downward for loading and unloading at a constant height through a slot type door commonly referred to as a "pizza door." Loading through a slot door allows the chamber to be kept cool during loading without frost build up. Sometimes dry nitrogen gas may be used to purge the chamber further protecting the chamber and shelves against frost build-up.

Now that the basic operations and vial loading methods of the lyophilizer have been reviewed, how these operations and equipment can be integrated into a high containment isolator will be considered. Also, throw into the mix a highly potent drug compound and we have ourselves an entirely different ball game.

Selecting the loading method to be used for the lyophilizer operations early on in the project is critical to the building design and establishing space for the optimum filling line and lyophilizer configuration and room layout. Manually loaded lyophilizer chambers loaded via isolator glove ports will require a shallower shelf, one or two trays deep, as operator visibility of the chamber interior through an isolator view panel and pizza style slot door is extremely poor and manipulating the vial trays is very difficult in gloves. Trays may be clipped together, to be moved in and out together with guide rails on the lyophilizer shelf to prevent trays from sliding off the shelf during loading is recommended. An automatically loaded shelf can be configured to best accommodate the loading system and there are certain manufacturers who have their own dimensional limits for being able to utilize a shelf loader versus a row-by-row loading system. Being aware of this will assure you are properly matching up the lyophilizer with the loader. For lyophilizer operations being retro-fitted into existing space, understanding the space requirements and limitations can avoid costly re-designs and delays to your project.

Barrier Isolation and High Containment Isolators

Before we get too far along, let's consider the alternatives available for providing an aseptic environment for this filling and lyophilization operation. Why use isolators? The conventional cleanroom has significant problems associated with

Figure 12. Class 100 high containment isolator system.

the human occupancy of these rooms. Human operators have been determined to be the only significant source of microbial contamination in cleanrooms. Even with all the protective clothing and the latest clothing designs, they still release microorganisms into the environment. The more movement operators perform, the more organisms they release. Knowing this, how can we really achieve actual sterile conditions? Aseptic and sterile, contrary to some beliefs, are not synonymous. Aseptic denotes the method used to manufacture parenterals and other products free from microbial contamination. *Aseptic* means the absence of disease causing organisms (pathogens). *Sterile* means completely free of disease causing organisms that can reproduce.

Cleanroom designs deal with the human contamination problem by circulating large volumes of HEPA filtered air with relatively high velocities to minimize the number and size of air borne particles in the environment of the room. Standard design practices dictate that Class 100 with unidirectional airflow must be maintained in the critical areas where the aseptic operations are to take place - *Figure 12*. Conventional cleanrooms for aseptic processing also utilize 80 percent recirculated air and 20 percent fresh air make-up. The control of airborne contamination in cleanrooms by moving large volumes of diluted air (HEPA or ULPA filtered) is a very successful approach. However, this same strategy does not apply to isolators for a number of reasons:

- elimination of the human element inside the environment of the isolator which translates to no microorganisms being released into the product handling environment
- smaller volumes of air to move resulting in a higher number air changes per hour

Applying some common sense, the air velocities in the smaller volumes, such as inside isolators, would be extremely high and create problems for vials to remain upright and moving in a controlled manner throughout the vial path of the filling line increasing jams, breakage, and tip overs. Air velocities through a mouse hole connecting or exiting chambers of isolator systems would shoot vials out at the higher

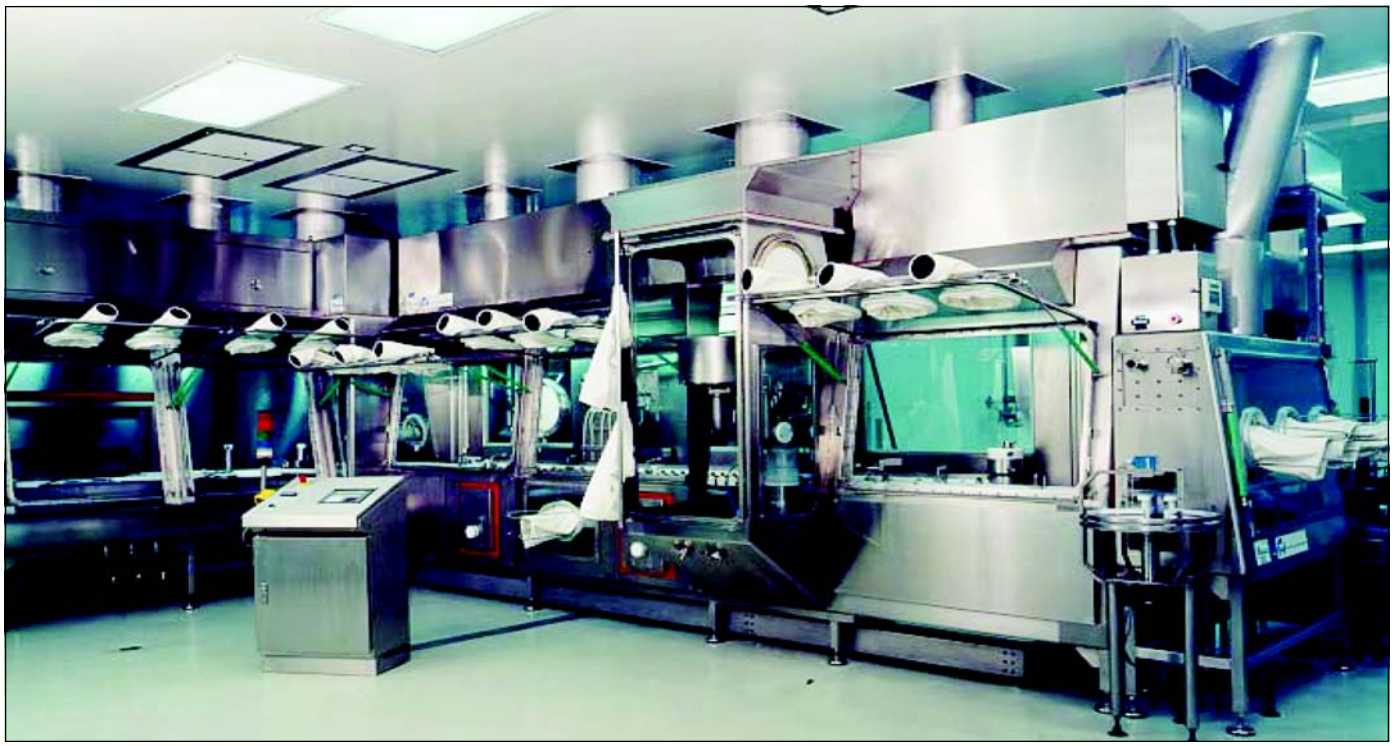

Figure 13. Isolated filling and lyophilizer operation.

"cleanroom" velocities. So, there are practical reasons for operating at lower air velocities. Operating an isolator using lower air velocities and lower air changers has been studied and reported in the PDA technical report No. 34, "Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Product." This is key in optimizing the air velocities and air changes within an isolator. It means that we no longer have to deal with the human generated contamination to the degree that cleanroom designs do. Much lower airborne contamination has been witnessed in isolators operating at as few as 20 air changes per hour.

Today's isolators can provide a near perfect aseptic environment and offer a viable alternative to clean rooms. A summary of the isolator benefits is as follows:

- operator protection
- elimination of the human airborne generation of microorganisms by removing operators from the process
- controlled environment to assure aseptic processing conditions, i.e., temperature, pressure, relative humidity, airflow, make-up air balancing
- elimination of product contamination
- containment of potent, hazardous, toxic, or biologically active compounds

Combining the Two Technologies

Combining aseptic filling and lyophilization processes with high containment isolation technology and integrating multiple manufacturers' equipment presents some design challenges. Working heights, vial conveying methods, transferring from one manufacturer's equipment to another's, control panels, control integration, utility drops, maintenance access, alarms, pausing the line, etc. These details, if not properly integrated, will inevitably become problematic.

Let's focus on the lyophilizer operation we described earlier, incorporating an automatic shelf system for loading and unloading at a constant height through a slot door, commonly referred to as a "pizza door." For large lyophilizer chambers with multiple shelves, the constant height loading eliminates the need to lift trays of vials onto each shelf. Transitioning vials from the cart or autoloader surface requires a bridge plate or dead plate to allow for the sliding or pushing of vial trays or vials without trays across the gap between the cart or autoloader surface and the lyophilizer shelves. This same plate is used repeatedly for each shelf during loading and is removed or retracted when advancing shelves during loading and unloading operations. Access to the lyophilizer chamber can be performed from a rear mechanical door located in a general manufacturing type space behind the process room wall. A biological seal and flange is incorporated onto the lyo chamber to provide separation between the process side of the lyophilizer and the mechanical space. For containment isolator applications, the isolator will be integrated to the front of the lyo (load side) and surround the slot door, completely sealing off the process side of the lyophilizer from the surrounding room.

Lyophilizer operations can be complicated to begin with; however, interfacing an isolator with these operations can become a challenge unless the design is well thought out and addresses all the handling, process operations, utilities requirements, and ergonomic issues - *Figure 13*.

Having spent two years involved with the design development and specification of a similar filling line and lyophilizer operation, I have some key design issues I thought would be

worth sharing. These are some of the design considerations which our project team addressed and I believe will benefit those who may get involved with isolating filling operation projects; however, every filling operation has its own unique concerns and good, sound engineering practices combined with common sense must guide you through addressing those issues:

Washer/Tunnel/Accumulator/Filler/Fencing or Traying Station

- integration with lyophilizer loading method
- bypassing lyo for liquid fill (conveyors or manual transport)

Filler/Lyophilizer/Isolator Operations

- determine all gloved operations
  - rejects and fallen vial handling
  - gloved manipulation techniques for incorporating thermocouples or RTDs in test/sample vials for temperature profiling of lyophilizer shelves during cycle development and validation
  - cleaning and decontamination
  - filling stopper and capper feed bowls
- determine conveying method for vials with liquid fill products (directly to capper from filler, bypassing the lyophilizer)
- bridge plate design for moving vials into the chamber
- biologically sealing the lyophilizer loading/unloading area in the process space from the mechanical space and the isolator interfacing details
- provisions for automated in-situ integrity testing of vent filter or manual testing - required connections to be provided
- cold shelf loading
- Nitrogen blanketing (chamber and heat transfer fluid expansion tank)
- lyophilizer clean-in-place system
- steam-in-place (door seal areas, ram bellows, chamber, and condenser)
- ability to Vaporous Hydrogen Peroxide (VHP) sterilize the isolator and the slot door seals
- decontamination method – inactivation of active ingredients and proper drainage. (deactivation/biowaste system or process waste)
- protection of vacuum systems from contamination
  - including vacuum systems for stoppering and capping mechanisms
- maintenance issues
- provisions for the stoppering/shelf movement system ram assembly – removal
- component equipment maintenance access
- isolator air handling and filtering systems
  - air velocity
  - number of air changes
  - Class 100 conditions
  - negative or positive pressure in isolator
  - glove breach system (negative pressure fan)
- loading methods
  - automatic or manual
  - row by row or flexible loading
  - pizza door or full door
  - isolator half suit or glove loading operations
- isolator CIP: spray wands or by manual wipe down?
- determine the proper electrical rating of electrical equipment. (Are products solvent based?)
  - inert atmosphere in isolators
  - oxygen detection (process room and isolator)
- interlocked load and rear maintenance doors to prevent the atmospheres in the isolator from becoming cross-contaminated with the mechanical room environment

Layout Issues

- single or multiple floor installation
  - side mounted condenser
  - above/below chamber mounted condenser
  - vertical or horizontal condenser
- single skid or multiple skidded system
- loading from an isolation barrier
  - manual loading using gloves
  - manual loading with fences or tray with bottoms
  - automatic loading systems in isolation barriers
  - loading/unloading heights
  - automated loading system
  - auto-loader configuration with multiple lyophilizers
  - auto loading - multiple units
  - auto-loader transfer cart and pusher details

Isolator Mock-Up Reviews

Prior to fabrication of any isolator, it is always advantageous to have a model of the isolator constructed to check out the ergonomic integration of the actual equipment and components to be used within and on the isolator. A plywood constructed isolator will provide insight to the look and feel of the isolator operations and reveal design flaws or operation difficulties that cannot be realized from a design drawing. Ergonomic considerations for how to reach the lyo shelves from an isolator may necessitate an autoloader in lieu of manual methods. Are tools necessary to work through normal glove ports? Is storage space required for items used repeatedly? Is there space in the isolators for testing indicators, liquid path assembly and disassembly, component removal? These and other questions will be answered during mock-up reviews. In addition to the ergonomic issues, the mock-up reviews also should be considered for preliminary air flow pattern studies, laminar or turbulent airflow, VHP injection port locations, CIP spray device locations, and other performance related concerns that will affect the final design and fabrication of the isolator.

Additional Considerations

Equipment FATs

- Review Vendor Procedures and advise them of any additional requirements necessary.
- Determine when, where, and what equipment will be FAT'd together.

  - Lyophilizers should be FAT'd independently from the rest of the line.
- Factory Acceptance Testing/Performance Guarantees need to be agreed upon in advance. Due to the number of pieces of equipment which have to be properly integrated functionally, operationally, and control wise, bringing all the pieces together under one roof for FAT would be advantages, but may not be practical in some cases. However, each component of the equipment line should be tested at the Vendors facility prior to shipping for the following:
- verify compliance with performance specifications
- functional/operational testing
- parametric testing
- surrogate testing to confirm that the design containment levels of the isolator were achieved
- deactivation cycle development for potent drug materials
- smoke tests to verify unidirectional airflow
- particulate testing
- microbial decontamination testing (VHP or other sterilant cycle development)
- performance guarantees
- To guarantee performance, frequent routine testing must be established. Direct and indirect (parametric) indicators must be established to substantiate a failure where no real time monitoring is possible. Standard methods of operations must be established and followed, together with surrogate material testing to determine proper performance verification.

Documentation Package

- Sample Vendor Documentation Packages should be reviewed for shortcomings based on your project requirements.

Controls Integration

- Equipment controls to be integrated with isolators. Control cabinets for individual equipment should be combined, wherever possible.
  - addressing GAMP and 21 CFR Part 11 requirements

Process Considerations

- Need to segregate effluents such as CIP and clean steam condensate from contaminated effluents, such as process condenser thaw water/liquid, and send these to a deactivation system.
- Decontamination method – determine if by chemicals or steam?
- Determine if a deactivation system is required at all.
- Coordination of the VHP sanitization with the SIP of the lyophilizer chamber and condenser (interior) – controls will need to allow the manipulation of the pizza or slot door to sterilize the door seal on both sides.

Summary

The use of barrier and isolation technologies in the aseptic processing of pharmaceutical products has grown substantially in the last few years. Successful designs and installations have now been achieved. These installations now enjoy a history of successful operation, which has removed the mystique surrounding isolator designs and has established this technology as a more attractive alternative approach to create the proper environments required for aseptic processing. The emphasis of this article was to provide the reader with a sense of the many design aspects which must be addressed to obtain a properly designed isolated aseptic liquid vial filling and lyophilization operation. The undertaking of such a project with all the design nuances and intricacies could easily overlook some of the more subtle concerns. Project success depends upon complete understanding of all the critical operations, material transfer issues, and safety concerns with regard to product quality, containment goals, operator protection, vial handling methods, performance, testing, and validation requirements. Plywood isolator mock-ups are strongly recommended to prove out the ergonomic viability, performance of the various operations, and are most beneficial when the actual equipment and operators, i.e., glove ports, RTP ports, and lyophilizer loading systems, etc., are incorporated into the mock-up reviews.

Developing a Design Team Approach can be a useful tool and reduce the integration problems, which could hinder a successful design, fabrication, installation, start-up/commissioning, and validation. In a team approach, a Filling Line Team would be selected based primarily on their expertise and experience in addressing key areas such as aseptic processing, high containment (very low Operator Exposure Levels (OEL) in the nanograms/cubic meter/ eight hrs range), system integration, and design of flexible filling line and lyophilization operations within isolators. The team members should consist of representatives of the equipment manufacturers involved, design engineers, the client user group, project managers, quality assurance, validation, and any outside consultants necessary to round out the level of expertise required. There are many good consultants and manufacturer's representatives that focus on high containment isolation technology. Collaborating with these individuals and taking advantage of their experiences will help you address the many design issues, avoid repeating mistakes made by others, and lead you down the road to a successfully contained and validatable aseptic filling and lyophilization operation.

Designing a filling line inside isolators in lieu of cleanrooms will provide improved safety and confidence levels in both operator and product protection. The use of containment isolators does not eliminate the need for adherence to cGMPs, especially with regard to operating an aseptic liquid filling line operation. For products that do not need to be lyophilized, the terminal sterilization of these products would still be required. The use of isolators is not a substitute for terminal sterilization.

Validation of an aseptic isolated filling and lyophilization equipment line should be planned for as early as possible in the design process. Documentation submittal requirements for each equipment manufacturer should be identified as early as possible. Equipment manufacturers have a commer-

cial responsibility to provide their equipment in compliance with the project equipment specifications and performance criteria established. CGMP, GAMP issues, and compliance with other related industry codes and standards must be confirmed prior to purchasing your equipment to avoid increased costs, and potential delays in the fabrication, commissioning, and validation of your system.

References

1. PDA Draft Technical Report No. 34, Design and Validation of Isolator Systems for Manufacturing and Testing of Health Care Products.

2. Lysfjord, J., Porter, M., "Barrier Isolation History and Trends," *Pharmaceutical Engineering*, Volume 23, No.2, 2003, pp 58-64.

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