The founders of CRB, Doyle Clark (DC), Gerry Richardson (GR), and Jeff Biskup (JB), discuss the changes they have seen in the industry and challenges they see for the future.

The interview was conducted by Jeff Odum, ISPE Publications/ Internet Committee Chairperson.

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An Interview with the Founders of Clark, Richardson & Biskup - ISPE Company of the Year

Clark, Richardson & Biskup Consulting Engineers, Inc. (CRB) was founded in April, 1984 through the visions of three entrepreneurial-minded engineers who wanted to provide engineering services to the biopharm market differently than they had experienced and with a customer-driven focus. So, in the basement of Gerry Richardson's home, friends, Doyle Clark and Jeff Biskup, formed what is now a 250-person consulting engineering firm that is heavily focused on the pharmaceutical and biotech industry.

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Q As a firm that provides engineering services to the pharmaceutical/ biotech industries, what are the significant changes you have seen in the industry over the past five years?

A **GR:** The biggest change that I have seen is the emergence of biotech as a viable pharmaceutical area and an area where demand for manufacturing capacity has been very significant. This has resulted in an increasing number of new products and the resultant demand for reduced time to market for our projects. Another change that I have seen is in the increased capabilities and use of automation in the research and manufacturing processes.

2000 ISPE Company of the Year, CRB Consulting Engineers, founders from left to right: Jeff Biskup, Gerry Richardson, and Doyle Clark.

JB: Probably the change with the most impact on our business is the tendency toward faster and faster project delivery. While there has always been a demand to get there faster, the technology boom fueled by high-speed computers and rapidly improving communications ability, has greatly accelerated the rate of change. The industry's push to get products to market more quickly is driving manufacturers to make significant process and facility decisions earlier. At the same time, it demands reductions in time spent in engineering and construction. This imposes a tremendous challenge and heightened risks on all involved.

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Q Of these changes, which have been the most difficult to deal with as a service provider?

A **JB:** Without a doubt, the most difficult to deal with is the speed of project delivery, especially on new products and processes. To complete projects faster, we are forced to make decisions earlier and more quickly. It really changes how you think and forces you to reevaluate priorities.

GR: I agree. The simultaneous need for speed and flexibility in the planning, design, construction, and start-up of manufacturing facilities has changed the way we approach our projects in order to provide value to our clients.

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Q Technologies have been rapidly changing, particularly in the bioprocess area. Do you see any particular changes that hold the most promise for the next five to ten years?

A **GR:** Automation and the inclusion of research and manufacturing into enterprise integration will take on ever-increasing importance and result in ever increasing quality.

JB: Relative to the engineering business, I believe the continued evolution of design software is about ready to pay dividends. Integrated design, simulation, and CAD software could help solve some of the speed to market challenges. It also will help reduce risks by producing better quality documents very quickly.

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Q What issues do you see as being the greatest challenge to the biopharm industry as it continues to grow?

A **GR:** For some time, adequate manufacturing capacity will be one of the greatest challenges. The need to improve research methods and models will continue to be a great challenge; continued incidences of very unpleasant surprises in large scale, as well as Phase 3 clinical trials, place access to adequate capital at risk.

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Q What was the driving force that led you to form CRB more than 15 years ago, and do you see that still being a driver of your work today?

A **DC:** The need for highly specialized consulting and engineering services focused upon the special needs of high technology manufacturers. Yes, more than ever.

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Q What are the new design tools that you see being implemented that will provide client firms with improved design methods and how do they specifically relate to the pharmaceutical/biotech industries?

A **DC:** Electronic tools that make it easy and cost effective to collaborate with any number of stakeholders and to better coordinate the planning, design, construction, and operation of facilities and processes. Project teams are becoming very diverse and these tools are becoming increasingly important in allowing better communication and control on projects.

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Q What are the key resources that you see necessary for success on process-driven projects involving manufacturing operations?

A **JB:** On the Owner's side, it is important to have a key decision making authority along with people knowledgeable in the manufacturing operation as well as the process technology. That could be one person or ten. On the design side, I believe it is critical to have excellent technical people who communicate well with operations people. It is also obviously very important to have people who understand the project needs and objectives and who can control the scope of the project so that those objectives are met on schedule and under budget.

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Q Is there a different philosophy for utility-driven projects?

A **JB:** I think no. Whether we are working with utilities or process flow streams, we still have to determine how the system relates to our goal of reliability and consistently producing quality and safe pharmaceutical products. Fundamentally, the closer we get to the product, the more cautious we get in our design. That is kind of what the Baseline® Guides are all about. So, if you move upstream in the process and facility, our design effort becomes more traditional Good Engineering Practice.

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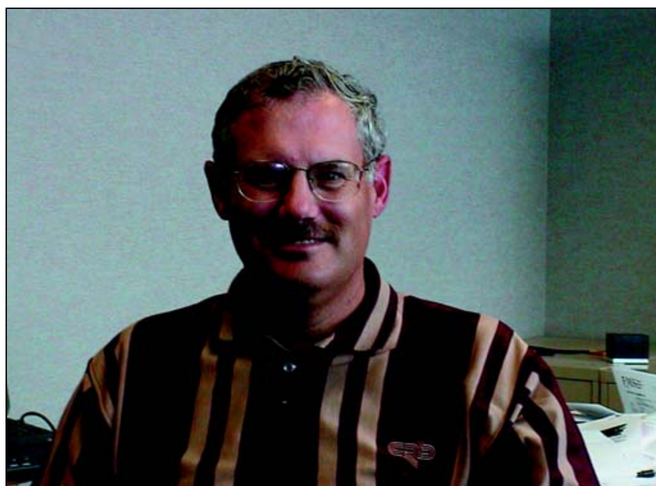

Doyle Clark.

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Gerry Richardson.

Q If you could look inside the crystal ball, what do you see being the industry outlook over the next five years?

A **DC:** The future looks very healthy. All indications are that biotech will become increasingly dominant as a platform for new drugs. We strongly feel that this will present numerous opportunities for everyone on our side of the service industry.

JB: It looks to me like the industry will be very active during at least the next five years. I think the transition from treating symptoms to targeting the source will generate many new drug products. The evolution of the biotech industry will result in far more bio-based drugs than chemical based.

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Q As the first engineering design firm to be recognized by ISPE as the Company of the Year, what do you feel are the primary qualities that led to the recognition of this firm?

A **DC:** I think sheer numbers and our long time participation in leadership led to this recognition. Our company is more heavily focused upon the pharmaceutical and biotechnology engineering business than virtually any other engineering firm. We have viewed ISPE as THE technical/professional organization for us to support and participate in since I first attended an annual meeting 15 years ago. Since then, we have encouraged everyone in our organization to get involved in and support ISPE.

JB: I think the second reason we were honored is because our commitment to ISPE is for the most part selfless. I have always believed that if you focus on the objective of the mission, the rewards will take care of themselves.

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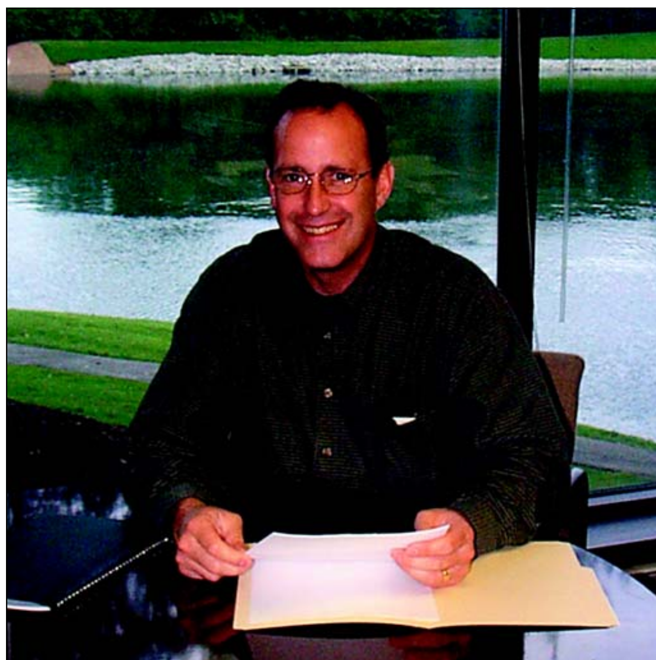
Q Any last thoughts on the industry you serve?

A **DC:** There are many benefits to successfully serving the pharmaceutical and biotechnology industry. The one that stands out for the long term is the feeling of satisfaction that we are doing (our small part) something important to increase the quality of life for everyone on the planet. My kids do not have a clear understanding of what I do at work, but they understand that medicines help people feel better; they understand that I help make medicine, and I think they are at least a little bit proud of me because of that.



Jeff Biskup.

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This case study describes how Computational Fluid Dynamics software was used to design a pharmaceutical containment system.

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The Use of Airflow Modelling in the Design of Pharmaceutical Containment Systems

by Andrew Ramsden

Introduction

Containment systems are an essential part of pharmaceutical current Good Manufacturing Practice (cGMP) and provide a high level of protection for both the process operatives and the product being processed. With currently recommended Operator Exposure Levels (OELs) being quoted in the order of micrograms for some products and nanograms for others, it becomes apparent that careful attention to the design of a given containment device is paramount. Furthermore, the safe and efficient evacuation of potentially toxic airborne particles from within the containment system is highly dependent upon the airflow characteristics of the given device.

The above comments generally relate to down-flow (flow-booth) and barrier containment (isolator) technology as typically employed in processes where powdered or vaporous products are handled manually. These processes include product sampling, dispensing, sub-division, packaging, and other related operations. It is during the handling process that the risks of operator exposure, direct product contamination, and the potential for cross batch product contaminations are at their greatest. To reduce these risks, the containment devices must be engineered to operate within limits set by the specified exposure levels for the processes or operations being undertaken within the confines of the containment system.

To achieve these low levels of exposure, we can exploit the dynamic characteristic of a fluid, and design a system that provides the optimum airflow conditions for efficient and effective evacuation of the containment system. The use of airflow modelling techniques during the design stages of a containment system allows the optimum operating conditions and dimensional parameters of the device to be explored. The resulting design should be a system that can be validated. One being as close to the optimum operating condition that may be defined by considering any local, physical, or environmental constraints. Airflow modelling gives the pharmaceutical process engineer the opportunity to assess a proposed containment solution prior to commissioning a final design. The following article describes, using a case study, how airflow modelling was used to solve an identified containment problem. The airflow modelling was performed using Computational Fluid Dynamics (CFD) software.

The MicroCharge Development Project

Defining the Problem

This project was initiated because it became apparent that pharmaceutical manufacturers require a compact and efficient device that can provide local containment during the charging of low volumes of product into production reactors. This process has typically involved the use of small vessels that are connected to the reactor via some form of split valve. This approach provides the required contained transfer; however, upon removal of the vessel, the two halves of the split valve frequently become a source of local contamination. This is due to a fine film of product residue, often found lodged around the edges of the valve flaps, being dissipated into the local environment, and hence creating the potential for product cross-contamination and unsafe OELs.

To counter this problem, a number of valve manufacturers provide a means to evacuate this residue by the use of air-blasts and local exhaust systems. This increases the secondary containment potential of the given valve by providing a level of containment suitable for use with relatively low risk active compounds and excipients classified as 510microgram/m^3 OEL. To further reduce the risk of residual product being dissipated into the surrounding environment, a compact and efficient secondary containment device appeared to offer an acceptable solution. Investigating current methods of providing this secondary containment indicated that isolator technology was being used, and

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while this method provides a high degree of containment, the isolators are typically large and can present problems of mobility during their use. It also became apparent that the isolator was typically 'over-specified' if products of only 0.5-1 microgram/m^3 OEL were being handled.

Developing a Solution

Prior to beginning development work on a project such as this, the aims and objectives of the project should be clearly defined. In this case, it was decided to concentrate on providing secondary containment for the charging of low microgram/m^3 OEL products by use of a local 'flow-hood.' The following list highlights a number of the primary objectives to be met by the device:

- secondary containment <1.0mg/m^3
- laminar air-flow through the containment chamber
- efficient operation
- self-contained exhaust system
- simple, low maintenance construction
- ease of installation
- suitable for temporary/mobile charging operations
- ease of cleaning, hygienic design

To meet these objectives, attention first was given to producing a mechanical concept model. Overall dimensions, geometry, and methods of construction were proposed that would fulfil the defined mechanical requirements. Once the basic concept was defined, attention was then given to providing the required airflow characteristics. During this second stage, it was decided that the project was suited to analysis by the application of CFD to help predict and assess the flow characteristics of the proposed device.

CFD is a software tool that is finding increased use during the solution of fluid related problems. It has been used by a wide range of diverse industry sectors covering areas involved in cleanroom operations, ventilation systems, and environmental pollutant dispersion as well as the more traditional areas of heat transfer and general fluid mechanics. For the purpose of this project, CFD allowed the design to be progressed, through a number of iterations, until the optimum solution was obtained.

The resulting analyses provided information predicting the airflow velocities, system pressures, and turbulence characteristics of the proposed device. This information normally can be obtained by producing accurate prototypes or physical models and subsequently performing tests under simulated or actual operating conditions. This traditional approach to project development typically incurs high design costs, leads to extended development times, and subsequently higher market costs to the end user. CFD can effectively help to reduce these costs and bring solutions to the market with high levels of confidence and relatively short development lead times. In the case of large scale containment solutions involving the movement of large volumes of air, as is typically found in suites of down-flow booths providing dispensing and packing facilities, the cost savings can be significant, both to the manufacturer of the equipment, and ultimately the end user.

The Development Process

Having briefly discussed some of the uses and benefits of CFD, some of the issues that were addressed with CFD during the development of this containment project will be described.

Design Geometry

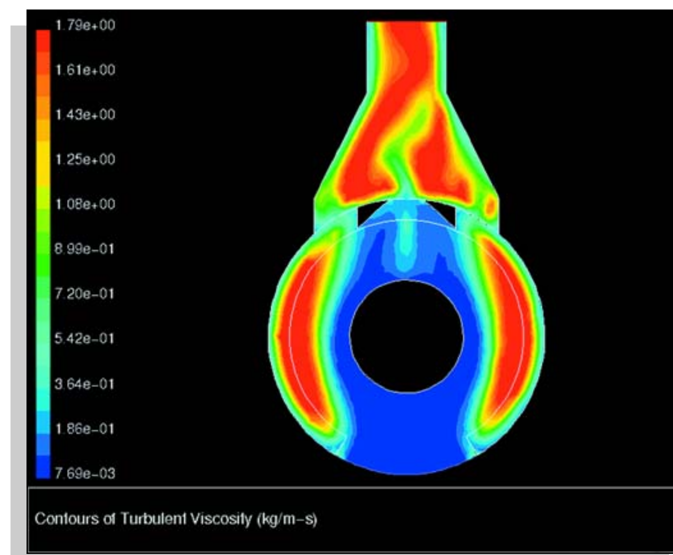

Figure 1. Turbulence plot from initial design.

Continued on page 42.

The initial concept was to produce a device that could be fitted directly to a reactor via a flange, or other connection device, on the main reactor charging manway. The device would house the active half of the split valve and provide a flow of air across the face of the valve when the product transfer bottle, which carries the passive valve half, is undocked and removed. The geometry and internal features are directly associated with the airflow through the system and can significantly influence the performance of the containment device. To this end, consideration was given to providing for the most efficient flow possible given the physical and environmental constraints under which the device would be operated.

Airflow Characteristics

The airflow characteristics are probably the single most important feature of a containment device, and as a result, the decision was made to model this project with the aid of CFD. During the modelling process, a number of geometries were analyzed and a few surprises were presented with the results. As described previously, the main objectives when designing a containment device are to provide for consistent airflow and low turbulence. The turbulence characteristics are particularly important since turbulence may cause suspended particles to be held within the body of the device, and hence present potential problems with OELs and product cross contamination. Both of these effects are detrimental to the overall efficiency of the device and must be controlled and minimized as much as possible. CFD offers a way to assess these effects at the design stage helping to avoid potentially costly mistakes and the manufacture of sub-standard devices. Time to market, development costs, and other associated overheads can all be reduced by using airflow modelling

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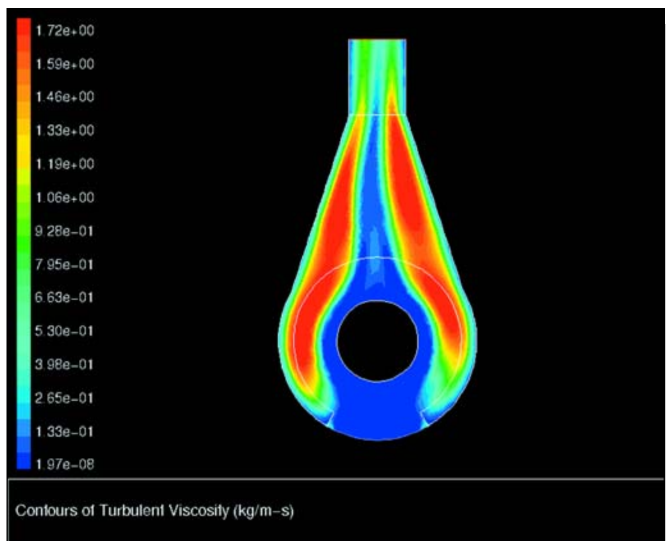

Figure 2. Improved airflow resulting from design change.

techniques in the early stages of the design process.

Internal Features

The term 'internal feature' is used here to describe those features within the confines of the device that may influence the desired airflow characteristics. Generally, in the context of containment devices, internal features represent obstructions to the free flow of air through the device and should be avoided. However, in some cases, they may not be easily removed and we then have to look for ways to reduce any detrimental effects that they may be causing. Typically, they are a source of turbulence, and as previously explained, turbulence is generally an undesirable characteristic.

This is exemplified in the way the analysis suggested that geometry changes were required and how these changes would result in the reduction of the magnitude of the local eddies downstream of the valve. These geometry changes ultimately improved the extraction efficiency of the device and this degree of 'fine-tuning' would not generally be possible without the insight of the predicted flow characteristics as suggested by a CFD analysis early in the design stages.

The CFD Method

To perform a CFD analysis requires the 'device' to be modelled in a CAD system. Typically, this can be any CAD package capable of exporting the geometry in one of a number of alternative formats, i.e. STEP, IGES, STL, etc. The geometry is then pre-processed by the CFD package resulting in a solid model of the flow domain. This model is then used to apply known or estimated boundary conditions that will define the characteristics of the flow domain. These could take the form of known inlet/outlet pressures or velocities, mass flows through the device (often the easiest parameter to set due to available design data in terms of required airflow and volume of the device/system), or known or required pressure domains. In fact, a whole array of conditions can be applied from which the analysis can be initiated. Identifying the relevant conditions and the mathematical algorithms used by the CFD solver is a matter of some experience and a subject of some conjecture. The science of CFD is incomplete and at best can only provide an approximation. This approximation is, however, in the majority of cases, perfectly acceptable for the requirement of the design engineers.

Following the application of the model's boundary conditions, the model is subjected to a volumetric meshing process that defines the nodes required to allow the solver to undertake its mathematical computations. Typically, the solver model uses a system of up to seven simultaneous equations. Those familiar with the Reynolds Stress Model and the Navier-Stokes equations of continuity will appreciate the computational effort required to solve a typical flow problem. Having completed the application of the boundary conditions and the meshing process, the solver can be run. In terms of computational effort, this process can take from several minutes to many hours. To put this into perspective, a study undertaken during the course of this case study consisted of more than 400,000 nodes took around 15 hours to solve - and this was on a relatively high specification workstation, (Dual 550Mhz CPUs).

Following the completion of the solving process, the results of the analysis can be assessed and interpreted from the wealth of both graphical and numerical data available from the majority of mainstream CFD packages. Many of these packages also can generate animated simulations of the flow fields and these can give a real insight into the typical operating characteristics of the given system. This is a bonus to a designer since as it will show, dynamically, areas that may need further attention.

How Airflow Modelling Helped the Design Process

During the development of this device, a particular internal feature became the subject of some controversy. Traditionally, within local extraction hoods, it has been customary to provide a perforated screen within the confines of the device. This has a two-fold function, a) it provides a pressure differential between the main chamber and the exhaust ducting, and b) it prevents large objects from being drawn into the exhaust system with potentially harmful effects to filters or fan elements.

This device was originally provided with such a screen that ran around the internal periphery of the containment chamber and was intended to create the appropriate pressure differentials. Figure 1 shows that the device was responsible for a very

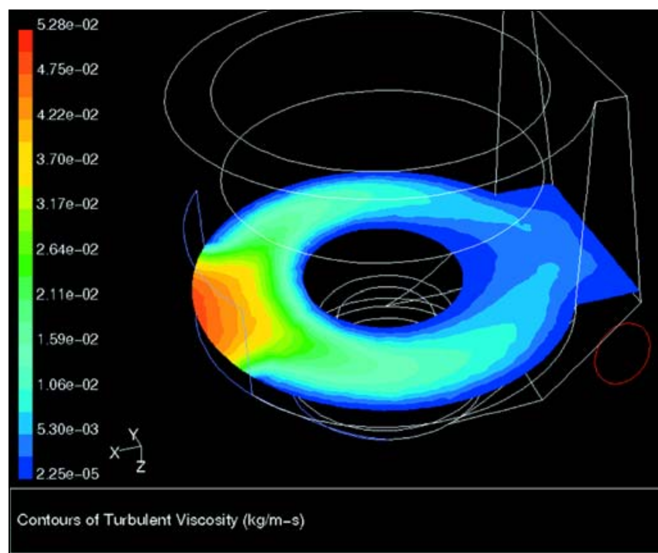

Figure 3. Turbulence plot from the optimized design.

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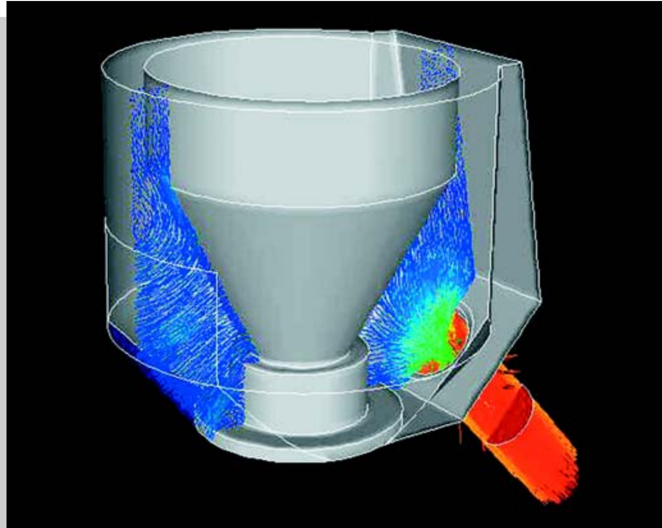

Figure 4. Velocity vectors.

high degree of turbulence, and upon closer inspection, it actually proved to be promoting a reverse flow behind the screen. This was an undesirable condition, and without the use of airflow modelling techniques, it could have been easily overlooked.

Re-modelling the device, and also altering the exhaust outlet geometry, resulted in the turbulence characteristics displayed in Figure 2. Here, we can immediately see the improvements, and though there is obviously still some work required on the geometry, CFD indicated that positive progress was being made. A number of design iterations were to follow until we arrived at the optimum geometry for the given operating conditions and local constraints. Figure 3 shows the predicted turbulence characteristics of the final design. Inspection of the numeric values, shown on the graphical scale, indicates a significant improvement over the original concept.

To confirm that the final turbulence characteristics would result in what should be, essentially, laminar flow, a velocity plot was generated. Figure 4 describes the airflow characteristics in terms of vectors and confirms that the flow through the device would be of an efficient nature with no eddies or backflows that could cause potential problems by holding contaminants within the body of the device. Subsequent testing of a physical prototype confirmed and validated the CFD predictions and led to the introduction of a new product to the range of containment solutions offered to the containment market - *Figure 5*.

The conclusions, following the modelling process, were that CFD provided an accurate insight in to how the airflow would behave during operation of the device. The technique allowed numerous variations of the device to be quickly assessed and the best solution identified prior to manufacturing a prototype. It was agreed in later design reviews that the use of airflow modelling was a valuable technique that would benefit the development of containment solutions and strategies as the pharmaceutical products being handled become increasingly potent. It also was found that the technique could identify and quantify flow characteristics in areas that are particularly difficult to assess in a physical prototype. The reversed flow behind the perforated screen of this particular device being a good example, and although this project may appear to be of a simplistic nature, it has demonstrated the value of CFD andairflow modelling when applied on a small scale.

Some Wider Implications of Using CFD and Airflow Modelling

It is now recognized that CFD technologies are generally available for use on desktop computer workstations. The advances in computer hardware and the availability of suitable machines have now brought these technologies within the scope of the working engineer. Where we once needed mainframes and massive computing resources, we can now run these applications alongside typical high-end CAD systems. The potential for performing concurrent engineering can be realized since CFD can be run parallel with the design process and the benefits of reduced design cycle times begin to be realized by both the manufacturers and their clients. Access to CFD and airflow modelling is becoming increasingly widespread and a growing number of consultancies now offer CFD analysis as a service. To further validate the use of CFD, many universities offer advanced courses of study in CFD related subjects and graduates are subsequently available with the necessary skills to perform meaningful analyses. This is resulting in the growth of the CFD community, and as market competition increases, what was once considered an expensive commodity is now becoming an accepted method of justifying a proposed design.

Expanding on the uses of CFD, particularly within the area of pharmaceutical containment, the methods can be used to

Figure 5. The resulting containment device.

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Airflow modelling gives the pharmaceutical process engineer the opportunity to assess a proposed containment solution prior to commissioning a final design.

assess the ventilation performance of an entire plant layout, 'what-if' scenarios can be analyzed and the effects of potential breeches in containment can be assessed. CFD technology also may allow the engineer to assess levels of airborne contamination by using various methods of 'particle dispersal modelling', and hence facilitate the planning of suitable ventilation and efficient containment strategies. There also are methods available for predicting cycle times during the purging of isolated systems, i.e. the levels of inert gas concentrations within an enclosure with respect to time. In all, a wide range of applications can be identified that could warrant investigation with the aid of CFD. The selection of appropriate equipment can have a significant effect on the overall performance of a given system, and in terms of containment equipment, the details become very important when considering the order of the OELs that the equipment must reliably provide.

This leads to the containment specialist now having access to a range of tools that allows designs to be optimized, tested, and pre-validated against specifications before the product manufacturing process begins. A number of United Kingdom based companies have pioneered these techniques and this is resulting in a range of containment solutions that offer the pharmaceutical manufacturing industry a guarantee of designs that are 'fit for purpose,' of industrial quality, and capable of performing consistently and reliably over extended periods of time. CFD also provides the designers with the ability to innovate and investigate new ideas in containment solutions and compare these innovations against what often are tried, tested, and 'accepted' designs. Repeatedly, the conclusions reached by this analysis process suggest that improvements can be made and the company acts upon these conclusions to result in a regime of continuous product improvement. The ultimate outcome of this is improved products for the end user, i.e. the pharmaceutical manufacturer.

Airflow Schematic

Figure 6 shows the airflow through the device when the transfer vessel is undocked from the active split butterfly valve. The intention is to prevent any airborne particulates from being allowed to escape into the surrounding environment, outside of the confines of the containment chamber. The exhaust airflow is ducted away to a HEPA filtration unit prior to being released back into the atmosphere.

The Future

The benefits of using CFD should now be quite obvious to even the impartial onlooker. To see the results of an analysis session transform into a working prototype, and eventually a finished product, in a much shorter time scale than that offered by traditional prototyping routes, is nothing less than enlightening. The degree of confidence in these techniques increases as more designs are optimized, subsequently built, validated, and put into service in the pharmaceutical manufacturing plants.

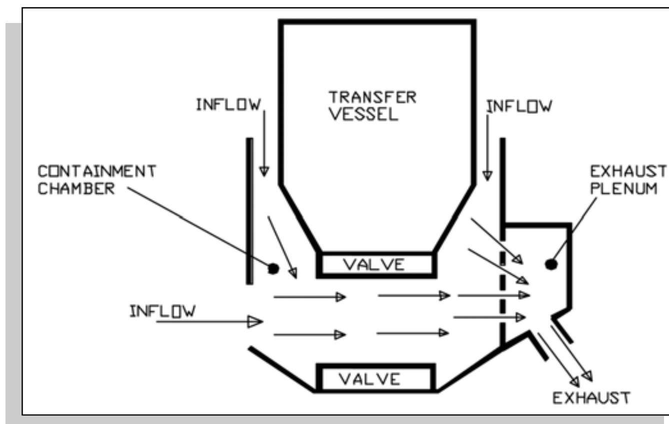

Figure 6. Airflow schematic.

The containment and ventilation technology we have become familiar with over the last few decades is beginning to reach the end of its useful life. The advent of high potency drug compounds, responsible for slowly driving the current generation of containment solutions to their limits, has begun to highlight some of the deficiencies in the existing designs. The future of high-containment solutions therefore appears to rely on the development of equipment that optimizes the flow characteristics of the given equipment, and hence provides an efficient, safe, and reliable combination of operating characteristics.

Reference to fundamental principles and tables of airflow coefficients, etc, during the design of containment solutions, can no longer guarantee the levels of performance dictated by the OELs required to safely handle these highly active compounds. World leaders in the formulation of containment solutions have recognized this trend and have subsequently embarked upon a route of continuous development that reassesses the integrity of traditional designs against the predictions of CFD analyses and their many years of 'hands-on' experience. Invariably, the results of these analyses offer opportunities to improve upon existing containment technology, and this innovation is ultimately being passed on to the consumer. Those who appreciate and take advantage of the value of these efforts will be rewarded with equipment that fulfills their design expectations by providing both a reliable and safe environment for their operations.

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Andrew Ramsden is a Senior Development Engineer with Extract Technology Ltd. and works with the Special Projects and Research and Development groups within the company. He has worked for the company for three years, and his main responsibilities are in the design and development of new and existing containment solutions. Ramsden is an engineering graduate and his practical experience is formed from more than 20 years of involvement in engineering design and manufacture. His specialty, within the Extract group of companies, is in the development and application of fluid analysis systems to the company's design projects. He is a member of the Institute of Electrical Engineers and focuses primarily on the design, automation, and manufacturing groups.

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This article describes an approach to process potent compounds using pharmaceutical solid dosage form equipment.

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Barrier Isolation Technology: A Safe and Effective Solution for Providing Pharmaceutical Development Facilities

by Daniel Liberman, Christopher Lockwood, Mary McConnell-Meachen, Eugene McNally, Hank Rahe, Kevin Shepard, and Glenn Snow

Introduction

In the last 10 years, the pharmaceutical industry has been discovering and developing increasingly more potent drugs. This increase in potency of new drug substances has reduced patient dosage for new drug approvals. While this trend is a positive outcome for the patients requiring the medication, it has created increasing problems for individuals involved with the development of these potent New Chemical Entities (NCEs).

The trend toward increased potency of the active drug substance not only includes cytotoxics, but also most major categories of pharmaceutical compounds. With this increase in potency of NCEs comes the need for greater safety measures to protect workers developing these compounds. Traditionally, formulation and process development work with NCEs has been performed in open laboratories with scientists wearing personal protective clothing and respirators to guard against skin contamination and inhalation exposure during dusty processing operations. However, this dependence on personal protective equipment may be inappropriate when the exposure limit for some of these compounds is in the sub-microgram region.

Boehringer Ingelheim (BI) has adopted a strategy that does not rely on Personal Protective Equipment (PPE) to protect workers. They have adopted the philosophy of containing the potent material at its source, the processing equipment itself. Using barrier isolators, contaminants are confined to the equipment that generates the contaminants. In this way, very low exposure levels can be achieved, and the dependence on PPE to protect workers can be minimized or even eliminated.

This article will describe an approach for processing potent compounds using pharmaceutical solid dosage form equipment. Isolating the worker from the potent compound prevents worker exposure without relying on PPE. The isolator systems, the work practices necessary to maintain containment of the potent material, and the validation data generated that demonstrate containment has been achieved will be described.

Background

Like many of the major pharmaceutical companies, BI developed a classification system for describing the level of potency of materials. Table A summarizes a five-category classification system for NCEs and the criteria used in assigning a classification to a compound. All relevant data about the compound are reviewed. This includes chemical, physical, pharmacological, and toxicological data from both human and animal subjects. A hazard assessment is conducted and a determination is made as to which Hazard Category is the "best fit." Team members collectively apply their expertise in industrial hygiene, toxicology, pharmacology, occupational medicine, and clinical medicine to review the data for the pharmaceutical active ingredient and make the hazard category assignment. Both acute and chronic data are considered, and the assignment relies on professional judgment. To assess potential acute effects, both the toxicity and pharmacological activity of the compound are evaluated. The type of pharmacological effect(s) expected, the mechanism of action, and the dose required to produce these pharmacological effects are important considerations, as is the severity of acute (life threatening) effects. This latter assessment is a determination of whether medical intervention might be required and how rapid the response must be if an overexposure occurs. This information in conjunction with the results of acute toxicity studies in animals provides the likelihood that the compound may produce immediate adverse effects. Compounds with a high order of acute toxicity and poor or

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	CATEGORY 1	CATEGORY 2	CATEGORY 3	CATEGORY 4	CATEGORY 5
DESCRIPTION	Low toxicity or pharmaceutical activity	Moderate toxicity or pharmaceutical activity	High toxicity or pharmaceutical activity	Very high toxicity or pharmaceutical activity	Extremely high toxicity or pharmaceutical activity
Pharmacological Potency	10-100 mg/kg	0.10-10 mg/kg	0.10-1 mg/kg	<0.01 mg/kg	<0.01 mg/kg
Acute Toxicity	Low	Low/moderate	Severe systemic effect	Very severe	Very severe
Chronic Toxicity	Low	Moderate	Severe systemic effects	Very severe	Very severe
Absorption by Skin/Inhalation	Skin absorption	Moderately absorbed via both	Well absorbed via both	Very well absorbed via both	Completely absorbed via both
ECL (Exposure Control Limits)	>1000 mcg/m^3	100µg/m^3 - 1000µ g/m^3	0.1µg/m^3 - 100µg/m^3	<1µg/m^3	<<1µ/m^3
Mutagenic	No	No	Potentially mutagenic	Mutagenic	Highly mutagenic
Reproductive Hazard	No	No	Potentially teratogenic	Teratogenic	Reproductive toxin both M/F
Carcinogenic	No	No	Potentially carcinogenic	Carcinogen	Potent carcinogen
Acute Warning Symptoms	Immediate	Immediate	Delayed	None	None
Cumulative Effects	None	Minimal	Moderate	High	Very high
Reversibility	Reversible	Reversible	Possibly irreversible	Irreversible	Irreversible
Sensitization	Not sensitizing	Not sensitizing	Sensitizer	Highly sensitizing	Extremely High
Warning Properties	Good	Good to poor	Poor to none	None	None

Table A. NCE classification system.

delayed warning properties are of concern.

A determination is made on the likelihood and severity of possible chronic effects. This weight-of-evidence evaluation is based on the results of genotoxicity assays in cell culture, in vitro experiments, in vivo studies in laboratory animals that are designed to determine the potential for the material to produce target organ effects, reproductive or developmental toxicity, cancer, or other chronic effects. Where possible, the results of clinical studies in humans are used as well. A key piece of information is the dose required to produce these effects, or preferably, the highest dose that does not produce a toxic or pharmacological effect (i.e., the No Observable Effect Level or NOEL). In the event that a NOEL cannot be defined, we attempt to define a No Toxic Effect Level or NOTEL.

A judgment is made regarding the severity of chronic effects and whether they may have disabling consequences or the potential to cause early death. A very important consideration is whether effects are reversible or irreversible.

The procedure that we follow in developing Occupational Exposure Levels (OEL) consists of the five steps outlined in Table B. Often the hazard category assignment is conservatively based on the most sensitive health effect endpoint, especially when there is potential for life threatening, disabling, or other irreversible chronic effects. During the early discovery phase of a compound, toxicological profiling is limited by the small quantities available. In the absence of valid toxicological information, research compounds are provisionally assigned to Category 3, unless the molecular structure or other indicators suggest a higher or lower classification. As additional data defining the risk of exposure becomes available, the categorization of the new chemical entity can be changed.

The equipment and containment devices that will be described have been designed to handle material in Categories 1-3 without the use of PPE. Category 4 compounds will require additional evaluation of both the compound and the containment devices to determine if they can be processed safely. Additional decontamination techniques, the use of PPE, and direct exhaust of the isolator are areas which would reduce potential personnel exposures and allow for the safe processing of compounds in Category 4. The derivation of OELs for therapeutic substances is not a precise scientific exercise; it is a matter of judgment involving medical, toxicological, and industrial hygiene disciplines.

Processing of Potent Compounds

At larger scale (50 kg and above), pharmaceutical equipment can be purchased with containment options that limit worker exposure to dust during processing; transport of materials between unit operations can be accomplished by vacuum transfer between closed bins. However, such containment options are not available on smaller capacity laboratory equip-

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ment used when making the first solid dosage form for a NCE at the 200g - 1 kg scale. At this small scale, past practice has been to work in a chemical fume hood, or in an open lab wearing some form of respirator to prevent inhalation of dust. However, the goal was to be able to work with small-scale equipment in the lab in either a contained or non-contained manner without the PPE and the facility clean up issues. This will allow the development of all levels of compounds in house.

When performing analytical testing, potent compounds need to be treated as hazardous and work with them in a properly contained environment. This means that for processing operations that generate considerable amounts of dust (i.e. dispensing active, mixing, granulating, milling, tableting), containment strategies need to be developed in order to do prototype formulation development work. We found that we needed to develop criteria to guide our decisions. These criteria evolved as we learned the advantages and disadvantages to various isolation/containment approaches. The initial criteria were:

1. safety of personnel working with the potent material and those scientists in adjacent labs not involved with these materials

Step 1 Determine the impact of the pharmacological effect on normal healthy individuals. Identify the lowest appropriate estimated or known NOEL/NOTEL for a pharmacological effect in animals or humans.

Step 2 Compile available information concerning the occupational toxicity of the substance by any relevant route of exposure. The following are considered in this review:
- Human and animal pharmacology and doses
- Skin toxicity, eye irritation and sensitization
- Metabolism
- Genetic Toxicity
- Carcinogenicity
- Mutagenicity
- Reproductive and developmental effects
- Reports of occupational exposures

Step 3 Collect information pertaining to the exposure route and human/medical experience:
- Routes of exposure and exposure conditions
- Industrial Hygiene analytical method developed
- Exposure data
- Medical surveillance

Step 4 Assign and document appropriate safety factors (or uncertainty factors) taking into account:
- Interspecies extrapolation
- Serious or irreversible effects
- Relevance of the observed action/mechanism for human group at special risk
- Mode of action
- Half-life, accumulation, etc.

Step 5 Use the following formula to calculate the occupational exposure level (expressed in milligrams per cubic meter of air) based on an 8 hour work shift:

$$\text{OEL} = \frac{(\text{NOEL or NOTEL}) \times (\text{50 kg average female worker})}{(\text{serum half life}) \times (\text{\% absorption}) \times (\text{respiration over 8 hour work day}) \times (\text{safety factor})}$$

This formula or a similar one is widely used within the industry to calculate the occupational exposure level.

Table B. Procedure for development of Occupational Exposure Levels (OEL).

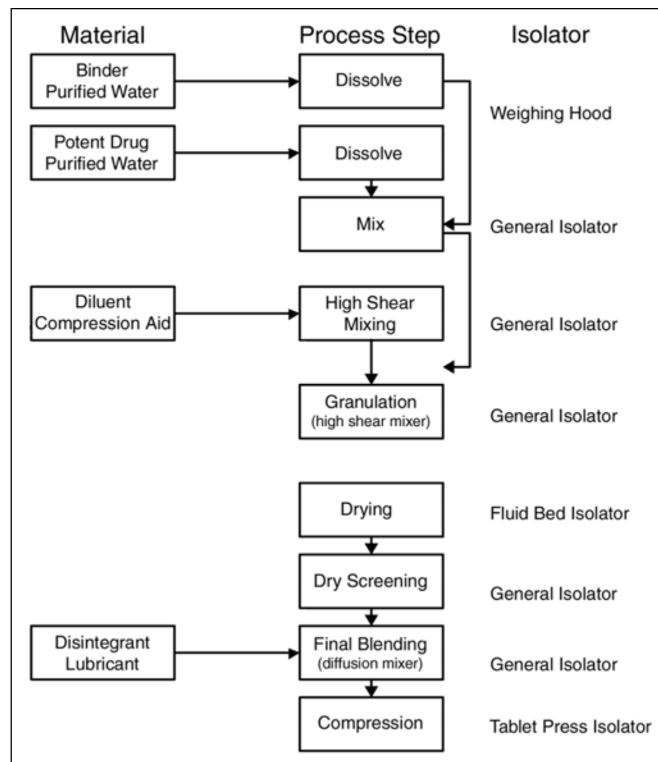

Figure 1. Typical wet granulation process using containment isolators.

2. flexibility for using lab for both potent and non-potent compounds

3. ability to work on a scale of 200 grams to 2 kg

4. ability to adopt new process equipment into the lab without redesigning containment practices

5. allow development on compounds with an OEL on the order of 0.1 micrograms/cubic meter of air

Strategy Development

A discussion of how our containment strategy evolved is informative since it identifies the approaches that were evaluated and abandoned due to their impracticality.

Our first generation concept was to construct a down draft booth that would be used in conjunction with PPE. It was felt that this would be a quick solution for handling potent compounds; however, based on achievable particle capture, this approach would not be useful for compounds with OELs of 50µg/cubic meter or below without using PPE. When the operation was complete, the entire laboratory potentially would have to be cleaned, and we would need to engineer a means of entry and exit into the lab for workers to safely remove their PPE.

The second generation approach was adopted to decrease our reliance on PPE and to minimize the need to clean a large laboratory space upon completion of an operation. We envisioned that all work would take place in a HEPA filtered lab fitted with airlocks and mist showers to contain the material within a smaller lab space. This would allow personnel to exit and then remove their PPE safely. All material transfers and dust generating operations would be performed in a glove box within the HEPA filtered laboratory. One large glove box

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would accommodate the operations of weighing active drug, granulating, milling, blending, and tableting. An initial cleaning of residual powder would be performed inside the glove box and then the equipment would be removed for final cleaning and breakdown during which lab personnel would be wearing PPE. As we worked through the logistics of this approach, several problems were identified. First, the concept that one glove box could support all of the equipment in a standard wet granulation process was impractical. The ergonomics associated with operating and cleaning a tablet press, a high shear granulator, a mill, a fluid bed granulator/dryer/coater, etc., were unique enough that one glove box could not accommodate all of these operations. Several stopping points would have to be designed into the usual work flow of the granulation process to clean equipment, move it out of the lab, and pull new equipment in. Depending on the OEL of the drug being processed, this movement of equipment in and out would necessitate a cleaning of the entire laboratory prior to equipment change over. These potential stopping points in the process to clean the lab and move equipment in and out contradicted our preferred work practice of cleaning after completing the entire manufacturing process.

Our third and final concept was to contain the potent compound at source in the equipment. We developed an isolator system, which included a HEPA filtered air design component such that all of the engineering containment controls would be designed into the isolator and not into the laboratory as in our earlier approaches. All material transfers would take place in a closed environment, either inside the barrier isolators or within a HEPA filtered weighing hood. This allowed the equipment to be operated in normal laboratory space and did not require air locks and exit showers.

Figure 2. Tablet press isolator.

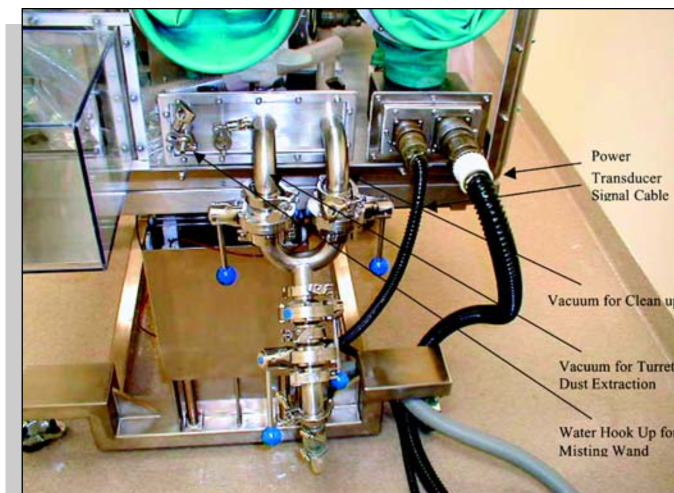

Figure 3. Tablet press isolator hook ups.

Description of Equipment and Isolators

Figure 1 depicts a typical wet granulation process for producing pharmaceutical tablets. The process is a series of weighing, mixing, granulating, drying, and compression operations all of which are contained in isolators or performed inside a HEPA filtered weighing hood. No material transfers take place outside of a HEPA filtered environment. There are a total of three isolators and a weighing hood. The weighing hood is connected to a HEPA filter and is used to weigh out the active ingredient, and to dissolve this material in water before being added to the binder solution. The general isolator is designed to contain multiple pieces of equipment one at a time. It is used for operating an oscillating mill, a high shear co-mill, and a high shear granulator. In addition, it can be used for charging and discharging mixing totes, that once loaded, can be cleaned, removed, and mixed in the open lab using a drive unit that is not contained. The fluid bed isolator is used to operate a bench top, fluid bed unit that can be used for granulation, drying, and Wurster coating. The third isolator is dedicated to operation of a bench top 10 station instrumented rotary tablet press. All of the isolators are complete with HEPA filters that re-circulate air back into the isolator with a small amount of the filtered air being vented into the room to keep the unit under negative pressure. For the purpose of this article, we will focus on describing the process by which tablets are made inside the containment isolator dedicated to the tablet press. Ergonomically, this is the most challenging operation to achieve inside an isolator and illustrates all of the handling practices used throughout a wet granulation process using all of the isolators.

Operation of Tablet Press Inside Isolator

The first step is to tool up the press as needed, connect the electrical cables, misting wand, interior vacuum hose, and transfer all materials required for compression into the isolator at this time. The tablet press isolator is shown in Figure 2. If an isolator panel has been removed, it is more convenient to tool up and make all connections prior to reinstallation of the panel. Once this isolator panel has been reinstalled, the Ultra Low Penetration Air Filters (ULPA) equipped vacuum is connected to the isolator manifold - *Figure 3*. Sealed polyeth-

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Figure 4. Press isolator magnehelic gauge.

ylene sleeves are installed on the bag out ports. Once these installations are complete, the isolator is turned on and the chamber air pressure is checked via a magnehelic gauge located on the front panel - *Figure 4*. This ensures the unit is sealed and not leaking. To start the tableting operation, the powder hopper is filled with granulation and the manifold is adjusted to turn on the vacuum for local dust collection within the tablet press. The tablet press force monitoring system is turned on and the press is started using the externally mounted press control panel - *Figure 5*. The vacuum is adjusted for the proper amount of turret dust extraction using a butterfly valve connected to the isolator manifold. The isolator chamber air pressure is adjusted to compensate for the turret vacuum by adjusting a slide gate valve located on top of the isolator - *Figure 6*. Initial tablet samples are collected by passing tablets out the tablet chute directly into a polyethylene bag for evaluation of tablet weight, thickness, and hardness. The press is then adjusted as needed and granulation can be added to the hopper as required by filling from inside the isolator or bagging material in from the outside via the sealed polyethylene sleeve located just above the hopper. When compression is complete, the product can be removed through a bag out port or through the pass through chamber - *Figure 7*. The tablet press and isolator are now ready for cleaning.

Cleaning Strategy

The term cleaning means to reduce the concentration of the active ingredient on surfaces of the machine and the enclosure to an established acceptable level. Cleaning is divided into deactivation and cleaning. Deactivation is the operation that is performed to reduce or immobilize the potent compound to the point that the material cannot produce an airborne concentration exceeding the exposure guideline for the compound. This is accomplished by a number of steps and should be validated for individual compounds because each has different characteristics in terms of particle size, solubility, density, surface characteristics, etc. The validation of cleaning is required for the protection of employees when working with potent compounds.

Description of Cleaning Process

After processing is complete, an initial vacuuming (ULPA filtered Vacuum) is performed to remove gross powder. Parts routinely cleaned in a sink can be "bagged-out" for cleaning. These bags are opened in the sink under water to minimize dust exposure. Larger pieces of the equipment are cleaned inside the isolator by wiping first with a cleaning solution in which the compound is soluble, followed by rinsing with water. Based on the sampling results described later, a misting wand was attached to the manifold for a direct supply of water. For hard to reach places a series of special tools such as squeegees are useful. Testing of the deactivated equipment inside the isolator is routinely performed as part of the validation process that will be described later. In the case of non-GMP operations, if the deactivation step is being used as a cleaning step, a final rinse may be used. All deactivation materials are bagged out of the isolator and disposed of in a safe manner. Once the unit has dried, a visual inspection is conducted to determine if any visible powder can be detected. If the compound is highly potent at levels of less than one microgram, it is good practice to collect a swab from several locations within the enclosure and have it analyzed to determine that the potent compound is not present above the exposure limit before opening the isolator.

Once the isolator has been cleaned, it can be opened and the equipment can be further cleaned if GMP cleaning clearance is needed to release the equipment prior to the production of a

Figure 5. Tablet press controls.

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Figure 6. Tablet press isolator slide gates for controlling isolator air pressure differential.

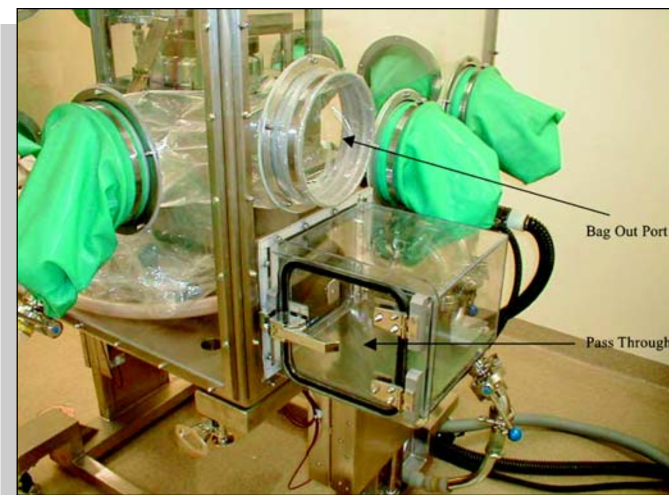

Figure 7. Tablet press isolator bag out port and pass through.

future GMP batch. Such cleaning can be performed in accordance with the standard operating procedures for a particular piece of equipment.

Validation

Our approach has been to use lactose as a surrogate for the drug in the first round of validation experiments. Lactose was selected due to its dustiness and the availability of sensitive analytical methods. The low detection limit allowed sample collection intervals to coincide with the normal work activities: set up, compression, tablet testing, and cleaning. Prior to safety batch operations, background samples were collected in the lab during routine activities. During safety batch operations, personal sampling pumps equipped with 25mm glass fiber filters were placed on both operators, downstream of the HEPA filter exhaust from the isolator and next to the ULPA filtered vacuum. The filters were changed out at various stages of the process to quantify exposures specific to each part of the process. Upon completion of testing, the filters were sent to an independent testing laboratory for HPLC analysis. The personal sampling results were used to generate eight hour Time Weighted Average (TWA) exposures. These TWA exposures were then compared to the OEL established for the compound of interest. In addition, a P Trak ™ Ultra fine Particle Counter was used to identify possible points of contaminant release. Upon completion of the cleaning operation, a sample was collected inside the isolator.

The initial personal and area samples results are shown in Table C. Measured concentrations ranged from 0.12 µg/m^3 to 4.4 µg/m^3. Using the particle counter, leakage from the ULPA filtered vacuum at a level of 19,000 particles/cm^3 was measured at one location at the filtered exhaust. The leak was a likely contributor to the higher than expected personal exposures. As a result, the ULPA filter was changed and tested again prior to use in the next batch. The sample collected inside the isolator after cleaning had measurable levels of lactose (0.44 µg/m^3). To reduce residual airborne dust, the cleaning procedure was revised to include covering the press with a polyethylene bag after the press was cleaned and misting the interior of the isolator using a misting wand.

The next simulation batch was sampled as described previously. Results from air monitoring are shown in Table D. Personal sampling results ranged from 0.21 µg/m^3 to 0.91 µg/m^3 for Operator 1 and were below the limit of detection for Operator 2. The highest concentration measured for Operator 1 occurred during cleanup. While collecting this sample, the seal on an out port bag ruptured possibly resulting in a significant release of lactose. Equipment was heat and tie sealed when being bagged out of the isolator to prevent bag ruptures in all future batches. Area samples were below the OEL with the exception of one sample collected near the vacuum (2.3 µg/m^3).

Due to the continuing high concentration of lactose measured near the vacuum, we replaced the ULPA filtered vacuum and isolated the vacuum from the lab. Exposures were higher for Operator 1 who removed the tablets from the isolator and performed tablet testing in the vented weighing hood than for Operator 2 who worked at the isolator only - *Table D*. Due to these differences, tablets were removed from the isolator in bags or covered weigh boats. In addition, PPE was upgraded to double gloves and sleeves for tablet testing, and the operator performing testing removed and bagged the outer layer of PPE inside the hood before taking his hands out of the hood. Results from the third validation batch are shown in Table E. These results were all below the detectable limit of the lactose assay. The experiment was replicated to demonstrate repeatability and similar results were obtained and are shown in Table F.

Discussion/Conclusions

The primary objective of this work was to develop an approach that would provide adequate worker safety during small scale processing of potent compounds classified as Category 3. The approach was to include a strategy for protecting both the operators working directly with the potent materials and other laboratory personnel throughout the facility. The approach described above provides processing capability under the high level of worker protection appropriate for Category 3 while allowing processing in general laboratory space. This feature minimizes the need for costly facility modifications such as airlocks, showers, and changing rooms, which would be required to contain material to a given laboratory and effectively protect the surrounding facility in the absence of a barrier isolator. While this approach minimizes the need for worker PPE for processing most Category 3 compounds, one can still work with the more toxic Category 4 materials by adding the

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Location	Concentration $\mu g/m^3$	TWA $\mu g/m^3$
Area Sample Background	<0.12	N/A
Area Sample Background	<0.098	N/A
Operator 1 tabletting and testing	1.4	0.33
Operator 1 tabletting and testing	<0.15	0.33
Operator 1 tabletting and testing	<0.13	0.33
Operator 1 cleanup	0.82	0.33
Area inside enclosure post clean up	0.44	N/A

Table C. Lactose validation batch 1.

appropriate PPE and administrative controls as additional protection. Lastly, the use of isolator technology is consistent with the OSHA directive to minimize reliance on PPE controls and to maximize the role of engineering controls as the main basis of worker protection when handling potent compounds.

Barrier isolation is not an instantaneous fix for handling potent compounds. The proper design of the isolator for a particular piece of equipment or process is a nontrivial task. It requires an intimate knowledge of the manufacturing process and equipment operation. The development of each isolator has been a multi step process. A detailed mock-up of the isolator to determine the optimal configuration of gloves, sample ports, and equipment utilities is needed. This mock up also allows the user to address ergonomic issues of the process. Evaluation of each stage of the design by skilled operators with detailed knowledge about the process is crucial to developing an effective isolator that is easy to use. Identification of the optimal location of controls to minimize exposure of electronic and pneumatic controls required considerable consideration and evaluation of the functional operation of the equipment to obviate cleaning and contamination issues. This ensured that the equipment was safe for operation outside of the isolator using Category 1 and 2 compounds. Next, after the design was structurally sound, a prototype isolator was constructed. Performance testing and validation were then performed with lactose to determine the best operating practices to minimize contamination and maximize ease of use prior to working with potent material. As more experience was gained working with the isolator, minor modifications were made to the prototype to arrive at the final working configuration.

The use of an easily detectable surrogate compound (lactose) during the initial stages of the isolator validation proved very useful. We were able to test the integrity of the isolators as well as the adequacy of procedures for operating the equipment and handling of potent materials without operator exposure. After achieving acceptable air monitoring and cleaning level results using lactose, active batches may be tested using the procedures developed with the lactose batches.

During initial batch development, workers should be in PPE and the room closed for use until containment of the compounds of interest could be demonstrated using analytical results from swabbing the equipment, including areas outside of the isolator for the potent compound. This type of validation procedure should be completed for each new compound used inside the isolator.

It is important to note that the design of any containment system for working with potent compounds should not be "cookie-cutter" approach. The system must be designed with the needs of the operators, the existing facility, and the process

Location	Concentration $\mu g/m^3$	TWA $\mu g/m^3$
Operator 1 tabletting and testing	0.27	0.24
Operator 1 tabletting and testing	0.21	0.24
Operator 1 cleanup	0.91	0.24
Operator 2 tabletting and testing	<0.11	<0.04
Operator 2 tabletting and testing	<0.12	<0.04
Operator 2 cleanup	<0.059	<0.04
Area sample by vacuum	2.3	N/A
Area inside enclosure post cleanup	<0.14	N/A

Table D. Lactose validation batch 2.

Location	Concentration $\mu g/m^3$	TWA $\mu g/m^3$
Operator 1 tabletting and sampling	<0.15	<0.04
Operator 1 tabletting and bagging	<0.16	<0.04
Operator 1 tablet testing	<0.15	<0.04
Operator 1 clean up	<0.071	<0.02
Operator 2 charging and operating press	<0.15	<0.04
Operator 2 tabletting and sampling	<0.15	<0.04
Operator 2 during testing (away from hood)	<0.17	<0.04
Operator 2 clean up	<0.071	<0.01
Area sample by vacuum	<0.13	N/A
Area by vacuum during clean up	<0.11	N/A

Table E. Lactose validation batch 3.

Location	Concentration $\mu g/m^3$	TWA $\mu g/m^3$
Operator 1 tabletting and sampling (bags)	<0.097	<0.07
Operator 1 tabletting and sampling (weigh boat)	<0.095	<0.07
Operator 1 tablet testing	<0.12	<0.07
Operator 1 tablet testing	<0.092	<0.07
Operator 1 clean up	<0.082	<0.07
Operator 2 tabletting and sampling (bags)	<0.1	<0.06
Operator 2 tabletting and sampling (weigh boat)	<0.1	<0.06
Operator 2 assisting tablet testing	<0.13	<0.06
Operator 2 assisting tablet testing	<0.1	<0.06
Operator 2 clean up	<0.089	<0.06
Area by vacuum	<0.047	N/A
Area by vacuum during clean up	<0.084	N/A

Table F. Lactose validation batch 4.

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in mind. Advantages and disadvantages exist for all of the containment options available. Not all processes are amenable to every containment technology. As indicated previously, barrier isolators were only one of the approaches considered for the containment of potent compounds. Several others, as discussed above, were evaluated for our particular situation, and several design iterations were completed before we selected this particular solution for our facility. For instance, we found containment of potent material in an existing tray dryer using isolators to be a difficult process to design while allowing for flexible and convenient operation and cleaning of the dryer. Table G outlines some of the advantages and disadvantages for the barrier isolator systems described in this work. After evaluating the level of protection needed, the ability to contain potent materials at the source, and the flexibility desired, we concluded that an isolator system was the best alternative to meet our particular needs.

Advantages	Disadvantages
• Reduces or eliminates reliance on PPE for worker protection • Does not require extensive facility modifications • Achieve extremely low (sub-nanogram) concentrations of potent materials • Reduces scope of necessary cleaning and facility/personnel monitoring • Isolators are mobile, allowing for efficient use of existing laboratory space • Complies with OSHA requirements for engineering controls as primary source of worker protection	• Greater degree of up front design work for proper equipment operation • Increased ergonomic difficulty working inside an isolator as compared to working in an open environment wearing PPE alone.

Table G. Advantages and disadvantages of barrier isolators.

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...the use of isolator technology is consistent with the OSHA directive to minimize reliance on PPE controls and to maximize the role of engineering controls as the main basis of worker protection...

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This article explores how better relationships between customers and engineering design companies result in improved quality, better performance, and a cost effective process.

The Changing Face of Engineering for Major Capital Projects

by Joseph R. Hettenbach, PE

Over the last several years, there have been some significant changes in engineering for major capital projects. The paradigm has been shifting as a result of changing attitudes and organizational structures, the needs of customers, and the major engineering design firms who service them. The partnering concept is now very much in vogue although somewhat limited in its application. The intent of this article is to explore where we have come from, what we are getting into, and where we seem to be heading in our relationships with engineering design firms.

A good working knowledge of the design process traditionally utilized for major capital projects was developed, working closely on several projects with design personnel from an engineering design company. Six projects were executed over a 12-year period, including five years as a resident in their facilities, and extensive work in the field. The scope of this involvement included management of the process design function for a number of projects ranging from $25 to $300 million, including new plants and upgrades for bulk pharmaceutical manufacturing; and a state-of-the-art research development complex encompassing a pilot plant, kilo lab, prep labs and laboratories. Insights into working relationships between customers and engineering design companies and changes we have experienced in our collaborations are presented.

In the 1980s, the working mode between clients and engineering companies could be characterized as strained. We didn't always do the best job defining the scope of our projects. The net result was that scope changes translated into higher design costs, schedule delays, and increased revenues for the engineering companies. Our experience shows us that this has been true for process control engineering firms as well - where the "dynamic scope" model (or the perceived moving target) generates higher design costs. The interaction between the two "opposing parties" was iterative in nature, and it was very difficult to manage the program from the client's side. As an example, while working at a big engineering company's "house" at the beginning of the first major project we did with this firm in 1987, a situation developed in which the number of design change orders was escalating and

Figure 1. Top of a reaction vessel - digital photograph of a plastic model.

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threatening the stability of the project. We engaged in some very heavy negotiating to come up with a mutually agreeable way to corral the design activities and better keep the cost in line with expectations. Of course, the development of a "hold back list" helped save the day. This list identified a number of project elements, which could be deferred without significantly affecting the mission of the project. We completed detailed engineering for these elements, but held up implementation until we were satisfied that sufficient funds would be available to include them in the construction phase. We have successfully incorporated this tactic into our strategy for several projects following that first one.

Having resolved those issues during the front end of that first major project, things seemed to be going smoothly as we were digging into the details. However, we were quite surprised to get some strong direction from our project manager to get more involved with the designers on a day-to-day basis.

We took steps to implement the directive, and it was at that point that we started to become more interactive with the designers. At first, there was quite a bit of resistance from their side, but in time they began to see the wisdom of it. We had a small staff in residence varying from 6 to 12 people from our corporate office and one of our operating facilities, and undertook a number of initiatives.

- We worked with the designers much more closely to make sure they satisfied our needs.
- We increased the level of our involvement during the detailed design.
- We developed relationships with the key design personnel, typically layout/piping design people.
- We concentrated on communications and the development of "win-win" approaches, and built trust in a team building manner.

This partnering/team approach has worked quite well on later projects, but there are some pitfalls. The project organization needs leadership and direction to keep the partners in tune with the program, and to most efficiently use the resources at hand.

In the early 1990s, we once again engaged the same engineering design company to do a much larger project. This time around, we were more experienced, better prepared, and managed our side of the program differently.

- We "demanded" to have certain key individuals in the respective design disciplines as part of their team. This helped build our confidence since it would effectively short-circuit the project learning curve.
- We developed and handed over more refined General Arrangement drawings (GAs) and Process and Instrumentation Diagrams (P&IDs) to the engineering design company than we had in the past. GAs show the details of equipment and floor layouts. P&IDs show the process equipment, piping, instrumentation, and the interconnectivity with other piping and equipment.
- We started out by taking the position that this project was very similar to the previous one that we had done together, and therefore, we were primed to save lots of money on the design. However, we performed analyses with the cooperation of the engineering company's key piping/layout lead person to assure ourselves that we were on the right track. As a result of these analyses, we came to an agreement and understanding regarding those specific elements appropriately selected from the earlier project that we could safely use for the current project. We effectively avoided the trap of maintaining the stance that "this job was the same as the other job," which we all know is never quite the case.
- We had a much larger staff in residence this time around (up to 18 engineers) and mostly avoided the anguish of managing significant change orders by having a system in place to deal with the changes.

The cost performance on this second project was very good with both sides benefiting by the virtues of an incentive program developed between the parties. We negotiated a metric of average man hours for design per equipment piece based on an equipment list agreed to by both parties, and our past experiences (historical data). Good performance resulting in fewer man-hours per equipment item was rewarded as savings shared by both parties. This translated into lower costs for us, and higher profits for the engineering design company. At the same time, our working relationship was improved in the process. In many respects we were operating as a partnership before "partnering" became popularized in the project engineering business.

We developed a plastic detailed scale model for this project, which incidentally was the last one done by this company. We were told that this was one of the best models they had ever built, and one of their best projects (see Figure 1).

However, 3-D computer design (see Figure 2) was on the horizon and the use of a plastic model was becoming history, which was disappointing to those seasoned in the use of the plastic model tool. For the record, use of the plastic scaled model had several advantages.

- It was much easier on the eyes and the faculties than its computer 3-D counterpart.
- It allowed the project team to view the process facility design development from an overall perspective.

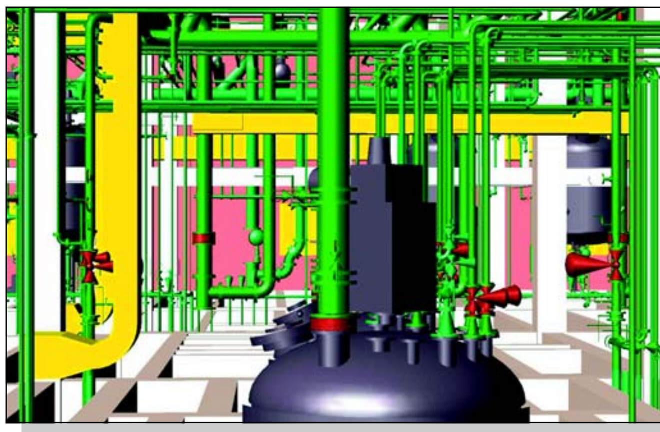

Figure 2. Top of a reaction vessel - computer graphic 3-D picture.

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- It provided a constant ready reference, and was very user friendly for lengthy reviews by relatively large groups.
- The plastic model was not subject to computer system upsets/failures, and it was useful to construction personnel for visualization and logistics.
- It provided a vehicle for training of operating personnel, and ultimately provided a nice showcase for the entrance lobby of the facility.

With regard to costs of the different methods versus benefits achieved, no cost comparisons or detailed performance comparisons are included in the scope of this article. The ½ inch scale plastic model is rarely used now by engineering companies, and there are many variables that affect the cost of applications using the various 3-D computer design systems.

We followed up with this same company on a number of other projects, enjoying the fruits of our partnership. We set some records along the way for metrics such as piping manhours per pipe line using the evolving 3-D computer design tools, but the climate was changing. We, as clients, were subject to increasing pressures to reduce costs. Having decided to no longer employ in-house detailed design engineering resources, we were unable to muster the numbers of qualified engineers we had become accustomed to, and we were less than comfortable with regard to the makeup of our project teams. In addition, the retirement of some key personnel and the lack of training of their replacements had taken a toll on the process engineering capabilities of this particular company, and others we were dealing with. A number of smaller engineering companies entered the arena, some with very good process expertise and much lower turnover of personnel.

It was becoming increasingly clear that there was a need to change our approach, and for the engineering companies to consider changing the way they do business. This was not a small chore from our side with limited resources. On the other hand, the prospects of transforming the traditional "machine works" operations typical of the large engineering houses to be better in tune with our needs in the shorter term, did not look too promising.

The use of 3-D computer design systems was sold on the premise (actually the promise) that the design process would be much better and cheaper than the manual systems. In practice, based on some of the earlier applications of this software tool, the costs of the 3-D designs were at first higher when compared to the use of a plastic model for design execution. However, the 3-D approach offered many benefits in the construction phase.

- The 3-D design provided machine drawn isometrics.
- The "clash check" tool helps to avoid (minimize) interference in the field.
- The 3-D software provides a readily available bill of materials.
- The ability to produce plans/orthographics and elevations/sections on demand is useful to improve visualization and support construction activities.

The 3-D computer design systems have been in use for more than 10 years, and many of the companies with significant experience using 3-D design can now report overall project cost savings (Total Installed Cost) using this tool when it is applied properly. Re-work during construction due to design errors on many projects has been generally reduced to below 1%, which translates into considerable cost savings. However, there are a number of issues which still need to be resolved in the application of this tool.

A few years ago we challenged a number of engineering companies to address our concerns with 3-D computer design systems. We asked these companies to come up with ways to allow us to mimic a semblance of the "control" we enjoyed using the plastic model.

In practice:

- Many people have trouble visualizing what they're shown on the screen.
- Depth perception is not nearly as good, compared to working with the plastic model.
- It also is difficult (tedious) to spend the extended time periods required for design reviews, and cumbersome to involve larger groups for such reviews.
- Of course, larger screens and "layered" approaches help, but these features alone can not solve all the problems associated with the use of this high-powered tool.
- Clients don't always take the time to acquire training in the 3-D design system they select for their project execution.

Interestingly enough, from our perspective, none of the engineering companies has met the challenge - to make the 3-D tools more client user friendly. In the spirit of "partnership," ***we***, the clients, should work with these companies to improve ***our*** situation.

It also is fair to say that the engineering companies are just beginning to take more advantage of the potentials the 3-D computer design tools offer. One example of this is the use of the "intelligent P&ID's" tool which should improve the overall design approach by providing a more disciplined structure to develop the design. The tool also offers means to "program in" detailed information on equipment, instruments etc. which will be invaluable during design, construction, commissioning, qualification, and validation. While this is a good, positive development, ***we*** have a lot of work to do ***together*** with the engineering companies to realize the quality improvements and cost reductions possible with this tool. Beyond 3-D design, other tools that can enhance the design process are the process simulation models, which some operating and engineering design companies are applying to projects during the conceptual development phase.

There are a number of common mistakes made on 3-D design jobs.

- The first and most basic is the lack of a well defined scope by the client along with an appreciation for how much money the client's management will support for the total project cost.

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- The second is starting the detailed 3-D model before having a sufficient "body of information" in hand. Optimally, this would include:
  - fairly well developed P&ID's
  - GAs including equipment and floor layouts
  - piping specifications IFD (Issue for Design)
  - equipment and instrument specifications and physical dimensions suitable to model
  - preliminary structural design (main support steel and columns)
  - heating, ventilation and air conditioning (HVAC) including major duct work design
  - electrical design
  - piping routing studies for process and utility services
- The third is the lack of a proper level of attention afforded by the client to the 3-D design during its development.
- The fourth is the tendency to go out too soon with construction bid packages (before the 3-D design is essentially complete) due to scheduling pressures.
- An additional aggravating factor is the absence of participation by representatives of the construction management team and the construction contractors in the model development process.

All sub-par 3-D designed project performances can be traced to any or all of these mistakes. Analysis of the record indicates a wide range of 14 to 55 piping design man-hours per pipe line as reported for a number of different projects of different sizes. A close examination of these projects indicates that the better, more efficient ones were those with stronger front-end efforts. This holds true for all of the 3-D computer design packages that are commercially available.

While working on the conceptual phase of a major pilot plant project recently, it occurred to us that there was a way to improve our ability to "manage" a project with less people resources, and at the same time reduce the overall design costs. The key is to "front-load" the project with more detailed work done during an extended preliminary engineering phase using a smaller team to best prepare for the detailed phase (before "letting all the horses out of the barn"!). The elements of such a program could include:

- Developing a solid scope definition as a team with the engineering design company.
- Ideally, following a solid scope development, a number of items should be developed during the preliminary phase to a higher quality level to feed a highly efficient detailed phase.

This would include:

- P&IDs (subject to hazard and operational analysis, and relatively conceptually change free)
- GAs (layouts) - plans and elevation studies (to set floor heights)
- equipment list and specifications (sufficient to model)
- process controls (systems and instrumentation with potential impact)
- instrument list and specifications (sufficient to model)
- piping specifications (issued for design and ready for input to the model)
- a structural design with conservative column and main beam sizes
- HVAC (including major duct routing and equipment space allocation), and electrical designs
- A 3-D study model program, including reactor head nozzle configurations and piping routing studies (keying in on main headers and sub header distributions) for: process (including the special cases of manifold rooms/transfer station "panels"), solvents, drainage, utilities, and venting systems. This is done to assure the facility is the right size, constructability has been considered, and costs are well understood.
- Details of process cleaning, materials movement, containment, and solids charging and discharging (packout) strategies worked out since these effects significantly impact the layout.

This should translate to fewer changes and significant overall project design cost reductions and schedule improvements. To the extent possible, the construction management and contractors, as well as operations, maintenance, Environmental, Health & Safety (EH&S), quality assurance, and other interested groups from the client's side should be involved as early as possible to get their buy-in and support. This in turn also will minimize changes, cost increases, and schedule upsets down the road. Delaying commencement of the detailed phase by not committing too soon to a full blown 3-D program can actually save time, money, and *stress* overall. Optimally, a 3-D study model would be constructed and a number of studies performed at the right time during the preliminary phase (along with the P&IDs, GAs and the development of the other documents listed in the "body of information" above). This would be done to deliver a Basis Of Design (BOD) package to feed the detailed engineering phase.

While working recently on the front end of that same major pilot plant project, a piping designer on contract working in our office (with 40 years of experience) was intrigued with this "strong front end" approach. This designer still works by hand and at times dabbles with AutoCAD for 2-D work, but the 3-D computer design tool is beyond his reach as he winds down his career. He told us that this was the way they used to do

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projects, and that this approach had been abandoned along the way although he could not understand why that happened. Indeed, this puzzles this writer as well. We surely can learn a lot by listening to the designers, who are dedicated to their craft, and we can improve our performance by sticking with what works well. We don't always find all the answers by application of new technologies, and should not lose sight of the basics.

The potential of the 3-D tool for piping design will be achieved, providing that solid piping designers (not just computer technicians) are applying that tool. There is an analog in process control design, where properly trained chemical engineers improve the quality of the programming effort.

With regard to how the clients can better "manage" the 3-D design effort, there is no substitute for experience, and working with known designers. Short of any revelations in this area from the engineering companies, the only practical way of reasonably staying on top of the design is to have confidence in the designers who are applying this powerful tool.

In the limit, it would be great if we could use the same designers all the time to the extent they are made available. This would avoid (reduce) learning curves and further build confidence. This is part of the logic of the "partnership." On the other hand, we have to keep the engineering companies cost down and our management assured by competitively bidding out detailed designs, which we continue to do.

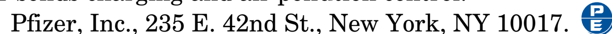
With regard to our project resource constraints, we have had issues, at times, with process engineering expertise with some of the larger engineering companies. We have, on a few occasions, evaluated and used some smaller companies to do conceptual front-end studies and some preliminary engineering packages. Further partnering the smaller company with the larger company for the detailed phase offers potential improvements in more focused coverage as well as challenges from a project management perspective (more players to be managed). Of course, the larger engineering companies should work to strengthen their process engineering and conceptual design capabilities. This would improve their position, and better suit our needs.

It would be helpful to develop standard approaches within a client company for managing the design of major capital projects. There is experience and lessons learned from major projects executed throughout a company, which can be learned from, here in the US as well as at locations throughout the world. Best Practice standards, developed by the clients, should be integrated into the design process. We also should strive to maintain a good process engineering pool to support the process design function and work with the engineering design companies. With regard to developing our relationships with engineering design companies, it is essential to maintain a regular dialog between the parties so that we can improve our performance while the design business changes. Openness and cooperation are the keys with quality and cost effectiveness the main goals.

It has been observed that the larger engineering companies are prone to building up and staffing down in response to market needs. This pattern is disruptive, a "morale" killer for the engineering design firm employees, and takes away from the positive effects of training programs, which would be more beneficial if they had a more stable work force. It is postulated that the implementation of more timely, streamlined, and cooperative approaches, along the lines of what has been presented here, will help stabilize the rosters of the bigger companies. This in turn would benefit the clients. By working better together, ***we*** can be more cost effective, have more fun at it, and share in ***our*** successes!

About the Author

Joseph R. Hettenbach is a Principal Engineer - Process, for the Pfizer Global Engineering group in Pfizer, Inc. He has a BS and MS in chemical engineering and an MS in environmental engineering, all from Manhattan College. He is a licensed Professional Engineer in New York state. He has served on the steering committee for the Graduate Chemical Engineering program at Manhattan College, and contributed to the development of their undergraduate environmental program curriculum. He has served as a process design manager on a number of major Pfizer projects, responsible for interface on the design floor with the design disciplines of the Engineering Design companies involved. This work included detailed scope development, process, and facility design. He has more than 30 years of experience, concentrating on process engineering; process development; project management; environmental, health and safety. He has been instrumental in the introduction of a number of new technologies as first time applications in the US pharmaceutical industry, including novel approaches for solids charging and air pollution control.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These acronyms were compiled to help engineers understand basic terminology as it applies to the relatively new biotechnology industry, as well as the more established pharmaceutical industry.

The complete glossary is available on ISPE's Web site www.ispe.org. It will include definitions of terms used in biology, chemistry, HVAC, manufacturing processes, medicine, materials, metallurgy, regulatory concerns, water treatment, and welding.

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Pharmaceutical Glossary: C-E

by Michelle M. Gonzalez, Engineering/Quality Manager, Fluor Daniel

- C -

Calcium - A metallic dyad element of a lustrous yellow color, symbol Ca, atomic number 20, atomic weight 40.09, melting point 810°, often found in water usually as dissolved calcium carbonate, chalk ($CaCO_3$). Soluble in water, it causes hardness and subsequent scaling.

Calcium Carbonate Equivalent - The value obtained when salts are calculated in terms of equivalent quantities of calcium carbonate. This is a convenient method of reducing all salts to a common basis for comparison.

$$\text{ppm } CaCO_3 = \text{ppm ion X} \frac{\text{Equivalent weight of } CaCO_3}{\text{Equivalent weight of ion}}$$

Where ion = magnesium, calcium, or other elements that contribute to hardness.

Calibration - A comparison of a measurement standard or instrument of unknown accuracy to detect, correlate, report, or eliminate by adjustment of any variation in the accuracy of the unknown standard or instrument.

Calibration (ICH API defintion) - The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Calorie - Any of several approximately equal units of heat, each measured as the quantity of heat required to raise the temperature of one (1) gram of water by 1°C from a standard initial temperature, specially from 3.98°C, 14.5°C, or 19.5°C, at a constant pressure of one (1) atmosphere. Also called *"gram calorie"*, *"small calorie"*.

The unit of heat equal to 1/100 the quantity of heat required to raise the temperature of one (1) gram of water from 0°C to 100°C at one (10 atmosphere pressure. Also called *"mean calorie"*.

The unit required to raise the temperature of one (1) Kilogram of water by 1°C at one (1) atmosphere pressure. Also called *"kilogram calorie"*, *"large calorie"*.

Calorimetry - Analytical method that measures heat loss or gain resulting from physical or chemical changes in a sample. Differential scanning calorimetry compares the results of heating a sample to those for heating a reference material. For example, a method to measure the temperature at which the sample crystallizes, changes phases, or decomposes.

Cancer - The name given to a group of diseases that are characterized by uncontrolled cellular growth.

Capsid - The external protein shell or coat of a virus particle.

Carbohydrates - A large class of carbon-hydrogen-oxygen compounds that includes the sugars and their polymers (mainly starch, glycogen and cellulose). Most carbohydrates are produced by photosynthesis in plants. They are the major food compounds for both plants and animals. One group of carbohydrates, cellulose, is the primary structural material of plants.

Carbon Filter - A vessel loaded with activated carbon and used to remove organics, chlorine, tastes, and odors from liquids, operating on the principle of adsorption.

Carbon Thickness - A measurement of surface organic material. Carbon thickness values typically range from 5 to 20 angstroms (Å). Significantly contaminated surfaces can show surface carbon thickness of 20 angstroms (Å) or more.

Carbonate Hardness - That hardness in water caused by bicarbonates and carbonates of calcium and magnesium. If alkalinity exceeds total hardness, all hardness is carbonate hardness; if hardness exceeds alkalinity, the carbonate hardness equals the alkalinity. *(also see: Calcium)*

Carcinogen - A substance that causes the development of cancerous growths in living tissue. A chemical is considered to be a carcinogen if it has been evaluated by the International Agency for Cancer Research (IARC) and found to be a carcinogen or potential carcinogen, or if it is listed in the Annual Report on Carcinogens published by the National Toxicology Program, or if it is regulated by OSHA as a carcinogen.

Carcinogenic - Cancer-causing. Many agents that are carcinogenic are mutagens.

Carrier - A person who has a recessive mutated gene, together with its normal allele. Carriers do not usually develop disease but can pass the mutated gene on to their children.

Catabolism - The intracellular phase of metabolism involved in the energy-yielding degradation of nutrient molecules (for example, glucose to CO_2 and H_2O). Waste products are called catabolites. *(also see: Anabolism, and Dissimilation))*

Catalase - An enzyme that catalyzes the decomposition of hydrogen peroxide and molecular oxygen and water.

Catalyst - A compound that increases the rate of a chemical reaction without being consumed or changed. In the biosciences, the term *enzyme* is used. Enzymes catalyze biological reactions.

Cation - A positively charged particle or ion. *(also see: Ion)*

Cation Exchange - The displacement of one positively charged particle by another on a cation-exchange material.

Cation Exchange Resin - An Ion exchange resin, which removes positively charged ions (cations) by exchanging them for hydrogen ions.

Cavitation - A condition of liquid flow where, after partial vaporization of the liquid, the subsequent collapse of vapor bubbles can produce surface damage.

CBER - *(also see: center for Biologics Evaluation and Research)*

Center For Biologics Evaluation and Research (CBER) - The FDA successor to the Bureau of Biologics concerned with biologic drugs, and most importantly, with the new protein and peptide drugs emanating from biotechnology.

Center For Drug Evaluation and Research (CDER) - The successor to the Bureau of Drugs of the FDA concerned with all SVPs (Small Volume Parenterals), LVPs (Large Volume Parenterals), and non-biological drugs.

Certified Vendor Drawings - Drawings prepared by vendors for the fabrication of equipment, specialty components and skid mounted systems. These are certified as fabricated by the vendor and become the official document for the equipment involved.

CDER - *(also see: Center for Drug Evaluation and Research)*

cDNA - *(also see: Complementary DNA)*

Celsius - Of or pertaining to a temperature scale that registers the freezing point of water as 0°C and the boiling point as 100°C under normal atmospheric pressure. Also called "centigrade". The designation *Celsius* has been official since 1948, but *centigrade* remains in common use. *(also see: Fahrenheit)*

Cell - The fundamental unit of life. The living tissue of almost every organism is composed of these fundamental living units. Unicellular organisms, such as yeast or a bacterium, perform all life functions within the one cell. In a higher organism, a multicellular organism, entire populations of cells may be designated a particular task. The cells of muscle tissue, for example, are specialized for movement.

Cell Bank -

Master Cell Bank: The bank of cells, which contain the original unused mutated cells from which, the Manufacturing Working Cell Bank is taken. This is usually kept under lock with very limited access.

Manufacturing Working Cell Bank: The bank of cells derived from the Master Cell Bank, which are used to seed the fermentation manufacturing process.

Cell Culture - The *in vitro* propagation of cells removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirement; also used to refer to any particular individual sample. Usually, cell culture takes place in a bioreactor.

Cell Differentiation - The process whereby descendants of a common parental cell achieve and maintain specialization of structure and function. Muscle cells become muscle cells and bone cells develop. In humans all the different types of cells differentiate from the simple sperm and egg.

Cell Fusion - The fusing together of two or more cells to become a single cell. This technique has had important consequences in immunology, developmental biology, and genetics. For example, monoclonal antibodies are produced by fusing a spleen cell (producing an antibody specific for the antigen of interest) with a mouse myeloma cell to produce a hybridoma which has an indefinitely long life because of the myeloma component and which secretes a specific antibody. When a human cell is fused with a mouse cell, the human chromosomes are progressively lost from the resultant hybrid and by correlating the presence of proteins in the hybrid with the presence of particular human chromosomes, genes can be assigned to individual chromosomes.

Cell Lines - When cells from the first culture (taken from the organism) are used to make subsequent cultures, a cell line is established. "Immortal" cell lines can replicate indefinitely.

Cellulose - A polymer of six-carbon sugars found in all plant matter, the most abundant biological compound on earth.

Centigrade - *(also see: Celsius)*

Centimorgan (cM) - A unit of measure of recombination frequency. One centimorgan is equal to a 1% chance that a marker at one genetic locus will be separated from a marker at a second locus due to crossing over in a single generation. In human beings, one centimorgan is equivalent, on average, to one million base pairs.

Centrifugation - Mechanical means of separation based on differences in sedimentation rates due to differences in density between the suspended particles in the liquid.

Centrifuge - A centrifuge operates on the principle of centrifugal force, the inertial reaction by which a body tends to move away from a center about which it revolves. This technique is commonly used to separate solids from liquids or liquids of different densities. Centrifugal equipment is divided into two major types, sedimenters and filters:

1. **Sedimenters:** For sedimentation, batch and continuous centrifuges are available. There are three types of centrifuges for continuous sedimentation.
   a) **Disc:** constructed on the vertical axis, disc centrifuges are solid-bowl units. All are capable of separating liquids from solids, solids from two immiscible liquids and two immiscible liquids. Disc-stack centrifuges differ in their ability to handle different volumes of solids in the feed stream, and in the way that the separated solids are removed from the separation vessel: *solids-retaining*, *solids-ejecting,* and *nozzle-bowl separators*.
   b) **Decanters:** consists of a cylindrical settling section with a tapered end. Inside the bowl is a scroll conveyor that is driven usually at a slightly faster rate than the and peeler centrifuges, can separate almost any liquid-solid slurry. For continuous operation, there are pusher and conical centrifuges.
   a) **Pusher:** with a horizontal axis, the pusher centrifuge operates at a constant fixed speed. It has a perforated bowl, generally with a bar-type screen. One end of the bowl is open while the opposite end is closed with a reciprocating diaphragm, or disc, which rotates with the bowl.
   b) **Conical:** the *standard conical* centrifuge consists of a cone with a small closed end and a large open end to which is attached a coarsely woven drainage screen, topped with a filter screen or perforated plate. A compartmentalized casing surrounds the bowl. There are two variations of the basic conical centrifuge: the *tilting conical* centrifuge and the *conveyor conical* type.

Centromere - A specialized chromosome region to which mitotic or meiotic spindle fibers attach during cell division.

Certification - Documented testimony by qualified authorities that a system qualification, calibration, validation, or

revalidation has been performed appropriately and that the results are acceptable. Personnel certification is proof that a person has achieved a certain level of qualification.

CFR (Code of Federal regulations) Title 21 - The U.S. regulations that directly apply to biopharmaceutical development are contained in Title 21 parts **58** (Good Laboratory Practice for Nonclinical Laboratory Studies), **210** (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General), **211** (Current Good Manufacturing Practice for Finished Pharmaceuticals), and **600** (Biological Products: General).

Parts **50** (Protection of Human Subjects), **56** (Institutional Review Boards), and **312** (Investigational New Drugs) apply to critical trials.

Part **11** provides criteria which will consider electronic records to be equivalent to paper records and electronic signatures to be equivalent to traditional handwritten signatures. *(also see: cGMPs (current Good Manufacturing Practices))*

CFU (Colony Forming Unit) - A measure of the number of bacteria present in the environment or on the surfaces of an aseptic processing room, measured as part of qualification and ongoing monitoring. Also applied to the testing of purified water samples.

cGMPs (current Good Manufacturing Practices) - *Current* accepted standards of design, operation, practice, and sanitization. The FDA is empowered to inspect drug-manufacturing plants in which drugs are processed, manufactured, packaged, and stored for compliance with these standards. *(also see: CFR (Code of Federal Regulations) Title 21)*

Change Control - A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated process's status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

Change Over - The program by which a processing area is cleared of supplies and components used in the manufacture of a previous product and then readied for production of a new product. This often includes parts change over and/or special cleaning to eliminate cross-contamination.

Channeling - Cleavage, cracking, and furrowing of a resin bed due to resin age, a change in one of the feed solutions, or faulty operational procedures. The solution being treated follows the path of least resistance, runs through these furrows, and fails to contact active resin material in other parts of the bed.

Characterization - Precisely deciphering and describing all the characteristics of a drug substance that affect its efficacy and its purity. Or the chemical, physical, and sometimes biological properties that are attributes of a specific drug substance.

Checksum - A record of the number of bits transmitted and included with the transmission so that the receiving program can check to see whether the same number of bits arrived. If the counts match, it is assumed that the complete transmission was received.

Chelating Agents - Organic compounds that can withdraw ions from solution, forming insoluble complexes.

Chemical Oxygen Demand (COD) - *(also see: COD (Chemical Oxygen Demand))*

Chemoautotrophs - Facultative autotrophs that obtain their energy from the oxidation of inorganic compounds.

Chemostat - A growth chamber that keeps a bacterial culture at a specific volume and rate of growth by limiting nutrient medium and removing spent culture.

Chemotherapy - Treatment of disease by means of chemical substances or drugs.

Chimeric - An organism, especially a plant, containing tissues from at least two genetically distinct parents. Type of antibody, partially human and partially mouse.

Chloramine - A chlorine compound formed by reaction with organic amines or ammonia.

Chlorinated Vinyls - Thermoplastic chlorinated vinyls include **PVC**, **CPVC**, and **VDC**. PVC and CPVC are very similar materials, the primary difference being the addition of more chlorine to the PVC molecule to synthesize CPVC. This results in a higher glass transition temperature that equates to a higher use temperature for CPVC. The polymerization with chlorine also makes these materials inherently flame resistant. In addition to being resistant to higher temperatures, CPVC is more resistant to process chemicals.

Chlorination - Adding chlorine or chlorine compounds to water for disinfection.

Chlorine - An element used to kill microorganisms in water. At room temperature and atmospheric pressure a greenish yellow gas.

Chlorine Demand - Amount of chlorine used up by reacting with oxidizable substances in water before chlorine residual can be measured.

Chlorine Residual - Portion of free or combined chlorine that remains active after specified contact period.

Chloroplasts - Relatively large, chlorophyll containing, green organelles responsible for photosynthesis in photosynthetic eukaryotes, such as algae and plant cells. Every chloroplast contains an outer membrane and a large number of inner membranes called *thylakoids*.

CHO (Chinese Hamster Ovary) Cells - In cell culture, the cells of a female hamster's reproductive organs, which historically have proven to be excellent expression systems in analytical studies and for producing pharmaceutical proteins.

Chromatids - Copies of a chromosome produced by replication.

Chromatin - The complex of DNA and protein in the nucleus of the interphase cell, originally recognized by its reaction with stains specific for DNA.

Chromatography - Procedure by which solutes (e.g., proteins and other chemical products) are selectively separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus obtained can be identified or determined by analytical methods. There are several types of chromatography in use with different operating principles:

1. **Adsorption:** separates products by their different affinities for the surface of a solid medium, either an inorganic carrier such as silica gel, alumina, or hydroxyapatite, or an organic polymer.
2. **Ion Exchange:** uses ion exchange resin to which ionized functional groups have been attached. At an appropriate pH, target proteins acquire a net surface charge that allows them to selectively bind to an ion exchange resin. Other impurities are eluted through the column.
3. **Gel Filtration:** employs a neutral cross-linked carrier with a defined pore size for molecular fractionation. Molecules larger than the largest pores cannot enter the matrix and pass directly through the column; smaller

molecules enter the carrier and are retarded. Gel filtration thus separates on the basis of molecular size, eluting larger molecules first, followed by progressively smaller species.

4. **Affinity:** relies on the propensity of each biomolecule to have an affinity for another highly specific biomolecule, such as an antibody-antigen relationship. Once bound together, the drug molecules can be detached by altering various chemical attributes in the column.
5. **Hydrophobic:** separates by molecule polarity and reverse interaction with water.
6. **High Pressure Liquid Chromatography (HPLC):** (*also see: High Pressure Liquid Chromatography*).

Chromium Enrichment Layer Thickness - In stainless steel, the same as its maximum depth of enrichment, unless a surface iron layer is present in which case the chromium enrichment layer is calculated as the maximum depth of enrichment minus the thickness of the surface iron oxide layer. *(also see: Maximum Depth of Enrichment)*

Chromosome - The self-replicating genetic structure of cells containing the cellular DNA that bears in its nucleotide sequence the linear array of genes. In prokaryotes, chromosomal DNA is circular, and the entire genome is carried on one chromosome. Eukaryotic genomes consist of a number of chromosomes whose DNA is associated with different kind of proteins. *(also see: Autosome)*

CIP (Clean In Place) - Internally cleaning a piece of equipment without relocation or disassembly. The equipment is cleaned but not necessarily sterilized. The cleaning is normally done by acid, caustic, or a combination of both, with WFI rinse. The design of a CIP system should considered the operating volume design for the water consumption, chemical and biowaste effluent, and energy required to clean a given circuit or piece of equipment.

Class 100 - Classification of an aseptic processing area where particle count should not exceed 100 particles (3,530 particles per cubic meter) 0.5µm or larger, per cubic foot of air, and no more than 0.1 CFU (Colony Forming Units) per cubic foot. Target uniform air velocity is 90 fpm plus or minus 20%, HEPA filtered air. *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Class 1,000 - Classification of an area where particle count should not exceed 1,000 particles (35,300 particles per cubic meter) 0.5µm or larger, per cubic foot of air. Supplied by HEPA filtered air. Class 1,000 is not a pharmaceutical GMP expectation. *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Class 10,000 - Classification of an area where particle count should not exceed 10,000 particles (353,000 particles per cubic meter) 0.5µm or larger, per cubic foot of air. Minimum of 20 air changes per hour, HEPA filtered air. *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Class 100,000 - Classification of an area where particle count should not exceed 100,000 particles (3,530,000 particles per cubic meter) 0.5µm or larger, per cubic foot of air, and no more than 2.5 CFU (Colony Forming Units) per cubic foot. Minimum of 20 air changes per hour of HEPA filtered air. *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Class Name - "For naming and describing the classes, **SI** names and units are preferred; however, English (U.S. customary) units may be used". Federal Standard 209E superseded by ISO 14644-1). *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Class 95% ASHRAE Area - This area designation refers to the efficiency of the filters based on ASHRAE standard 52-76. These areas would have 95% efficient supply air filtration, unlike classified areas, which would have HEPA filtration. This classification is not specified in Federal Standard 209E or ISO 14644-1.

Class 65% ASHRAE Area - This area would have 65% efficient filtration. This classification is not specified in Federal Standard 209E or ISO 14644-1.

Class 30% ASHRAE Area - This area would have 30% efficient filtration. This classification is not specified in Federal Standard 209E or ISO 14644-1.

Classical Pharmaceuticals - Small-molecule, nonbiotech drugs produced by chemical synthesis.

Classification - The level (or the process of specifying or determining the level) of airborne particulate cleanliness applicable to a cleanroom or clean zone, expressed in terms of an ISO Class **N**, which represents maximum allowable concentrations (in particles per cubic meter of air) for considered sizes of particles. ISO 14644-1 *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Classified Space - A space in which the number of airborne particles is limited. This is accomplished by the strict use of HVAC systems. Areas are classified as Class 10, Class 100, Class 1,000, Class 10,000, and Class 100,000. In pharmaceutical production, only classes 100, 10,000, and 100,000 are used. *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Clean Air Device - Stand-alone equipment for treating and distributing clean air to achieve defined environmental conditions.

Clean Air Projector - Fan and filter unit used to locally clean room air and deliver it to a desired location. Often called a fan/filter unit.

Clean Area - An area where particulate and microbial levels are specified (e.g., Filling Room - Class 10,000 "In Operation")

Clean In Place (CIP) - *(also see: CIP (Clean In Place))*

Cleanroom - A specially constructed space environmentally controlled with respect to airborne particles (size and count), temperature, humidity, air pressure, airflow patterns, air motion, and lighting. ISO 14644-1 defines it as "a room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary." *(also see Table I, Section II - Comparison of Airborne Particulate Cleanliness Classes)*

Cleanroom Classification - The maximum number of particles greater than or equal to 0.5µm in diameter that may be present in a cubic foot of room air. (*also see: Classified Space*)

Clean Space - A room or volume controlled to meet a certain airborne particulate limit (Class or Grade). In pharmaceutical facilities, clean spaces are usually classified and controlled only for aseptic processing facilities, but may also be defined for certain biotech processes. Final non-sterile bulk facilities, oral product, most topical product manufacturing facilities, and warehouses are normally **not** classified as clean spaces.

Clean Steam - Steam free from boiler additives that may be purified, filtered, or separated. When condensed, clean steam meets the specification for WFI. Usually utilized to sterilize process equipment.

Clean Zone - ISO 14644-1 defines it as "a dedicated space in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize

the introduction, generation, and retention of particles inside the zone and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary". Additionally, ISO 14644-1 states, "this zone may be open or enclosed and may or may not be located within a cleanroom".

Cleavage - The splitting up of a complex molecule into two or more simpler molecules. The series of cell divisions occurring in the ovum immediately following its fertilization.

Clinical Endpoint - An indicator (such as blood pressure) measured in a human subject to asses the safety, efficacy, or other objective of a clinical trial.

Clinical Hold - The temporary cessation of a clinical trial by FDA if the agency is concerned about a drug or study protocol. The trial may resume when the problem is solved.

Clinical Trials - Testing of INDs (Investigational New Drugs) in human subjects to prove safety and efficacy prior to the drug's approval for marketing. The investigation of a previously untested drug is generally divided into three phases:

1. **Phase I:** Introducing the product (or drug) into a small number, generally 20 to 80, patients or healthy volunteers to determine the drug's metabolism, pharmacological actions, and side effects associated with increasing doses.
2. **Phase II:** introducing the product (or drug) into a small number, generally no more than several hundred, patients with the disease or condition under study to evaluate the effectiveness of the drug, common short-term side effects and risks associated with its use.
3. **Phase III:** Introducing the product (or drug) into several hundred to several thousand subjects. Studies are expanded controlled and uncontrolled trials performed after preliminary evidence suggesting effectiveness of the drug has been obtained. If the results of the Phase III Clinical Trials are favorable, then the FDA will normally license the drug for manufacture and sale. This phase is usually performed using double blind studies with a placebo and the actual drug.
4. **Phase IV:** Ongoing testing studies conducted after the drug is approved. This is done to ensure the long-term efficacy of the drug, detect any long-term beneficial and/ or detrimental side effects, and to determine additional potential uses for the drug.

Clone - A population of genetically identical cells derived from the multiplication of a single cell. It is the basis of rDNA and monoclonal antibody production.

Clone - A group of individuals produced from one individual through asexual processes that do not involve the interchange or combination of genetic material. As a result, members of a clone have identical genetic compositions. Protozoa and bacteria, for example, frequently reproduce asexually by a process called binary fission. In binary fission, a single-celled organism undergoes cell division and the result is two cells with identical genetic composition. Next, these two identical cells undergo division and the result is four cells with identical genetic composition. These identical offspring are all members of a clone.

Clone Bank - *(also see: Genomic Library)*

Cloning - Using specialized DNA technology *(also see: Cloning Vector)* to produce multiple, exact copies of a single gene or other segment of DNA to obtain enough material for further study. This process is used by researchers in the Human Genome Project, and is referred to as cloning DNA. The resulting cloned (copied) collections of DNA molecules are called clone libraries. A second type of cloning exploits the natural process of cell division to make many copies of an entire cell. The genetic makeup of these cloned cells, called a cell line, is identical to the original cell. A third type of cloning produces complete, genetically identical animals such as the famous Scottish sheep, Dolly.

Cloning Vector - DNA molecule originating from a virus, a plasmid, or the cell of a higher organism into which another DNA fragment of appropriate size can be integrated without loss of the vectors capacity for self-replication; vectors introduce foreign DNA into host cells, where it can be reproduced in large quantities. Examples are plasmids, cosmids, and yeast artificial chromosomes; vectors are often recombinant molecules containing DNA sequences from several sources.

Closed System - One in which by its design and proper operation, prevents release of a microbiological agent or eukaryotic cell contained therein.

Closed System - System sterilized-in-place or sterilized while closed prior to use, is pressure or vacuum tight to some predefined leak rate, can be utilized for its intended purpose without breach to the integrity of the system, can be adapted for fluid transfers in or out while maintaining asepsis, and is connectable to other closed systems while maintaining integrity of all closed systems. (From PDA TR-28 for sterile product manufacture) *(also see: Open System)*

Clostridium - A genus of bacteria, most are obligate anaerobes and form endospores.

cM - *(also see: Centimorgan)*

Coagulation - Adding insoluble compounds to water to neutralize the electrical charge on colloids, causing them to coalesce to form larger particles that can be removed by settling. (*also see: flocculation*).

Coaguligand - A VTA (Vascular Targeting Agent) that utilizes a human coagulation protein to induce tumor blood vessel clotting.

Coccus - A bacterium of round, spheroidal, or ovoid form, including *micrococcus*, *staphylococcus*, *streptococcus*, and *pneumococcus*.

COD (Chemical Oxygen Demand) - The amount of oxygen needed to completely oxidize all oxidizable organic and inorganic substances in water.

Code - *(also see: Genetic Code)*

Coding Sequence - The region of a gene (DNA) that encodes the amino acid sequence of a protein.

Codon - *(also see: Genetic Code)*

Coenzyme - A non-polypeptide molecule required for the action of certain enzymes; often contains a vitamin as a component. *(also see: Enzyme)*

Cofactor - Small molecular weight, heat stable inorganic or organic substance required for the action of an enzyme.

Coliform Bacteria - A group of bacteria found in mammalian intestines and soil, used as a measure of fecal pollution in water. They are easy to identify and count in the laboratory because of their ability to ferment lactose.

Colonoscopy - Examination of the colon through a flexible, lighted instrument called a colonoscope.

Colony - A growth of microorganisms on a solid medium. The growth is visible without magnification.

Collagen - An albuminoid present in connective tissue, bone (ossein), and cartilage (chondrin), notable for its high content of the imino acids proline and hydroproxilone. On boiling with water it is converted into gelatin.

Collateral Targeting - The therapeutic strategy of targeting structures and cell types other than cancer cells common to all solid tumors as a means to attack a solid tumor.

Colloid - A translucent, yellowish material of the consistency of glue, less fluid than mucoid or mucinoid, found in the cells

and tissues in a state of colloid degeneration or colloid carcinoma.

A substance, such as gelatin or cytoplasm that because of the size of its molecules, is slowly diffusible rather than soluble in water and is incapable of passing through an animal membrane.

Colloids - Particles so fine they will not settle without prior coagulation. They range from 10 Å to 1,000 Å (Angstroms). They have a net negative charge and readily clog membranes and foul resin beds. Examples are bacteria, silica, and clay.

CMC (Chemistry, Manufacturing, and Controls)
The section on a BLA (Biologics License Application) or IND (Investigational New Drug) describing the composition, manufacture, and specifications of a drug product and its ingredients.

Combustible Dust
Any finely divided solid material that is 420µ or 0.017 inches or less in diameter, or any material capable of passing through an US No. 40 standard sieve that when dispersed in air in the proper proportions, could be ignited by a flame, spark or other source of ignition.

Combustible Liquid - A liquid having a closed cup flash point at or above 100°F (37.8°C). Combustible liquids do not include compressed gases or cryogenic fluids. Combustible liquids are subdivided as follows:

1. **Class II:** Liquids having a closed cup flash point at or above 100°F (37.8°C) and below 140°F (60°C)
2. **Class III-A:** liquids having a closed cup flash point at or above 140°F (60°C) and below 200°F (93.3°C)
3. **Class III-B:** liquids having a closed cup flash point at or above 200°F (93.3°C).

Commissioning - A prescribed number of activities designed to take equipment and systems from static, substantially complete state to an operable state.

Commissioning - The documented process, verifying that equipment and systems are installed according to specifications, placing the equipment and systems into active service and verifying its proper operation. Commissioning is done for good business, but can include many Qualification activities.

Compatibility - *(also see: Backward Compatibility, and Upward Compatibility)*

Complementary DNA (cDNA) - DNA that is synthesized from a messenger RNA template; the single-stranded form is often used as a probe in physical mapping.

Complementary Sequence - Nucleic acid base sequence that can form a doublestranded structure by matching base pairs with another sequence; the complementary sequence to GTAC is CATG.

Compounding - The bringing together of excipient and solvent components into a homogeneous mix of active ingredients.

Compressed Gas - A material, or mixture of materials that are either liquefied, nonliquefied, or in solution having a boiling point of 68°F (20°C) or less at 14.7 psia (101.3 kPa) of pressure. The exceptions to this rule are those gases that have no health or physical hazard properties. These gases are not considered compressed until the pressure in their packaging exceeds 41 psia (282.5 kPa) at 68°F (20°C).

Computer Controlled System - Computer system plus its controlled function.

Computer Related System - Computerized system plus its operating environment.

Computer System - A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System - A process or operation integrated with a computer system.

Concavity (welding) - A condition in which the surface of a welded joint is depressed relative to the surface of the tube or pipe. Concavity is measured as a maximum distance from the outside or the inside diameter surface of a welded joint along a line perpendicular to a line joining the weld toes. *(also see: Toe of Weld)*

Concentration Polarization - The phenomenon in ultrafiltration (UF) in which solutes form a dense, polarized layer next to the membrane surface eventually blocking further flow. UF systems counteract this by continuously flushing the solute away from the membrane surface.

Concurrent Process Validation - Establishing documented evidence that a process does what it purports to do based on information generated during actual implementation of the process.

Condensate - Distillate just after it has been cooled from steam into the liquid state.

Condenser - The heat exchanger used in distillation to cool steam in order to convert it from the vapor to the liquid state.

Conductivity - The reciprocal of resistivity (C=1/R). A measure of the ability to conduct an electric current. Since ionized impurities increase the conductivity of water, it is also an accurate measure of ionic purity. Conductivity is normally expressed in micromhos/cm (µmho/cm) or microsiemens/cm (µS/cm). To measure it, current is passed between two electrodes a fixed distance apart.

Configurable Software - Commercial, off-the-shelf software that can be configured to specific user applications without altering the basic program.

Configuration - The three-dimensional shape or form of a macromolecule.

Conformation - The characteristic three-dimensional shape (tertiary structure) of a macromolecule.

Conjugated Protein - A protein containing a metal or an organic prosthetic group or both. Hemoglobin is a conjugated protein.

Consent Decree - The result of a serious violation of federal regulations and related safety and quality standards. A company must agree to a series of measures aimed at bringing its manufacturing standards in compliance with federal regulations. Until agreed-upon conditions are met, a company may be forbidden to distribute its products in interstate commerce, except for those products deemed essential for the public health.

Conserved Sequence - A base sequence in a DNA molecule (or an amino acid sequence in a protein) that has remained essentially unchanged throughout evolution.

Containment - The action of confining within a defined space a microbiological agent or other entity that is being cultured, stored, manipulated, transported, or destroyed in order to prevent or limit its contact with people and/or the environment. Methods to achieve containment include physical and biological barriers and inactivation using physical or chemical means.

1. **Primary Containment:** Addresses the protection of personnel and the immediate laboratory environment from exposure to infectious agents. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.
2. **Secondary Containment:** A system of containment that prevents the escape of infectious agents into the environment external to the laboratory. It involves the

use of rooms with specially designed air handling, the existence of airlocks and/or sterilizers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

The main three elements of containment include laboratory practice and technique (most important element), safety equipment (primary barriers), and facility design (secondary barriers). *(also see: Biological Safety Cabinets)*

Containment Level - The National Institutes of Health (NIH) specifies physical containment levels and defines Biosafety Levels in their Guidelines for Research Involving Recombinant DNA Molecules - May 1999:

1. **Appendix G - Physical Containment** specifies physical containment for standard laboratory experiments and defines Biosafety Level 1 (BL1) through Biosafety Level 4 (BL4). (*also see: Biosafety Level, and Table II - Section II - Comparison of Good Large Scale Practice (GLSP) and Biosafety Level (BL) - Large Scale (LS) Practice)*
2. **Appendix I - Biological Containment** specifies levels of biological containment (host vector systems) for prokaryotes and defines Host Vector 1 Systems (HV1) and Host Vector 2 Systems (HV2). *(also see: Host Vector (HV) System)*
3. **Appendix K - Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules** specifies physical containment guidelines for large scale (over 10 liters) research or production involving viable organisms containing recombinant DNA molecules, and defines GLSP (Good Large Scale Practice) through Biosafety Level 3-LS (Large Scale). (*also see: Biosafety Level, and Table II - Section II - Comparison of Good Large Scale Practice (GLSP) and Biosafety Level (BL) - Large Scale (LS) Practice*)
4. **Appendix P - Physical and Biological Containment for Recombinant DNA Research Involving Plants** specifies physical and biological containment conditions and practices suitable to the greenhouse conduct of experiments involving recombinant DNA-containing plants, plant-associated microorganisms, and small animals, and defines Biosafety Level 1-Plants (BL1-P) through Biosafety Level 4-Plants (BL4-P).
5. **Appendix Q - Physical and Biological Containment for Recombinant DNA Research Involving Animals** specifies containment and confinement practices for research involving whole animals, both those in which the animal's genome has been altered by stable introduction of recombinant DNA, and experiments involving viable recombinant DNA-modified microorganisms tested on whole animals, and defines Biosafety Level 1-Animals (BL1-N) through Biosafety Level 4-Animals (BL4-N).

Contaminant - Any unwanted or undesired component in a process fluid or controlled environment.

Contamination - The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API (Active Pharmaceutical Ingredient) during production, sampling, packaging or repackaging, storage or transport.

Contig - Group of cloned (copied) pieces of DNA representing overlapping regions of a particular chromosome.

Contig Map - A map depicting the relative order of a linked library of small overlapping clones representing a complete chromosomal segment.

Continuous Fermentation - A process in which sterile medium is added without interruption to the fermentation system with a balancing withdrawal (or "harvesting") of broth for product extraction. The length of fermentation can be measured in weeks or months. Commercial applications of continuous fermentation are limited in number, with ethanol production by yeast the most important example.

Contract Manufacturer - A company holding an agreement requiring the performance of some aspect of API manufacturing

Control Area - A building or portion of a building within which the exempted amounts of hazardous materials may be stored, dispensed, handled, or used.

Control Group - The group of subjects in a controlled study that receives no treatment, receives a standard treatment, or receives a placebo.

Control Number - *(also see: Lot Number)*

Control Parameters - Those operating variables that can be assigned values and are used as control levels.

Control Serum - Serum used as a standard for clinical chemistry lab tests. Most often produced from outdated whole blood plasma. Most often turbid and difficult to filter *(also see: Salvage Plasma, Serum)*

Controlled Area - An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination, and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

Controlled Area - Area of restricted access. A term for areas and rooms adjoining a critical area in aseptic production facilities.

Conventional Drugs - New compounds made up by chemical synthesis or fermentation. These are termed by the FDA as NCEs (New Chemical Entities). The FDA rates conventional drugs with important therapeutic gain as 1-A drugs, for priority review. For example, *AIDS drugs* are conventional drugs approved for AIDS or AIDS-associated conditions.

Conventional Flow Cleanroom - A room supplied with filtered air with no specified requirement for uniform airflow patterns or velocity. Airflow patterns are usually turbulent.

Converted Data - Any original data that has been entered into a user-developed application (spreadsheet, database, report, etc.) for manipulation, evaluation, or review.

Convexity - A condition in which the surface of a welded joint is extended relative to the surface of the tube or pipe. Convexity is measured as a maximum distance from the outside or inside diameter surface of a welded joint along a line perpendicular to a line joining the weld toes. *(also see: Toe of Weld)*

Corn Steep Liquor - An ingredient in the culture medium for producing penicillin. A natural nitrogenous material that is a by-product of the corn milling industry.

Corrosive - A chemical that causes visible destruction or irreversible alterations in living tissue by chemical action at the site of contact. A chemical is considered corrosive if, when tested on the intact skin of albino rabbits by the method described in Appendix A of CFR 49 Part 173, it destroys or changes irreversibly the structure of the tissue at the site of contact following an exposure period of four hours. This term shall not refer to action on inanimate surfaces.

Corrosive Liquid - A liquid which when in contact with living tissue, will cause destruction or irreversible alteration of such tissue by chemical action. Examples include acidic, alkaline, or caustic materials.

Cosmid - Artificially constructed cloning vector containing the cos gene of phage lambda. Cosmids can be packaged in lambda p0hage particles for infection into *E. coli*: this permits cloning of larger DNA fragments (up to 45kb) that can be introduced into bacterial hosts in plasmid vectors.

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

Creutzfeld-Jacob Disease - *(also see: (Bovine Spongiform Encephalopathy))*

Critical - A material, process step, or process condition, test requirement, or any other relevant parameter is considered critical when non-compliance with predetermined criteria directly influences the quality attributes of the API (Active Pharmaceutical Ingredient) in a detrimental manner.

Critical Area - An area where (sterile) product or contact surface is exposed, normally Class 100 (e.g., Point of Fill). *(also see: Background Environment)*

Critical Device - A device that directly ensures that a GMP Critical Parameter is maintained within predetermined limits (e.g., terminal HEPA filter, point of use filter). A malfunction of such a device would place product quality directly at risk.

Critical Instrument - An instrument that measures a GMP Critical Parameter, used to monitor and document that parameter. *(also see: Critical Device)*

Critical Parameter - A GMP or product quality parameter (e.g., differential pressure, unidirectional airflow pattern) that must be maintained within predefined limits to ensure product SISPQ (Strength, Identity, Safety, Purity, or Quality).

Critical Point - The combination of pressure and temperature at which the gas and liquid phases of a substance become indistinguishable.

Critical Process Step - For sterile products, this normally is an activity where product or product contact parts are exposed to the surrounding environment.

Critical Step(s) - The point or points in the process which, if not carried out properly or if contaminated, will not allow drug substances to be made such that they will meet their intended characterizations and impurity profiles.

Critical Surface - The part of the working surface to be protected from particulate contamination. It is within the Critical Zone.

Critical System - A structural, mechanical, or electrical system that can impact the processing parameters and attributes of the finished product or regulatory study. Critical systems may include utilities, process equipment, and systems.

Cross Contamination - The measurable and detrimental contamination of a material or product with another material or product. *(also see: Contamination)*

Crossing Over - The breaking during meiosis of one maternal and one paternal chromosome, the exchanging of corresponding sections of DNA, and the rejoining of the chromosomes. This process can result in an exchange of alleles between chromosomes. *(also see: Recombination)*

Cryogenic Liquid - A fluid that has a normal boiling point below -150°F (-101.1°C).

Cryptography - The mathematical science of deliberately scrambling and unscrambling information. Information is protected by being transformed (encrypted) into an unreadable format, called cipher text. Only those who posses a secret key can decypher (or decrypt) that message into plain text.

Culture Medium - Any nutrient system for the artificial cultivation of bacteria or other cells; usually a complex mixture of organic and inorganic materials.

current Good Manufacturing Practices (cGMP's) - *(also see: cGMPs (current Good Manufacturing Practices))*

Cut - An enzymatic break that occurs in both strands of a DNA molecule opposite one another by restriction enzymes.

Cystic Fibrosis - An inherited disease in which thick mucus clogs the lungs and blocks the ducts of the pancreas.

Cytokine - A protein that acts as a chemical messenger to stimulate cell migration, usually toward where the protein is released. Interlukins, lymphokines, and interferons are the most common.

Cytolysis - The dissolution of cells particularly by destruction of their cell membrane.

Cytopathic - Damaging to cells.

Cytoplasm - The protoplasmic contents of the cell outside the nucleus in which the cell's organelles are suspended.

Cytosine (C) - A pyrimidine occurring as a fundamental unit or base of nucleic acids. *(also see: Nucleic Acids)*

Cytostatic Agents - Therapeutics that inhibit cell division and growth. This term can refer to machinery, such as those that would freeze cells.

Cytotoxic - Poisonous to cells.

Cytotoxicity - The ability of a substance or compound to cause a cytotoxic effect.

- D -

D5W (5 D/W) - One of the most prevalent of LVPs *(also see: LVP (Large Volume Parenteral))*. Five percent dextrose in water. Presence of dextrose presents significant filtration problems. Usually requires activated charcoal pretreatment.

Dalton - The unit of molecular weight, equal to the weight of a hydrogen atom.

Data Integrity - The validity of data and their relationships. For electronic records to be trustworthy and reliable, the links between raw data, metadata, and results must not be compromised or broken. Without data integrity, it is not possible to regenerate a previous result reliably.

Data Migration - The process of translating data from one system to another when a company replaces the current computing systems with a new one. CFR 21 Part 11 mandates that data migration implementation create accurate and complete copies of the records when they are moved to a new system.

DDC (Direct Digital Control) - A collection of control units (analog and discrete) connected into a data highway, usually with a host or alarming/recording computer attached.

D Value - The time under a stated set of exposure conditions (temperature in an autoclave) required to reduce a microbial population by a factor of 90% (e.g. from 10,000 to 1,000).

Dead Leg - An area of entrapment in a vessel or piping run that could lead to contamination of the product. In a piping system, a non-flowing pocket, tee, or extension from a primary piping run that exceeds a defined number of pipe diameters from the ID of the primary pipe. Denoted by the term L/D or L/A, where L is equal to the leg extension

perpendicular to the normal flow pattern or direction, *A* is the annular gap width, and *D* is equal to the ID (or inside dimension) of the extension or leg. In some existing standards, the dimension *L* is measured from the centerline of the primary pipe. For bioprocessing systems, an *L/D* of 2:1 is achievable with today's component technology for most valving and piping configurations.

Decontamination - A process that reduces contaminating substances to a defined acceptance level.

Deflagration - An exothermic reaction, such as the extremely rapid oxidation of a combustible dust or flammable vapor in air, in which the reaction progresses through the unburned material at a rate less than the velocity of sound. A deflagration can have an explosive effect. *(also see: Detonation)*

Degrading - Deterioration of a surface finish so that pieces of the finish (or substrate) material large enough to be visible to the unaided eye, dislodge without any direct physical contact and fall from the surface of the material.

Deionization - Removing dissolved ions from solution by passing the solution through a bed of ion exchange resin, consisting of polymer beads that exchange hydrogen ions for cations and hydroxyl ions for anions in solution. The ionic impurities remain bound to the resins and the hydrogen and hydroxyl ions combine with each other to form water.

Deletion Map - A description of a specific chromosome that uses defined mutations - specific deleted areas in the genome - as "biochemical signposts", or markers for specific areas.

***De Minimis* Release** - The release of viable microbiological agents or eukaryotic cells that does not result in the establishment of disease in healthy people, plants, or animals; or in uncontrolled proliferation of any microbiological agents or eukaryotic cells. *(also see: Release)*

Dementia - Severe impairment of mental functioning.

Demineralization - Sometimes used interchangeably with deionization, it refers to the removal of minerals and mineral salts using ion exchange. Water softening is a common form of demineralization.

Denaturation - The loss of the native structure of a macromolecule resulting, from heat treatment, extreme pH changes, chemical treatment, etc. It is accompanied by loss of biological activity. For example, proteins may be denatured by heat, pH extremes, or addition of agents such as urea or guanidinium hydrochloride.

Dent - A typical stainless steel interior surface anomaly that refers to a large, smooth-bottomed depression whose diameter or width is greater than its depth and which will not produce an indication.

Deoxyribonucleotide - *(also see: Nucleotide)*

Depyrogenation - The removal or destruction of endotoxins.

Desalination - The removal of dissolved salts from brine to produce potable water.

Design Condition - The specified range or accuracy of a controlled variable used by the designer to determine performance requirements of an engineered system.

Design Specification - A specification that defines the design of a system or system component.

Desiccant - Chemical salt used to dehumidify air, to control moisture in materials contacting that air.

Desiccators - Closed containers, usually made of glass or plastic, with an airtight seal used for drying materials.

Detonation - An exothermic reaction characterized by the presence of a shock wave in a material that establishes and maintains the reaction. The reaction zone progresses through the material at a rate greater than the velocity of sound. The principal heating mechanism is one of shock compression. Detonations have an explosive effect. *(also see: Deflagration)*

Deuteromycetes - Molds that cannot reproduce by sexual means. Some pathogenic fungi such as *Trichophyton*, which causes athlete's foot, belong to this family.

Devices - *(also see: Medical Devices)*

Dewpoint Temperature (DP) - *(also see: Temperature)*

DHL Vaccine - A tri-valent vaccine. Also, the most common veterinary vaccine that has a combination of viral and bacterial vaccines. Used for distemper, hepatitis (canine), and leptospira. *(also see: Vaccine)*.

Diagnostic - A substance or group of substances used to identify a disease by analyzing the cause and symptoms.

Dialysis - The separation of low-molecular weight compounds from high molecular weight components by diffusion through a semipermeable membrane. Frequently utilized to remove salts, introduce salts, remove biological effectors such as nicotinamide adenine dinucleotides, nucleotides phosphates, etc. from polymeric molecules such as protein, DNA, RNA, etc. Commonly used membranes have a molecular weight cutoff around 10,000 but other membrane pore sizes are available.

Diatom - Any minute, unicellular or colonial algae of the class *Bacillariophyceae* having siliceous cells walls consisting of two overlapping symmetrical parts.

Diatomaceous Earth, Diatomite, Kiselguhr (DE) - Fine silicaceous powder used as a filter aid.

Diffusion - The random thermal motion of particles, which causes them to flow from a region of higher concentration to one of lower concentration until they are uniformly distributed.

Digestion - The enzymatic hydrolysis of major nutrients in the gastrointestinal system to yield their building-block components.

Digital - A series of on and off pulses arranged to convey information.

Digital Certificate - An attachment to an electronic message used for security purposes. The most common use of a digital certificate is to verify that a user sending a message is who he or she claims to be and to provide the receiver with the means to encode a reply.

Digital Representation - Biometric parameters such as a fingerprint or retinal pattern are turned into data that a computer understands: the digital representation of the biometric. The pattern in the biometric divides it into a grid of boxes, and a zero or a one, depending on whether the box is filled in, marks each box.

Digital Signature - An electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified. *(also see: Electronic Signature)*

Dilution - Lowering the concentration of a solution by adding more solvent.

Dilution Factor - The ratio of solvent to solute by volume.

Diploid - A full set of genetic material, consisting of paired chromosomes one chromosome from each parental set. Most animal cells except the gametes have a diploid set of chromosomes. The diploid human genome has 46 chromosomes. *(also see: Zygote, and Haploid)*

Diplophase - A phase in the life cycle of an organism where the organism has two copies of each gene. The organism is said to be diploid.

Direct Impact System - An engineering system that may have a direct impact on product quality.

Disaster - Any event (i.e. fire, earthquake, power failure etc.), which could have a detrimental effect upon an automated system or its associated information.

Discoloration (welding) - Any change in surface color from that of the base metal. Usually associated with oxidation occurring on the weld and heat affected zone (HAZ) on the outside diameter and inside diameter of the weld joint as a result of heating the metal during the welding. Colors may range from pale bluish-gray to deep blue, and from pale straw color to a black crusty coating.

Disinfection - Process by which viable microbiological agents or eukaryotic cells are reduced to a level unlikely to produce disease in healthy people, plants, or animals. These processes may use chemical agents, heat, ultraviolet light, etc. to destroy most (but not necessarily all) of the harmful or objectionable microorganisms, pathogens, and potential pathogens. Disinfection does not necessarily result in sterilization.

1. "High level disinfection" inactivates fungi, viruses, and bacteria. High-level chemical disinfectants maybe ineffective against bacterial spores if they are present in large numbers. Extended exposure times may be required.
2. "Intermediate level disinfection" destroys fungi, some viruses (lipid and most non-lipid medium-size and small viruses), mycobacteria, and bacteria.
3. "Low level disinfection" kills vegetative forms of bacteria, some fungi, and some medium-size and lipid-containing viruses. Low-level disinfectants do not reliably kill bacterial spores, mycobacteria, or small or non-lipid viruses.

(also see: Decontamination, Sanitization)

Dispensing - The pouring or transferring of any material from a container, tank or similar vessel, whereby vapors, dusts, fumes, mists or gases may be liberated to the atmosphere.

Dissimilation - The breakdown of food material to yield energy and building blocks for cellular synthesis.

Dissolved Solids - The amount of nonvolatile matter dissolved in a water sample, usually expressed in parts per million (PPM) by weight. (*also see: Total Dissolved Solids (TDS)*)

Distillation - The process of separating water from impurities by heating until it changes into vapor and then cooling the vapor to condense it into purified water.

DNA (Deoxyribonucleic Acid) - The molecule of which the genetic material is composed. It consists of two chains joined together as a double helix. Each chain is composed of a polymer of nucleotides (consisting of a nitrogenous base, a deoxyribosesugar ring, and a phosphate group) joined together by phosphodiester bonds between the 5'-phosphate of one nucleotide and the 3'-hydroxyl of the next. The two chains run in opposite directions and are held together by hydrogen bonds between the bases in equivalent positions in the two chains. There are various forms of double helical DNA. They are:

1. **B-DNA** (first described by Crick and Watson) is a right-handed helix with 10.6 base pairs per turn and is probably the main form of cellular DNA.
2. **A-DNA** is also a right-handed helix but is somewhat skewed and contains about 11 base pairs per turn. It is the form taken By DNA-RNA hybrid double helixes.
3. **Z-DNA** is a left-handed helix with 11 base pairs per turn. It is favored by regions rich in guanine cutosine base pairs and probably occurs infrequently in cellular DNA.

(also see: Nucleic Acids)

DNA (Deoxyribonucleic Acid) - The molecular basis for genes; every inherited characteristic has its origin somewhere in the code of the organism's complement of DNA. The code is made up of subunits, nucleic acids. The organism to produce the required proteins that compose the genetic traits of the organism and its life functions interprets the sequence of the four nucleic acids.

DNAse (Deoxyribonuclease) - An enzyme that degrades DNA.

DNA Array - Spots of DNA arranged on a slide support such as glass or silicon "DNA chip" (or microarray), used for screening, sequencing, genetic mapping, and so on.

DNA Probe - *(also see: Probe)*

DNA Replication - The use of existing DNA as a template for the synthesis of new DNA strands. In humans and other eukaryotes, replication occurs in the cell nucleus.

DNA Sequence - The relative order of base pairs, whether in a fragment of DNA, a gene, a chromosome, or an entire genome. *(also see: Base Sequence Analysis)*

DNA Vector - A DNA vehicle for transferring generic information from one cell to another.

Documentation - Written or pictorial information describing, defining, specifying, and/or reporting of certifying activities, requirements, procedures or results.

Domain - A discrete portion of a protein with its own function. The combination of domains in a single protein determines its overall function.

Dominant Allele - A gene that is expressed, regardless of whether its counterpart allele on the other chromosome is dominant or recessive. Autosomal dominant disorders are produced by a single mutated dominant allele, even though its corresponding allele is normal. *(also see: Recessive Allele)*

DOP (Dioctyl Phthalate) - A mono-dispersed test aerosol of sub-micron particles, generated to challenge (evaluate integrity) of HEPA filters for HVAC. *(also see: Polyalphaolefin)*

Double Helix (Duplex) - The structure of DNA as proposed by Watson and Crick. It consists of two right-handed helical polynucleotide chains coiled around the same axis. The two chains are anti-parallel with their 3rd to 5th internucleotide phosphodiester bonds running in opposite directions. Under most conditions, the coiling of the chains is such that if the ends are held still, as in circular DNA or in a large chromosome, the chains cannot be separated except by cleavage of one of the strands.

Drugs - "Articles intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals. *(also see: Generic Drug)*

Drug Product - A finished dosage form, for example, tablet, capsule, solution, etc., that contains one or more APIs (Active Pharmaceutical Ingredients) generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form, which does not contain an API but is intended to be used as a placebo.

Drug (Medicinal) Product - The dosage form in the final immediate packaging intended for marketing.

Drug Substance - *(also see: API (Active Pharmaceutical Ingredient))*

Durability - The ability to withstand the rigors of the environment without degrading or requiring repair.

Dry Air

Air from which all water vapor and contaminants have been removed. Its composition by volume is:

1. Nitrogen	78.08%
2. Oxygen	20.95%
3. Argon	0.93%
4. Carbon Dioxide	0.03
5. Other gases	0.00003

1. **Class I, Division 1:** A Class I, Division 1 location (1) is that in which ignitable concentrations of flammable

gases/vapors can exist under normal operating conditions; or (2) in which ignitable concentrations of such gases/vapors may exist frequently because of repair, maintenance operations or because of leakage; or (3) in which breakdown or faulty operation of equipment or process may release ignitable concentrations of flammable gases/vapors, and might also cause simultaneous failure of electric equipment.

2. **Class I, Division 2:** A Class I, Division 2 location (1) is that in which volatile flammable liquids or flammable gases are handled, processed, or used, but in which the liquids, vapors, or gases will normally be confined within closed containers or closed systems from which they can escape only in case of accidental rupture or breakdown of such containers or systems, or in case of abnormal operation of equipment; or (2) in which ignitable concentrations of gases or vapors are normally prevented by positive mechanical ventilation, and which might become hazardous through failure or abnormal operation of the ventilating equipment; or (3) that is adjacent to a class I, Division 1 location, and to which ignitable concentrations of gases or vapors might occasionally be communicated unless such communication is prevented by adequate positive-pressure ventilation from a source of clean air, and effective safeguards against ventilation failure are provided.
3. **Class II, Division 1:** A Class II, Division 1 location (1) is that in which combustible dust is in the air under normal operating conditions in quantities sufficient to produce explosive or ignitable mixtures; or (2) where mechanical failure or abnormal operation of machinery or equipment might cause such explosive or ignitable mixtures to be produced, and might also provide a source of ignition through simultaneous failure of electric equipment, operation of protection device, or from other causes; or (3) in which combustible dusts of an electrically conductive nature may be present in hazardous quantities.
4. **Class II, Division 2:** A Class II, Division 2 location (1) is that in which combustible dust is not normally in the air in quantities sufficient to produce explosive or ignitable mixtures, and dust accumulations are normally insufficient to interfere with the normal operation of electrical equipment or other apparatus but combustible dust may be in suspension in the air as a result of infrequent malfunctioning of handling or processing equipment and where combustible dust accumulations on, in, or in the vicinity of the electrical equipment may be sufficient to interfere with the safe dissipation of heat from electrical equipment or may be ignitable by abnormal operation or failure of electrical equipment.
5. **Class III, Division 1:** A Class III, Division 1 location is that in which easily ignitable fibers or materials producing combustible filings are handled, manufactured, or used.
6. **Class III, Division 2:** Class III, Division 2 location is that in which easily ignitable fibers are stored or handled.

Electrical Code - *(also see: National Electrical Code®)*

Electrical Groups - Electrical groupings are based on the characteristics of the materials involved. These include the following:

1. **Class I, Group A:** Atmospheres containing acetylene.
2. **Class I, Group B:** Atmospheres containing hydrogen, fuel and combustible process gases containing more than 30 percent hydrogen by volume, or gases or vapors of equivalent hazard such as butadiene, ethylene oxide, propylene oxide, and acrolein.
3. **Class I, Group C:** Atmospheres such as ethyl ether, ethylene, or gases or vapors of equivalent hazard.
4. **Class I, Group D:** Atmospheres such as acetone, ammonia, benzene, butane, cyclopropane, ethanol, gasoline, hexane, methanol, methane, natural gas, naphtha, propane, or gases or vapors of equivalent hazard.
5. **Class II, Group E:** Atmospheres containing combustible metal dusts, including aluminum, magnesium and their commercial alloys, or other combustible dusts whose particle size, abrasiveness, and conductivity present similar hazards in the use of electrical equipment.
6. **Class II, Group F:** Atmospheres containing combustible carbonaceous dusts, including carbon black, charcoal, coal, or coke dusts that have more that 8 percent entrapped volatiles, or dusts that have been sensitized by other materials so that they present an explosion hazard.
7. **Class II, Group G:** Atmospheres containing combustibles dusts not included in Group E or F, including flour, grain, wood, plastic, and chemicals.

Electrodialysis (ED) - A membrane separation method used for the separation of charged molecules from a solution by application of a direct current. The membranes contain ion-exchange groups and have a fixed electrical charge. This method is very effective in the concentration of electrolytes and proteins. (also see: Electrophoresis)

Electrolyte - A chemical compound which when dissolved or ionized in water allows it to conduct electric current.

Electron Microscopy (EM) - A technique for visualizing material that uses beams of electrons instead of light rays and that permits greater magnification than is possible with an optical microscope. Electron microscopes have been used to examine the structure of viruses and bacteria, to identify and classify pollen grains, etc.

Electronic Record - Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Electronic Signature or e-sig - According to FDA, an electronic signature is a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature. *(also see: Handwritten Signature, and Digital Signature)*

Electrophoresis - The migration of electrically charged proteins, colloids, molecules, or other particles when dissolved or suspended in an electrolyte through which an electric current is passed. The most important use of electrophoresis is in the analysis of blood proteins. Since the proportion of these proteins varies widely in different diseases, electrophoresis can be used for diagnostic purposes. Electrophoresis is used to study bacteria and viruses, nucleic acids, and some types of smaller molecules, including amino acids. *(also see: Immuno Electrophoresis, Gel Electrophoresis, and Agarose Gel Electrophoresis)*

Electropolishing - Also known as "chemical machining" and "reverse plating", electropolishing is an electrochemical process far superior to any available mechanical process for the removal of minute surface imperfections in stainless steel. It levels and brightens the material surface by anodic dissolution in an electrolyte flowing solution with an imposed electrical current. When the proper combination of electrolyte current & temperature is attained, the high points of surface irregularities, or high current density areas, are selectively removed at a greater rate than the remainder of the surface, resulting in improved surface

smoothness. During electropolishing, the polarized surface film is subjected to the combined effects of *gassing* (oxygen) that occurs with electromechanical metal removal, *saturation* of the surface with dissolved metal, and the *agitation* and *temperature* of the electrolyte.

Electrolyte - Any compound which in solution conducts a current of electricity and is decomposed by it. *(also see: Ampholyte)*

Electrostatic Fluidized Bed - A container holding powder coating material which is aerated from below so as to form an air-supported expanded cloud of such material which is electrically charged with a charge opposite to the charge of the object to be coated. Such object is transported through the container immediately above the charged and aerated materials in order to be coated. *(also see: Fluidized Bed)*

ELISA (Enzyme Linked Immunosorbent Assay) - A test to measure the concentration of antigens or antibodies.

Elute - To separate one solute from another by washing. Elution may include the removal by means of a suitable solvent of one material (absorbed material) from another (adsorbent) that is insoluble in that solvent.

Ellinghausen's Medium - A complex medium for growing Leptospira *(also see; DHL vaccine)*. Contains numerous salts, nutrients, and BSA (Bovine Serum Albumin).

Embriology - The study of the early stages in the development of an organism. In these stages a single highly specialized cell, the egg, is transformed into a complex, many-celled organism resembling its parents.

Endemic - A disease present in a community or among a group of people; used to describe a disease prevailing continually in a region. (*also see: Epidemic*)

Endergonic Reaction - A chemical reaction with a positive standard free energy change, an "uphill" reaction. *(also see: Exergonic Reaction)*

Endocrine Glands - The glands that secrete their products (hormones) into the blood that then carries them to their specific target organs. Endocrine glands are the pituitary, thyroids, adrenals, pancreas, ovaries (in females), and testes (in males). Endocrine glands are found in some invertebrates as well as in vertebrates.

Endocrine Hormones - The products secreted by the endocrine glands. These help control long-term processes, such as growth, lactation, sex cycles, and metabolic adjustment. The endocrine system and the nervous system are interdependent and are often referred to collectively as the neuroendocrine system. For example, the juvenile hormone, found in insects and annelids, affects sexual maturation. There is currently great interest in the possible use of such hormones in the control of destructive insects.

Endonuclease - An enzyme that cleaves its nucleic acid substrate at internal sites (other than the terminal bonds) in the nucleotide sequence.

Endorphins - Endogenous opiates having morphine-like effects consisting of small polypeptides such as enkephalin and leu-enkephalin and longer polypeptides such as alpha, ß-, and gamma-endorphins. They bind to opiate receptors in the brain. Endorphins induce analgesia when injected intraventricularly but not when administered peripherally, presumably because of their inability to cross the blood/brain barrier. The amino acid sequence of the endorphins is short enough to allow the gene sequences coding for them to be synthesized.

Endospore - A highly heat and chemical resistant dormant inclusion (spore) occurring within the substance of certain along the ribosome.

ESCA (Electron Spectroscopy for Chemical Analysis) - *(also see: XPS (X-Ray Photoelectron Spectroscopy))*

Essential Amino Acids - Amino acids that cannot be synthesized by human and other vertebrates and must be obtained from the diet.

Essential Fatty Acids - The group of polyunsaturated fatty acids of plants required in the human diet.

EST (Expressed Sequence Tag) - *(also see: STS (Sequence Tagged Site))*

Ethical Pharmaceutical - A controlled substance for the diagnosis or treatment of disease.

Ethylene Oxide (ETO) - A toxic compound used in gaseous form as a sterilizing agent, usually as a 10% mixture with carbon dioxide or 12% mixture with freon (referred as 12-88). Sterilization using ETO leaves residual chemicals such as ethylene chlorohydrin and ethylene glycol.

Etiologic Agent - A disease-causing organism or toxin.

Eukaryote - An organism that carries its genetic material physically constrained within a nuclear membrane, separate from the cytoplasm. All animal and plant cells except bacteria, viruses, and bluegreen algae are eukaryotic. Eukaryotes are five to ten times larger than prokaryotes in diameter. *(also see: Prokaryote)*

Eutectic - Of, pertaining to, or formed at the lowest possible temperature of solidification for any mixture of specified constituents. A common term used to describe metal alloys.

Evaporator - Apparatus used in distillation to heat a liquid and create a phase change from the liquid to the vapor state. A steam boiler is an evaporator.

Excipient - A more or less inert substance added in a prescription drug compound as a diluent or vehicle or to give form or consistency when the remedy is given in a pill form; simple syrup, aromatic powder, honey, and various elixirs are examples of excipients.

Exergonic reaction - Referring to a chemical reaction that takes place with release of negative standard energy to its surroundings, a "downhill" reaction. *(also see: Endergonic Reaction)*

Exfiltration - Leakage of air out of a room through cracks in doors and pass-throughs through material transfer openings, etc. due to a difference in room pressures.

Exhaustion - Occurs when absorbents, such as activated carbon or ion exchange resins, have depleted their capacity by using up all active sites. Ion exchange resins may be regenerated to reverse the process.

Exogenous DNA - DNA originating outside an organism.

Exon - The proteincoding DNA sequence of an eukaryotic gene. *(also see: Intron)*

Exonuclease - An enzyme that cleaves nucleotides sequentially from free ends of a linear nucleic acid substrate.

Exotic Organism - A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication program undertaken in the given country or geographical area.

Exotoxins - Proteins produced by bacteria that are able to diffuse into a medium through the bacterial cell membrane and cell wall. They are generally more potent and specific in their actions than endotoxins.

Expiration Date - The date placed on the container/labels of an API (Active Pharmaceutical Ingredient) designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Expiry Date - *(also see: Expiration Date)*

Explosion Resistance - A type of construction used to house solvents in sufficiently large quantities, to qualify the space electrically as an explosion potential area. Typically the

internal walls, ceiling, and floor are constructed of material strong enough to withstand a specified intensity of explosion, and at least one wall has explosion relief devices that direct the explosion outwardly. In a single story arrangement, or if the explosion resistant area is on the top floor, the roof may also have devices that can be used to relieve the explosion.

Explosive - A chemical that causes a sudden, almost instantaneous release of pressure, gas and heat when subjected to sudden shock, pressure, or high temperatures, or a material or chemical, other than a blasting agent, that is commonly used or intended for the purpose of producing an explosive effect.

Exposed or Open Process - The drug substance is exposed to the room environment during processing. *(also see: Open System)*

Express - To translate the genetic information stored in the DNA into protein.

Expressed Gene - *(also see: Gene Expression)*

Expression System - A host organism combined with a genetic vector (such as virus or circular DNA molecule called a plasmid) that is loaded with a gene of interest. The expression system provides the genetic context in which a gene will function in the cell – that is, the gene will be expressed as a protein.

Extractables - Undesirable foreign substances that are leached or dissolved by water or process streams from the materials of construction used in filters, storage vessels, distribution piping, and other wetted surfaces.

This article explores two models for speeding the process for producing simple formulation, powder, or liquid in bottle, investigational supplies for human and animal, Phase I clinical trials.

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Fast to Phase I Clinical Trials: A Comparison of In-House GMP Manufacturing and Clinical Trial Site Pharmacy Compounding

by Charles F. Carney and Eugene J. McNally, PhD

Introduction

There are a number of reasons to quickly move compounds into Phase I clinical trials once sufficient safety has been demonstrated in pre-clinical models and toxicology studies. For some compounds, there are no animal models for particular diseases. For others, pre-clinical models are not relevant to the disease being treated in man. For some development programs, several candidate molecules exist and the aim of the Phase I trial is to differentiate the metabolism and pharmacokinetic profiles in man.

Prior to the start of Phase I trials, there are often insufficient amounts of drug substance to perform dosage form development. It often takes several hundred grams of drug substance to develop a dosage form (tablet, capsule, or solution) and generate sufficient long term stability data to guarantee that the drug product will be stable throughout the clinical trial. In addition to the development activities, sufficient drug substance is needed to manufacture GMP supplies and perform full release/stability testing on the material being used in the clinic. All of these efforts are directed at producing supplies to dose 10 - 20 healthy subjects in a single rising dose Phase Ia clinical trial.

For the past several years, we have been searching for an approach that affords maximum flexibility in adjusting the dose at the clinical site balanced against the amount of resources devoted to preparing GMP supplies to dose this small number of subjects. The results from Phase Ia will drive the design of the Phase Ib multiple dose trial. Often our medical colleagues want to minimize the time between these trials which puts additional stresses and constraints on the processes for manufacture, QC testing, and release and stability of new strength dosage forms.

Our desire, therefore, is to move drugs quickly into Phase I while at the same time maintaining control over the preparation of the supplies to ensure a quality product from both a safety and clinical efficacy standpoint. Many companies, ours included, have used the "Compounding in the Clinic" approach as a means to achieve this. In this scenario, bulk drug substance is shipped to the CRO performing the Phase I trial, and the drug substance is compounded and dispensed by a pharmacist for use in the clinical trial just prior to each day of dosing. While this appears to be a simple enough operation at first glance, many sponsors devote resources to ensuring that the trial supplies prepared under the auspices of the clinical pharmacist are fit for purpose especially with respect to the potency of the supplies. Such activities are resource intensive and should be considered in a decision to take this approach. To overcome some of the uncertainty in having a third party pharmacist prepare supplies at the clinical site, an alternative is to manufacture and control the material under GMPs within the pharmaceutical company and treat the material as drug substance. This approach, commonly referred to as "powder in the bottle," allows sponsor control of the process without the time, expense, or drug substance requirements of formal quality control testing and stability that would normally be applied to production of a finished drug product. Performing this work in-house also negates the need for training clinical site pharmacy personnel and overseeing from a business standpoint, that controls and quality procedures are in place in the clinic pharmacy.

In either case, compounding or manufacturing, the procedure to be used will be described in the IND. This description should contain sufficient information concerning the controls applied to allow the FDA the opportunity to understand how the trial will be conducted and to evaluate the controls for the administered dose in the specific procedure and the compliance

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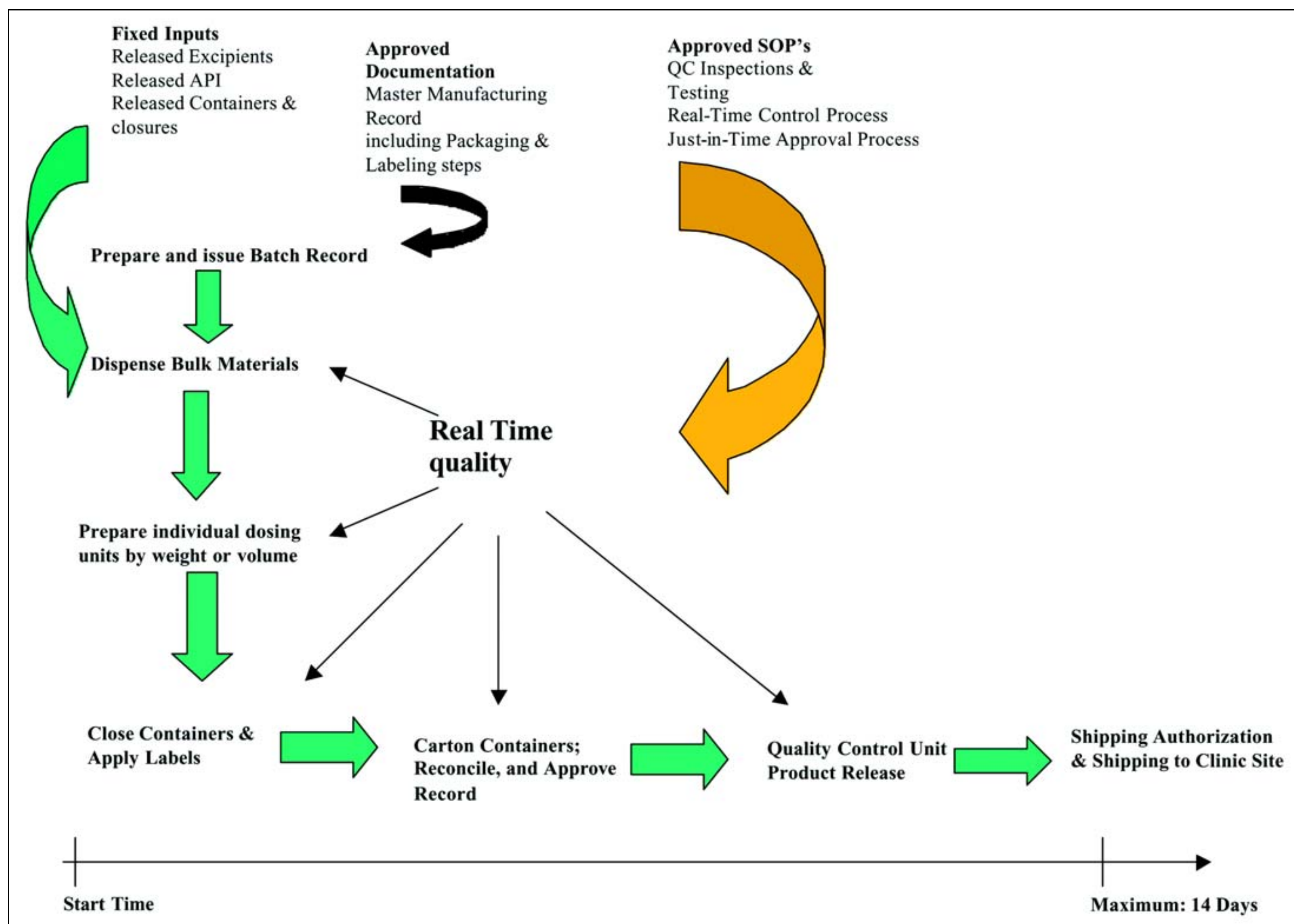

Figure 1. Fast to Phase I Trial: powder/liquid in bottle scenario.

aspects of the approach that will be used. This article will explore and compare the intricacies of these two approaches.

The Distinction Between Manufacturing and Compounding

There are significant distinctions between GMP manufacturing and compounding and it is worthwhile to spend some time discussing them. Compounding is considered an integral part of pharmacy practice and is undertaken pursuant to a prescription from a physician for a particular patient. The dispensing and sale of the preparation takes place under the auspices of a particular State Board of Pharmacy depending on where in the state the pharmacy is located. This same state licenses the pharmacist as a means of recognizing a certain degree of skill level in the compounding and dispensing of medication and also requires registration of the Pharmacy and its owner with the State Board of Pharmacy. In the case of compounding investigational drugs for use in a clinical trial, the material is prepared pursuant to the clinical protocol, which is subject to an IND filing by the sponsor.

In the case of GMP manufacturing, the pharmaceutical company (sponsor) is registered with the FDA and its technicians and scientists prepare drug products under the auspices of GMPs pursuant to batch manufacturing records under the watchful eye of the quality control unit.

Compounding at the Clinical Site

While the practice of having clinical drug products prepared at a clinical site by pharmacy personnel seems rather logical and simplistic, there are a number of issues that should be addressed prior to embarking on this approach. First and foremost is that whatever approach is taken, that it be discussed, understood, and agreed to by all responsible parties within the sponsor company (i.e. clinical supply, formulation, quality control, and quality assurance groups). The FDA guidance on the preparation of investigational materials[1] says, "FDA, while recognizing the differences between the manufacture of investigational products and commercial products, believes that it is nonetheless vital that investigational products be made in conformance with current good manufacturing practice." A good place to start the discussion between these groups in the sponsor company is to establish a definition for your organization of what "conformance with current good manufacturing practice" means. It is beneficial to reach agreement on the types of operations your company is willing to perform at the clinical site under the classification of "compounding." A recent addition to the USP[2] outlines the practice of pharmacy compounding. These practices also have been discussed in the literature.[3] Such a discussion to distinguish "compounding" versus "manufacturing" versus "dispensing" from each other and how each might fit into the definition of "conformance with

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Point of Control	Responsible Party
Definition of Prescription	Company Medical Dept through clinical trial protocol
Evaluation of Facilities	Clinic QA group
Compounding Formula and Process	Specified by Formulation Scientist, summarized in formal document included in clinical trial protocol
Training of Pharmacist	Performed by Formulation Scientist, Documented by pharmacist according to requirements for state licensure
Container/Closure System	Specified by Formulation Scientist, implementation controlled by pharmacist according to requirements for state licensure
Beyond Use Dating	Supportive data provided by Formulation Scientist, implementation by Pharmacist
Labeling (open label or double blind)	Specified by clinical trial protocol, controlled by Clinic QA group
Documentation and Record Keeping	Controlled by Pharmacist according to requirements for state licensure
Quality Control	Controlled by Pharmacist and Clinic QA group and supported by sponsor QC group if necessary

Table A. Controls and organizational responsibilities for "Compounding in the Clinic."

current good manufacturing practice" will help clarify responsibilities and procedures among the clinical investigator, the pharmacist, the company medical monitor, and the R&D GMP structure. In addition, the FDA has recently released a concept paper proposing the formation of a list of dosage forms it feels present difficulties for compounding in a pharmacy because of concerns for safety and efficacy of the drug product. Dosage forms such as metered dose inhalers, sterile products, dry powder inhalers and transdermal delivery systems are being considered for inclusion on this list.[4]

For some sponsors, compounding is confined to performing dilutions (liquid and solid-state), weighing, and encapsulation. Other sponsors actually perform formulation at the clinic trial site which could include extraction of drugs from tablets, assay of active substance, and formulation into a solution or suspension with pH adjustment etc. At the end of such a discussion, consensus should be reached regarding the degree of real time control the company wants to have by its own personnel for clinical site compounding, and whether such compounding meets the spirit of the requirements for preparation of clinical drug product according to the cGMP[5] and associated guidelines.[1]

Table A summarizes our approach to this exercise and the corresponding organizational control assignments that we have made. Our approach has been to separate the compounding activities into a category of operations which are performed in the pharmacy and controlled completely by the pharmacist and the clinic site quality assurance group. This is in contrast to manufacturing activities which are done by and completely controlled in the company by manufacturing scientists and technicians. Input from the company to the clinical site pharmacist is from a scientific or a medical perspective.

Some of the advantages of compounding in the clinic have been introduced earlier in this article. Table B lists a number of issues that should be considered when evaluating a project with respect to preparing doses at the clinical site. It is important to realize that from a resource standpoint, the company is still involved in seeing that the process for compounding is established in the spirit of the cGMPs and there will be support activities ongoing at the company of a scientific nature. The exact nature and extent of these issues change depending on the requirements for preparing the final dosage form. For simple operations such as weighing drug substance and filling into capsules or preparing simple solutions, the issues will not be as difficult when compared to operations in which the physical properties of the drug substance are being altered and concerns of dose uniformity or stability can arise. The main concern is always that the prepared doses are of an acceptable quality, purity, and strength, in addition to being sufficiently stable to ensure that the subject receives the intended dose.

To ensure that the drug substance will be sufficiently stable in the "compounded" drug product, an in-use stability study should be performed at the company by the formulation development group. This is in contrast to the normal practice of compounding in which the pharmacist would consult appropriate references[6] to establish the beyond-use date. However, since these materials are investigational drugs, and no drug specific compendial data would be available, it is appropriate that this exercise be supported by the company formulation group with oversight by its Quality Control Unit. Such a study would aim to collect sufficient data to demonstrate that the drug is stable over the time course of dose preparation, dispensing, and dosing of the subjects. For non-preserved formu-

Provide open label drug substance and placebo for compounding
Provide bottles, delivery devices etc if needed
Assist site in obtaining necessary import permits (if needed) for receipt of drug substance
Perform In-use stability Study to support dosing period in clinic
Provide assistance in Establishing Beyond-use expiration date for compounded materials
Provide double blind labels or protocol for third party blinding by pharmacist
Training of pharmacy personnel in preparation of supplies
Provide analytical support for training activities (potency assay of test materials)
Inspect pharmacy site and identify any practices that should be covered by site SOP's • receipt of supplies/inventory/storage • cleaning of pharmacy compounding area/controlled access • temperature/humidity control (if needed for product stability)
Provide example compounding records for pharmacy use and documentation
Have site QA group check pharmacy documentation prior to using prepared supplies in clinic
Retrospectively assay retained samples to confirm dose prepared and used in trial

Table B. Activities performed by sponsor company to support compounding in the clinic of Phase I investigational materials.

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The alternative to using a pharmacist to compound these small amounts of Phase I supplies is to manufacture them in-house using the clinical drug product GMP system.

lations that are capable of supporting microbial growth, it is important to establish a beyond-use date so subjects are not receiving doses containing organisms. Guidelines exist for establishing beyond-use dates[2] which would support the stability of the compounded supplies through their maximum intended use period.

Assignment of Controls and Responsibilities

If it is felt that the drug substance will be stable in the envisioned "compounded" dosage form, it is then important to quickly assess the capabilities of the pharmacy and pharmacy personnel at the clinical site. From a business perspective, it is important to evaluate whether control of the preparation of the investigational material can be delegated to a third party such that it can be prepared under a "compounding" operation. Specifically, it is necessary to confirm that they have adequate facilities for preparing the material and that the pharmacy personnel are sufficiently skilled for the task to be performed. It is important to evaluate the logistics and time required for supply preparation relative to the number of doses that will be needed, to be able to evaluate the capacity of the pharmacy and its personnel to accomplish the task without having to work around the clock. The facility should be of sufficient size and have the correct equipment (balances etc.) for preparing the materials. The operation of the pharmacy should be reviewed with respect to access, receipt, and control of materials as well as any special environmental controls that may be required such as temperature or humidity for preparation or storage of materials. Other issues that can be explored are listed in Table A and again depend on the degree of control the sponsor wants to maintain over the compounding process using its full-time personnel.

Our practice has been to provide as many of the required materials as possible, and to conduct a training session which includes analysis of the training batches to confirm that the dose required can be prepared accurately. During the training session, documentation is provided that details our thoughts on the compounding procedure. This is reviewed with pharmacy personnel for their input and finalized into a compounding record that is used by the pharmacy personnel when preparing each batch of material. This documentation then becomes part of the clinical trial records kept at the site.

The procedure for labeling the materials to be dispensed to the subjects should be established early in the logistics discussions with the clinic site. For complicated double blind trials, we have found it easier to provide the pharmacy with prepared double blind labels that are pre-attached to the bottle in which the drug will be dispensed to the subject. This makes the label accountability and reconciliation process easy to control by the pharmacist. An alternative is to have the pharmacist act as a third party blind in assigning the materials to subjects. Such an operation should be covered by a detailed procedure established and maintained by site personnel. A decision to use third party blinding performed by the pharmacist should be made in collaboration with the clinical trial coordinators from the sponsoring company and the appropriate quality assurance group. Such a decision should include a review of the site's SOP on this topic.

The last major decision to be made is whether or not quality control testing on the compounded material is thought to be necessary. Such testing can be performed subsequent to compounding and prior to dosing, or done retrospectively. If the retrospective approach is taken, it is important to consider the integrity/stability of the sample being shipped back to the quality control lab. When such retrospective data are generated in our quality control labs, our practice has been to send these data back to the clinical pharmacist for incorporation into the trial record maintained at the site. This ensures that the data are not lost as they do not fit into any of the systems established in-house for testing of GMP drug substances or drug products.

Expedited Manufacturing and Controls for Powder-in-Bottle Drug Products

The alternative to using a pharmacist to compound these small amounts of Phase I supplies is to manufacture them in-house using the clinical drug product GMP system. Fast, flexible, and efficient processes to produce clinical drug products of required quality are important for all phases of clinical research, but are particularly critical in Phase I. Some have argued that large pharmaceutical companies can only achieve such speed, flexibility, and efficiency by outsourcing the work to a quick turnaround contract organization. This argument has extended to the use of "third parties" for example, to prepare the drug products for use in clinical trials. However, another approach is to systematically evaluate the various process steps in the production of clinical drug products to find those ways to increase speed, flexibility, and efficiency in the in-house processes. One can argue that such in-house control should lead to greater flexibility and lower costs. Both the contractor and the sponsor must follow the same philosophical requirements and so it should be possible to develop systems in-house, that are equal to those in the contract facility. Furthermore, by performing the work in-house, one can avoid the additional efforts necessary to find and qualify a contractor, and can avoid the on-going costs for contract development, control, and auditing. Such an in-house system has been developed which meets all of the stated requirements of the GMP of the US, EU, and WHO. This system can be utilized to avoid the costs of outsourcing for those cases other than the need for additional capacity or expertise beyond the core competencies of the sponsor.

The powder-in-bottle dosage form is merely an accurately weighed amount of drug substance in a closed container which can be dissolved in a specified medium in the clinic for administration to the study subjects. The diluent in this case also can be a prepared, unit dose, liquid-in-bottle product manufactured by the sponsor and supplied to the clinic.

The powder in the bottle process described here has all the elements of the cGMPs. Control of starting materials can consist of the normal controls for Active Pharmaceutical Ingredient (API) and the controls for inactive ingredients (for the

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diluent). Testing and release of API and excipient(s) is usually not rate limiting for drug product development or manufacturing. Similarly, a fixed number of container/closure package types can be specified, maintained, and controlled in a ready inventory status for use in any manufacturing process.

The manufacturing process for powder-in-bottle and liquid-in-bottle dosage forms is simple and very straightforward. Efficiency and speed can be enhanced by developing manufacturing records which include dispensing, unit vial weighing/filling, closing, and labeling of all packages in a continuous process. This is similar to the continuous process taken when compounding in the clinic. Because the process can be the same, with the exception of amounts weighed or volume transferred into each vial, a master record can be developed which could be applicable to all projects. One must allow for the inclusion of the product name, amounts to be weighed or volume to be transferred, and specific label to be applied to be included at the time of the preparation of the specific batch manufacturing record from this master in the SOP system. This is fully in keeping with the guidance from the FDA[5] which states, "During the IND stage of drug development, written production and control procedures are developed and initially may be more general… It is important that initial procedures be reviewed and approved prior to implementation, that they be followed, and that they be documented at the time of performance." Calculations for yield, reconciliation, and accountability can all be easily accomplished because the continuous process will ensure that all material weights, volumes, and numbers are managed within this process and any residual small amounts will easily be measured at the end of the process.

The quality control of finished product can occur in real time. Every administration unit (powder-in-bottle or liquid-in-bottle) is individually controlled either by a weight or by a volume measurement. For powder, this weight can be the difference in the tare weight of the container and the gross weight after the specified amount of powder has been added. For liquid, this volume can be measured by use of a pipette, or the amount can be measured by a weight difference as with the powder. By having the quality control function observe these operations, one can avoid any post manufacturing chemical or physical testing. The identity of the material is confirmed through inventory controls (the chain of custody documentation and label information on the container) and the amount in each administration unit container is documented in the manufacturing records. The chemical evaluation is performed during the release testing of the API or of the excipient diluent. The controls during the manufacturing operations and the unit of administration content (ie, the amount of powder or the amount of liquid in the dosing container) can be confirmed in real time by the QC individual who is observing the process. This individual, for example, can ensure that the balance and pipettes being used have been calibrated and that each weight is accurately measured and recorded. These data also serve as the verification of process controls during the manufacturing run. "…data obtained from extensive in-process controls and intensive product testing may be used to demonstrate that the instant run yielded a finished product meeting all of its specifications and quality characteristics.[1]"

Review of documentation and final release of products produced in this continuous fashion can also occur in real time. Those companies who choose to have 100% audit of all GMP production can take advantage of the real time quality control activities to assure the compliance aspects. Today, most companies have a concept, which includes quality control and quality assurance activities into a singular quality concept. As long as the personnel who are performing the real time quality control during the manufacturing steps are organizationally independent from the manufacturing operations the real time control also can be utilized as real time assurance. As a result, final release can occur immediately with the completion of the final labeling and cartoning operations. Release and final disposition decisions can occur immediately after the final approval by the manufacturing supervisor.

Stability data in support of the expiry period for such powder-in-bottle drug products come from the API stability evaluation. Data can be collected prior to the manufacturing run on powder stored in the same container closure system. And other approaches for utilizing bulk storage stability data on the API could be utilized. A standard approach and philosophy should be established by the sponsor and applied consistently. Because nothing is added to the API in this dosage form, and because it is transferred from a bulk container to the individual dosing containers under controlled GMP conditions, the available stability data for the API can be utilized for this purpose.

Beyond use labeling for the reconstituted product, at the clinical site, can again be generated by the formulation group. From the start of dispensing, through weighing, filling, packaging, labeling, QC, and stability, the product can be produced and shipped to the clinical site in the matter of several days to two weeks, thus accomplishing the goal of fast and flexible production of a simple Phase I dosage form.

Discussion

Compounding has been a pharmacy practice since the beginning of medical practice. It has been utilized in the partnership between physician and pharmacist to provide the appropriate drug dosage to the patient in the care of the physician. It continues to be a practice for the treatment of disease using commercially recognized drugs and this is the reason for the monograph that exists in the US Pharmacopeia 24, where it states in the Preface, "...a resurgence in compounding practice has arisen out of the unavailability of strengths or forms suitable for special populations, especially pediatric needs, and for short-life preparations…" The International Association of Compounding Pharmacists is playing a key role in selecting among the many known formulae to identify those of more medical merit and wider usage. Additional monographs are expected to appear in subsequent supplements.[7]" In the general information compounding monograph,[2] it states, "Compounding is different from manufacturing, which is guided by the GMPs." And, "The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and label in accordance with good pharmacy practices, official standards, and relevant scientific data and information." The question before us at this point is whether compounding of investigational new chemical or biological entities (NCE or NBE) is included philosophically within these statements. If the answer is yes, then one can provide a system for incorporation of compounding into the preparation of administration units for performing clinical trials.

One can argue from the commercial side of this regulated business that compounding is a recognized and accepted alternative for the preparation of commercial drug products. When

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a dosage form or strength of a commercial drug is not available for the treatment of a specific patient, the physician can collaborate with the pharmacist to provide an appropriate dosage form or strength of that drug to the patient through extemporaneous compounding. Of course, this is supplemental to the usual practice of making batches of drug products according to information supplied in the approved NDA. While pharmacy practice does not have all of the controls required in the GMP for preparing administration forms, nevertheless it is accepted that a pharmacist can prepare administration forms for certain "special cases" (defined by the physician). The purity, strength, and quality of these preparations depend on the skills, integrity, and practical capabilities of the pharmacist.

Based on this argument for commercial products, one also could argue analogously for investigational products. In the case of clinical trials, especially where small numbers of subjects receive the administered product under well controlled conditions over a relatively short time frame, it can be argued that even greater assurance of purity, strength, and quality of the administered forms can be achieved by a close training of the pharmacist by the sponsor and a clear statement of need and expectation for results in the clinical study protocol. In such a case, a significant amount of supportive data can be developed in-house by the sponsor. These data can allow the conclusions to be drawn whether extemporaneous compounding of the administration form can be expected to have the appropriate strength and quality required for the clinical trial. From this argument, one can draw the conclusion that this satisfies the spirit of the GMP requirements for producing drug product for clinical trials. This extemporaneous compounding in support of Phase I short-term safety and dose ranging evaluations can occur quickly and could be viewed as resource and time sparing.

On the other hand, we have shown here an alternative process in which all of the requirements for drug product manufacture according to the cGMP can be achieved in-house in a rapid and flexible process for the preparation of appropriate administration forms for Phase I. In this model, one can save the time and costs required for pharmacist training, shipping, and performing confirmatory analytical testing after-the-fact which can be part of the necessary activities in support of the compounding scenario. In this model also, the sponsor has greater control of all of the technical information and can maintain greater degree of flexibility and response to changes in project needs.

Conclusion

For the virtual company, which must rely on out-sourced capacity, the compounding model may be very appropriate for the rapid entry into clinical trials for its new chemical entities. However, various boundary conditions must be established to ensure that the clinical administration forms, which are produced, meet the spirit of the requirements stated in the regulations for GMP manufacture of investigational drug products. However, for the larger pharmaceutical company which has all of the various functions in-house, we have described a model for fast and flexible entry of its NCE's into clinical trials which meets the full intention of the regulatory requirements for investigational drug products to be manufactured according to cGMPs. With this model, one can save costs and ensure that the sponsor's operating personnel are focused on the science and technology supporting development of a commercially viable drug product. Their efforts will not be diluted by the need to qualify, train, and oversee external resources, and to develop the data to support the assertion that the compounded administration form meets the "spirit," if not the "substance," of the stated regulatory requirements.

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