This article presents the advantages and disadvantages of various temperature measurement methods and highlights the use of a Platinum Resistance Thermometer (PRT) to measure the process.

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Measuring Process Temperature in Small Diameter Lines

by Greg Thorp, PE and John Zwak

Preface

In today's high-performance process systems, measuring the process temperature in small diameter lines down to .25 inch diameter must be understood. The most common applications have processes running in the temperature range of -50°C to +200°C. Measurement uncertainties can easily reach several degrees Celsius over this temperature range due to thermodynamics that can induce conduction effects of the sensor. Other real-world factors, such as the required time response of the temperature measurement, the ability to replace sensors during process operation, and the ability to Clean-In-Place (CIP) all contribute to the difficulty of this measurement. This article looks at several methods that can be used for making these measurements including direct immersion (without a thermowell), indirect immersion (with a thermowell), and non-intrusive methods. The temperature sensor assemblies range from a simple clamp-on surface sensor to sensors with elaborately designed thermowells. This article will focus on measuring the process using a Platinum Resistance Thermometer (PRT), due to the performance required for most applications. It also will discuss the advantages and disadvantages of each temperature measurement method along with uncertainty estimates based on some common conditions.

Introduction

Accurate temperature measurement of a fluid flowing in .25 to 4.0 inch diameter lines can be difficult to achieve. While thermocouples, bimetallic sensors, thermistors, or other devices may be used, they have limitations on performance that prevent them from meeting the long term accuracy, stability, and repeatability performance available in platinum resistance thermometers (PRTs). Pipes larger than 4

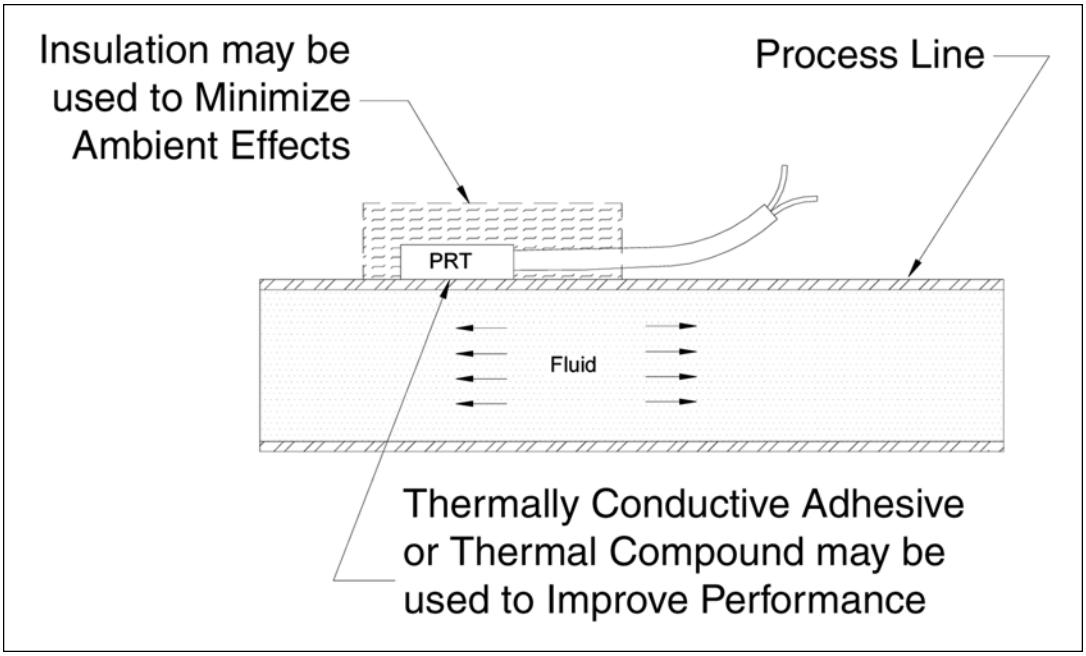

Figure 1. Typical surface sensor installation.

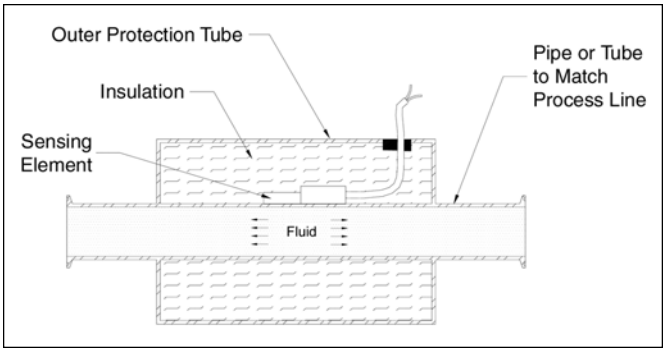

Figure 2. Non-intrusive sensor.

inches in diameter provide sufficient space for mounting standard PRT assembly configurations. However, lines from .25 inch to 4 inch diameter require special consideration. Many of the performance advantages of a PRT can be lost through improper use or selection of a PRT that is not designed for the application.

Industry standards for industrial PRTs, such as ASTM E1137 and IEC 60751, are concentrated on cylindrically sheathed, direct immersion style sensors. These documents provide no guidance on adapting these thermometer styles for use in applications such as the ones described above. Additionally, the performance demonstrated by the sensor in a test laboratory may be completely different than the results obtained when used in a production installation.

Measuring temperature in small diameter lines presents some unique challenges. This article examines several different methods for measuring temperature in lines down to .25 inch diameter, and provides test result for the various methods under some typical conditions.

Discussion

Expectations for PRT Sensors

PRT sensors are chosen when process temperature is critical because PRTs offer superior accuracy, stability, and repeatability compared to other temperature measuring devices. Many users of PRT sensors have expectations of accuracy based on the Resistance vs. Temperature tolerances in ASTM E1137 or IEC 60751, which at 100°C are ±0.3°C for the Grade A or Class A sensors, and ±0.67°C for the Grade B or Class B sensors. These tolerances apply only to the resistance of the PRT sensor when measured under ideal laboratory conditions. In addition, many users request individual PRT calibration and transmitter matching which can provide accuracy to better than ±0.05°C. While these accuracies are achievable in a vast number of process installations, they are not always achievable in unique installations like small diameter lines. In these applications, errors at 100°C could easily reach 3°C or larger and can fluctuate greatly depending on ambient conditions.

Temperature Measurement Methods for Small Diameter Lines

The following four typical methods for measuring the temperature of a fluid inside of a line will be discussed in this article:

1. using a surface sensor on the outside of the line
2. installing a non-intrusive sensor in the process line
3. directly immersing a sensor into the fluid flow

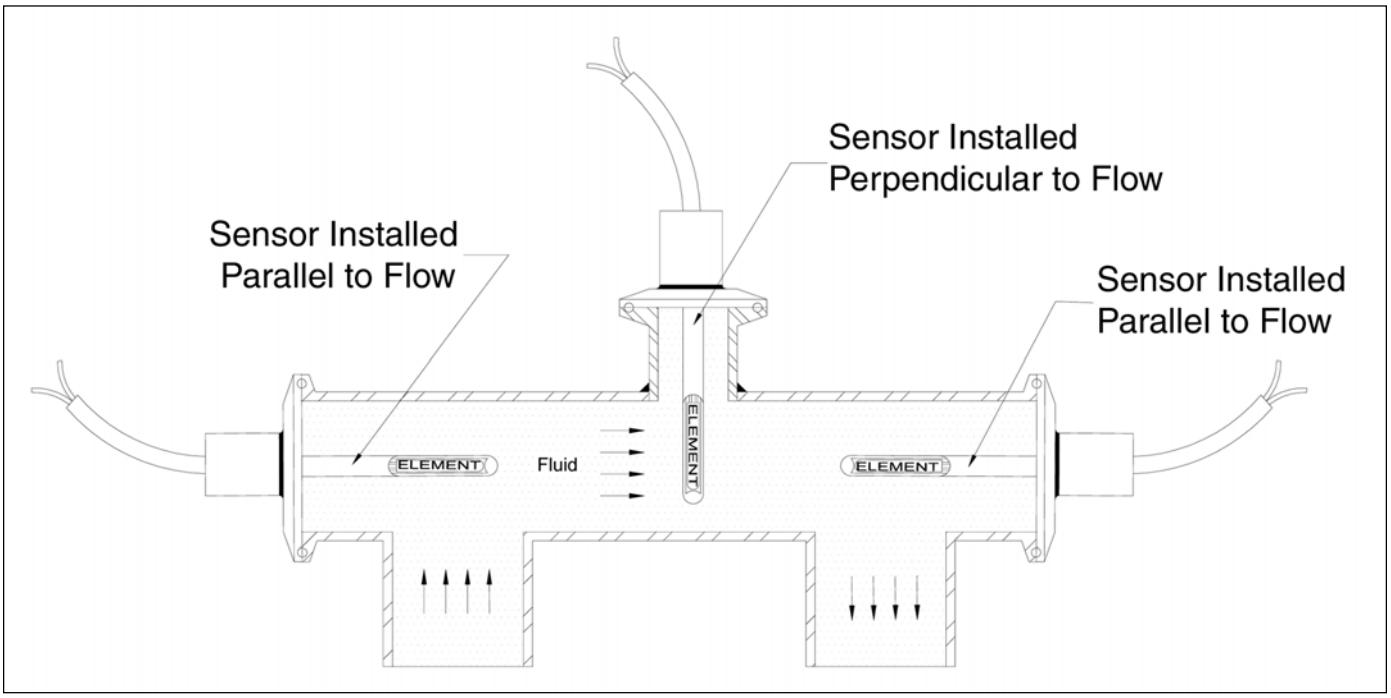

Figure 3. Direct immersion sensor installations.

Advantages	Disadvantages
Simple to use	Slow response time
No line modifications required	Highly influenced by ambient environment
Installation and replacement are easy	Performance variability due to mounting
No need to drain the system to replace	Exposed insulation can be undesirable
Flexibility in location possibilities	
No possibility for leaks	
No foreign material in process	
Low cost	

Table A. Surface sensor advantages and disadvantages.

4. installing a thermowell and sensor into the line (referred to as "indirect immersion")

Surface Sensor

One approach to measuring the temperature of the fluid inside the line is to clamp or glue a surface sensor on the outside of the pipe. Figure 1 shows a sectional drawing of a surface sensor that is attached to a line with an adhesive. This method is one of the simplest to use since the process line does not need to be changed by removing a section or adding a port. While adequate performance may be obtained by simply attaching the sensor to the line, in general, it is recommended that a thermally conductive adhesive or a thermal paste be used between the sensor and line to improve the heat transfer. By improving the heat transfer, a more accurate and faster responding measurement can be made. To further improve the sensor accuracy and minimize the effects of ambient airflow over the sensor, insulation may be added over the top of the sensor after installation. This decreases the effects of ambient temperature on the sensor.

Many users find that even with adequate installation precautions, the surface sensor method is adequate for process monitoring, but inadequate for control applications due to measurement errors and slow response times. However, this determination is highly dependent on the particular application requirements. Advantages and disadvantages of the surface sensor method are listed in Table A.

Advantages	Disadvantages
No immersion into process	Response time slower than immersion styles
No obstruction of process flow	Installations require planning
Element mounting and insulating are factory controlled for consistency	Must replace entire pipe section to replace sensor
Clean external envelope	Must drain system to replace sensor
Installation and replacement are easy	Calibration can require special baths
Faster response time than simple surface sensor	More expensive than most other PRT sensor options

Table B. Non-intrusive sensor advantages and disadvantages.

"Accuracy and response time can vary significantly based on the type of PRT used and the process conditions in which it will be used."

Non-Intrusive Sensor

A non-intrusive sensor is typically constructed using a surface sensor where the sensing element has been attached to a short section of pipe or tubing that is designed to replace a section of the process line. The sensing element is insulated and protected by a tube over the section of line. This style of sensor offers improvements over a standard surface sensor because the element mounting and insulation is less variable than when applied in the field. In addition, the outer sheath protects the element and insulation from damage and provides for a cleaner installation. Figure 2 shows a sectional view of a non-intrusive style sensor.

The non-intrusive style sensor solves several of the shortcomings of a simple surface sensor and offers improved accuracy and response time in a clean package. Advantages and disadvantages are given in Table B.

Direct Immersion Sensor

A sensor that is immersed directly into the flow is the typical solution that is used on many process lines, large or small, because it provides for accurate measurement and quick response time. However, for small diameter lines, the sensor immersion depth may not be adequate to obtain an accurate temperature measurement if the sensor is installed perpendicular to the flow. A general rule that is used for immersion PRT sensors is that the Minimum Immersion Length (MIL) into the flow should be at least 10 times the sheath diameter plus the length of the sensing element. This immersion length is required to minimize the stem conduction error, the error caused by heat transfer between the sensing element and the ambient conditions at the back of the sensor. For a typical .25 inch diameter sensor with a 1 inch long element, this guideline would require a 3.5 inch immersion into the

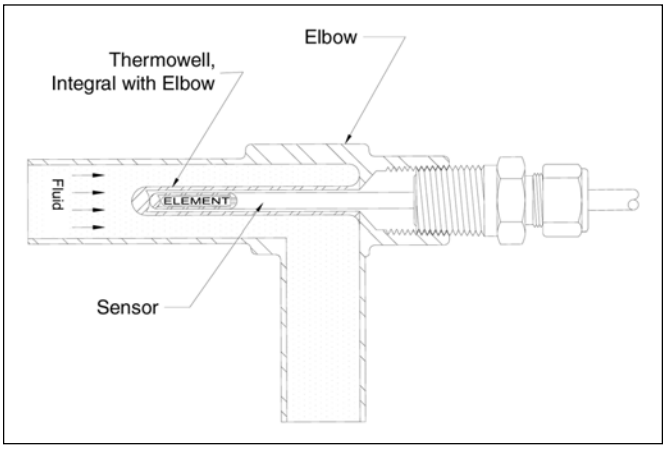

Figure 4. Indirect immersion sensor installation.

"The user needs to understand the accuracy and response time requirements in order to choose a measurement method which will meet the requirements, and avoid unexpected errors due to misapplication of an otherwise accurate PRT."

fluid. This may be achievable on lines with a 4 inch or larger Inside Diameter (ID), but is not achievable for lines smaller than this. For lines with an ID smaller than 4 inches, a smaller diameter sensor with a short element length may work; however, practical limitations on sensor construction and strength considerations make it difficult to reduce diameters to much less than .125 inches. With reduced diameters, the minimum immersion will still need to be approximately 1.5 inches.

As an alternate to immersing a sensor perpendicular to the flow, the sensor may be mounted in the end of a "tee" to allow a longer immersion depth. Figure 3 shows a direct immersion installation in a perpendicular orientation and in a tee with flow parallel to the sensor sheath. While it is conceivable to achieve a proper immersion depth when mounting the sensor in a parallel manner, consideration must be given to other factors such as flow blockage, pressure drop, and drainability. Advantages and disadvantages of direct immersion sensors are shown in Table C.

Indirect Immersion Sensor

One of the most significant disadvantages of the direct immersion sensor is that the system must be shut down and drained every time a sensor is removed for routine calibration or replacement. This disadvantage can be eliminated by using a thermowell, which creates an indirect immersion of the sensor. While the addition of the thermowell makes removal and replacement of the sensor easier, it complicates the thermodynamics of the measurement and can increase the measurement error and slow down the response of the sensor. A sectional view of an elbow with an integral thermowell is shown in Figure 4.

A significant error can occur if the sensor and thermowell are not designed as a system. It is not uncommon for the

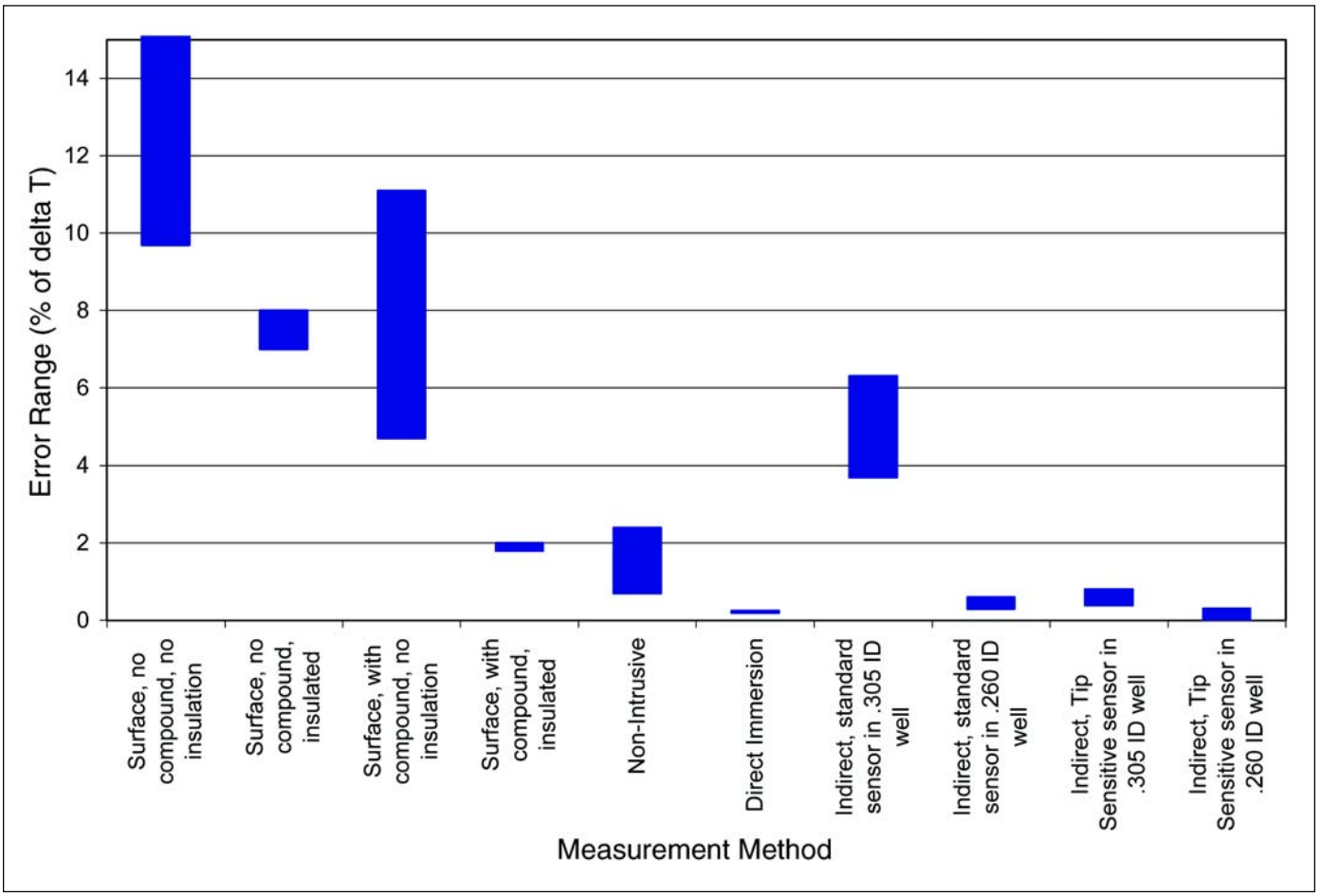

Figure 5. Accuracy comparison graph.

Advantages	Disadvantages
Fast response time	Installation requires planning
Unaffected by ambient conditions when proper immersion is used	Flow blockage and pressure drop must be considered
Simple installation	Installation could leak
Low cost	Stem conduction effects can be large if proper immersion is not used
	Must drain system to replace sensor

Table C. Direct immersion sensor advantages and disadvantages.

piping designer to specify the installation of an elbow with integral well where the well is made from standard .375 inch diameter tubing with a .035 inch wall thickness. While this standard size tubing is convenient to use, the resulting well has a nominal ID of .305 inch. Typical thermowells specified by instrumentation engineers for use with .25 inch diameter PRTs have a nominal ID of .26 inch. A .26 inch ID well, while less convenient to manufacture, will perform much better than a .305 ID well when used with a standard .25 diameter PRT. Further performance improvements can be made by using a PRT that has been custom designed for use in short thermowells, or thermowells with an oversized ID. A tip sensitive PRT, one that has a short element length and has the element in good thermal contact with the tip of the sensor while minimizing the thermal path to the back of the sensor, can improve accuracy and response time of the measurement. Smaller diameter thermowells with correspondingly smaller PRTs are available as well, when the application demands it.

The advantages and disadvantages of the indirect immersion method are listed in Table D.

Analysis of Measurement Errors

It is beyond the scope of this article to discuss the mathematical models that describe the heat transfer relationships for all the different styles of sensors. Suffice to say that when a high quality PRT is used to measure temperature, in most installations and under steady state conditions, thermal conduction effects are the dominant source of error. This error is directly related to the magnitude of the difference in temperature between the fluid being measured and the ambient surroundings, this difference is referred to as "Delta T" (ΔT). It can be shown that under steady state conditions the conduction error may be represented as a percent of ΔT. A very simplistic interpretation is to view every installation of a PRT as having a thermal profile that goes from "near fluid" temperature to ambient environment temperature. The goal for an accurate temperature measurement is to have the PRT sensing element located in the "near fluid" portion of this profile. The best way to accomplish this is to thermally couple the PRT element to the process fluid, and thermally isolate the PRT element from the ambient environment.

Experimentation

Accuracy Testing

Accuracy testing was performed in a laboratory controlled "sample process" on several of the different types of sensors

Advantages	Disadvantages
Sensor is replaceable without draining the system	Installation requires planning
Less affected by ambient conditions than surface methods	Flow blockage and pressure drop must be considered
No possibility for leaks	Stem conduction effects can be large
Sensor removal will not introduce contaminants into the process	More expensive than direct immersion methods

Table D. Indirect immersion sensor advantages and disadvantages.

previously described in this article. The "sample process" that was used to test these sensors was hot water flowing at approximately three feet per second through a .5 inch outside diameter stainless steel tube with a 0.065 wall. A brief description of the sensors that were tested are as follows:

Surface sensor - a typical clamp-on style surface sensor was tested as installed with and without thermal compound at the sensor to line interface, and with and without insulation over the sensor.

Non-intrusive sensor - a sensor of construction similar to that shown in Figure 2 with a .5 inch diameter process line with a 0.050 wall.

Direct immersion sensor - a .125 inch diameter by 1.0 inch long sensor with a sanitary cap process connection installed perpendicular to the flow.

Indirect immersion sensor - a process line elbow with an integral thermowell similar to that shown in Figure 4. The well was approximately 2 inches long by .375 inch OD with either a .305 or .260 ID and was tested with both a standard .25 inch diameter PRT and a tip sensitive .25 inch diameter PRT.

All of the PRTs used for this testing were calibrated at multiple temperature points using a method typical for industrial PRT calibration, the uncertainty of the calibration was estimated not to exceed 0.025°C. This calibration was

PRT sensor type	Error (% of ΔT) No ambient airflow	Error (% of ΔT) With ambient airflow
Surface Sensor - clamped on with:		
No thermal compound, no insulation	9.7%	26.6%
No thermal compound, insulated	7.0%	8.0%
With thermal compound, no insulation	4.7%	11.1%
With thermal compound, insulated	1.8%	2.0%
Non-Intrusive	0.7%	2.4%
Direct immersion (.125 diameter x 1.0 long)	0.2%	0.2%
Indirect immersion (.25 dia PRT):		
.305 ID well - standard PRT	3.7%	6.3%
.305 ID well - Tip sensitive PRT	0.4%	0.8%
.260 ID well - standard PRT	0.3%	0.6%
.260 ID well - Tip sensitive PRT	0.3%	0.0%

Table E. Accuracy test results for 4 different sensors on ½ inch diameter line. Water at 50°C (ΔT = 28°C), 3 feet per second.

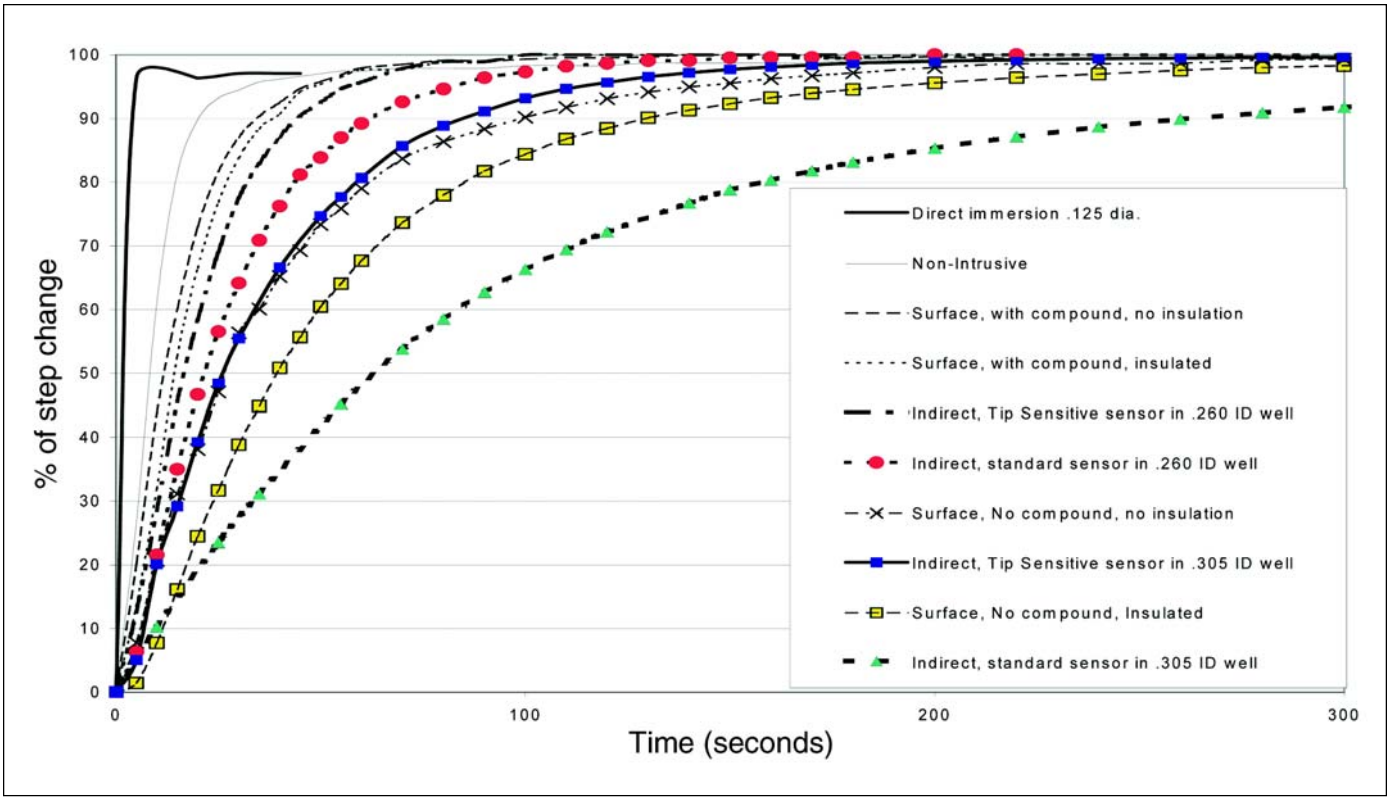

Figure 6. Response time comparison graph.

performed so that the individual resistance vs. temperature characteristics for each sensor could be used to accurately calculate the temperature and determine the measurement error. The sensors used for monitoring the water supply and ambient air temperatures were a secondary standard grade PRT that was matched to a precision digital thermometer, the overall accuracy of these monitoring systems is estimated to be less than 0.035°C.

Two variations of the test were performed. The first variation was at a fluid temperature of approximately 50°C with no ambient airflow over the portion of the sensor outside the process. The second condition was similar to the first except a 4 inch diameter fan was placed 12 inches from the sensors to circulate ambient air over the portion of the sensor outside the process. This was done to determine the sensitivity of the measurement method to ambient conditions. The results of the test are given in Table E and shown graphically in Figure 5. To account for variation in fluid temperatures, the errors are presented as a percent of ΔT. Presenting the results as a percent of ΔT not only normalizes the data, but also allows the data to be used to estimate expected errors under different temperatures. For example, a sensor that exhibited an error of 0.7% of ΔT, if used in a 121°C sterilization process (with similar heat transfer characteristics) would have an estimated error of 0.7°C (0.7% of the 100°C ΔT between the process temperature and ambient surrounding temperature). Therefore, the accuracy recorded can be used to approximate the actual uncertainty in a 121°C sterilization process.

PRT sensor type	63.2% Response
Clamp On Surface	
No thermal compound, no insulation	38 seconds
No thermal compound, insulated	55 seconds
Thermal compound, no insulation	17 seconds
Thermal compound, insulated	20 seconds
Non-Intrusive	11 seconds
Direct immersion (.125 diameter x 1.0 long)	< 5 seconds
Indirect immersion (.25 dia PRT):	
.305 ID well - standard PRT	91 seconds
.305 ID well - Tip sensitive PRT	40 seconds
.260 ID well - standard PRT	30 seconds
.260 ID well - Tip sensitive PRT	22 seconds

Table F. Response Time Test Results for 4 different sensors on ½ inch diameter line. Step change in water from 22°C to 50°C, 3 feet per second.

Response Time Testing

A test was conducted to determine the relative response time of the various PRT measurement methods. The test was conducted by pumping hot water through the lines, which were initially at room temperature, and determining how long each measurement method took to reach 63.2 percent of the step change in temperature. Since all methods were tested using identical flow conditions, a direct comparison can be made between methods. It is important to note that actual installation conditions will significantly affect this result so this test was meant to give relative information only. The results are given in Table F and shown graphically in Figure 6.

Conclusion

To achieve accurate temperature measurement in lines from .25 to 4 inches in diameter requires special consideration. Standard PRT sensors do not perform the same in small line installations as they do in calibration baths in laboratories primarily due to thermal conduction effects and ambient environment influences. Accuracy and response time can vary significantly based on the type of PRT used and the process conditions in which it will be used. The user needs to understand the accuracy and response time requirements in order to choose a measurement method which will meet the requirements, and avoid unexpected errors due to misapplication of an otherwise accurate PRT. Direct immersion PRTs should be considered where the highest accuracy is required for control of the process temperature. Non-intrusive or surface mount PRTs may be used where best accuracy is not required, such as process monitoring. Additional requirements such as the convenience of clamping a surface sensor on to the outside of a line, or the ability to remove a sensor without draining the system also will impact the final decision. With the proper choices, an accurate, stable, and repeatable measurement can be achieved.

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Biotech CIP Cycle Development

by Timothy Howard and Matt Wiencek

This article demonstrates how the principles of ISPE's C&Q Baseline® Guide can be applied to a cycle development program at a modern biotech manufacturing facility.

Introduction

CIP Cycle Development (CD) is a systematic approach of setting CIP systems to work in a manner that promotes rapid and successful execution of Cleaning Validation (CV) activities. The Cycle Development program is an integral part of the overall commissioning of a facility and its processes. It is not enough to merely confirm tubing, valves, pumps, controllers, and instrumentation are installed as designed, functioning as specified, and within acceptable tolerances. The act of running a cleaning cycle, and confirming the software and associated control elements respond as expected (or functional testing) does not constitute Cycle Development. All of these activities are elements that must take place prior to Cycle Development, but do not provide for development of a cleaning cycle. Cycle Development employs CIP skids that have been commissioned, and through a three step process, optimizes the cycle parameters for each cleaning circuit in the plant. A formal Cycle Development program will lead to robust CIP cleaning cycles, which in turn minimizes cleaning validation deviations, retests, and lengthy investigations of failures. The purpose of this article is to demonstrate how the principles of the ISPE Commissioning and Qualification (C&Q) Baseline® Guide can be applied to a Cycle Development program at a modern biotech manufacturing facility.[1]

Background

Cycle Development (CD) typically occurs after CIP and support systems are mechanically complete and prior to Cleaning Validation (CV) execution. CD is one subset of activities within the overall commissioning effort. The ISPE Baseline® Guide on Commissioning and Qualification (C&Q) can be applied to plan and execute an organized and efficient CD program.

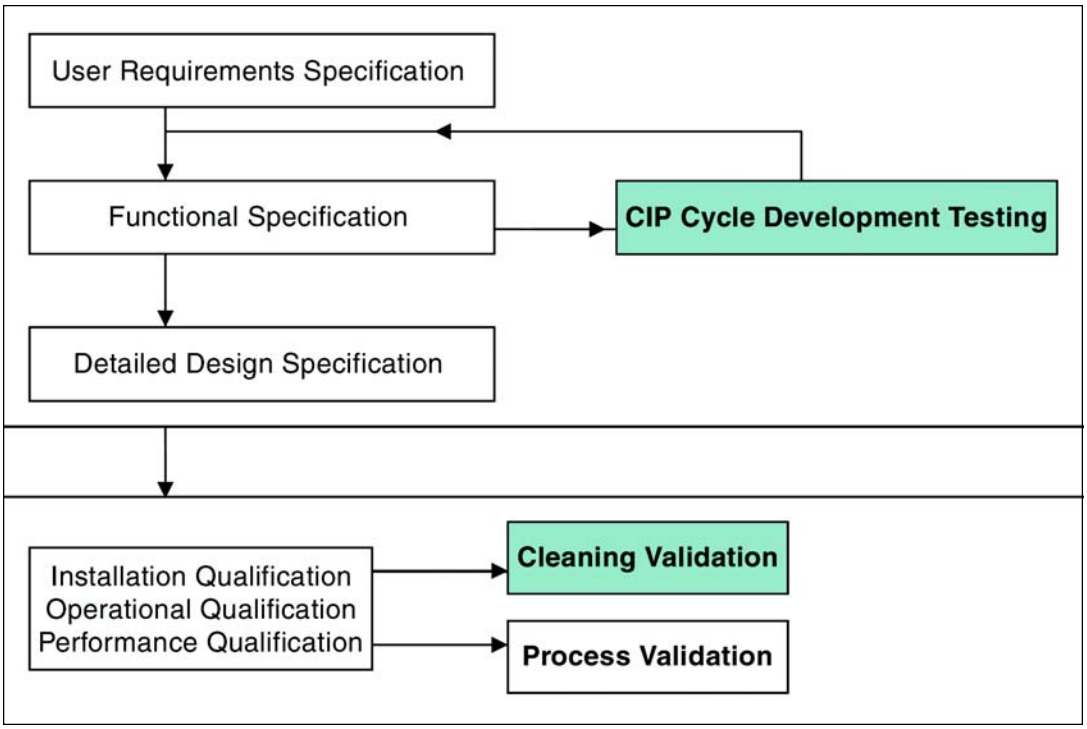

Figure 1. Overview of CD testing program and cleaning validation prerequisites.

Equipment	CIP Circuit	Circuit Name	Unique/ Clone
500L Buffer Prep Vessel #1	Tank	B-C01	Unique
	Inlet Line	B-C02	Unique
	Outlet Line	B-C03	Unique
500L Buffer Prep Vessel #2 (Vessel identical to #1)	Tank	B-C04	Clone
	Inlet Line	B-C05	Clone
	Outlet Line	B-C06	Clone
2000L Buffer Prep Vessel #3	Tank	B-C07	Unique
	Inlet Line	B-C08	Unique
	Outlet Line	B-C09	Unique
1000L Buffer Hold Vessel #4	Tank	B-C10	Unique
	Outlet Line	B-C11	Unique
2000L Buffer Hold Vessel #5	Tank	B-C12	Unique
	Outlet Line	B-C13	Unique
2000L Buffer Hold Vessel #6 (Vessel identical to #5)	Tank	B-C14	Clone
	Outlet Line	B-C15	Clone
3000L Buffer Hold Vessel #7	Tank	B-C16	Unique
	Outlet Line	B-C17	Unique

Table A. Functional test plan - buffer prep.

This article will examine the planning of a CD program for a modern biotechnology manufacturing facility and present two case studies for execution of the plan. The case studies will examine development of a process vessel cleaning circuit and a Tangential Flow Filter (TFF) skid cleaning circuit.

For the purposes of this case study, the CIP system is deemed to be a "direct impact" system as defined in the C&Q Guide.[2] The CIP system includes the CIP skid, supply and return piping, process equipment, and the instrumentation used to monitor critical parameters of the cycle. Direct Impact systems require full commissioning prior to or integrated with qualification activities. The Baseline® Guide defines commissioning as:

> *A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in safe and functional environment that meets established design requirements and stakeholder expectations.*[3]

The Commissioning Program is defined by a formal Commissioning Plan which lists a set of deliverables. The C&Q Guide defines these as follows:[4]

- Commissioning Schedule
- Budget, Pre-Delivery Inspection Plan, and Report
- Factory Acceptance Plan and Report
- On-Site Inspection Plan and Report
- Functional Test Plan and Report
- Commissioning Plan Summary Report.

The C&Q Guide describes the activities contained in the Functional Test Plan as follows:[5]

- setting equipment to work
- regulation and adjustment
- performance testing

CIP Cycle Development activities fall into the category of Performance Testing, and therefore should be defined within the Functional Test Plan of the Commissioning Program. CD requires a fully functional, integrated control system/physical installation. CD may result in changes to either the physical configuration of a system or to the cleaning sequence of operations. Therefore, it should occur after the functional testing phase of commissioning, but prior to formal operational qualification. Performing at least some CD before operational qualification (although perhaps not the soiled phase) will reduce the necessity for strict change control and the number of qualification deviations that may need to be processed as a result of changes to operational sequences or physical configuration – *Figure 1*.

Developing the Plan

The first step in developing a CD test plan is to define the functional boundaries. The functional boundaries can easily be defined as the individual CIP cleaning circuits. Today's biotechnology facilities have multiple CIP skids with each one typically dedicated to a manufacturing department or subset of similar equipment. In the example discussed below, one CIP skid services each of the following areas: Buffer Prep, Media Prep, Fermentation, and Purification. Each of these CIP skids will serve multiple cleaning circuits in its respective area. The exact number of circuits should be defined in a Functional Specification (FS). The number of cleaning circuits is based on the amount and type of unit operations in the plant. A CIP Cycle Development Test Plan for the Buffer Prep area is defined in Table A. Similar plans should be generated for the Media Prep, Fermentation, and Purification areas.

The process P&IDs will define the major equipment systems (column 1 of Table A). The FS will define the CIP circuit type and the unique circuit name (column 2 and 3 of Table A). Each circuit can be designated as "unique" or "clone" (column 4 of Table A). This designation is a necessary element of the test plan for accurate resource planning purposes. For example, two identical vessels located next to one another in the manufacturing area, and served by the same CIP Skid, may be considered the same for CD purposes. The 500L Buffer Prep Vessels in Table A meet these criteria. The "unique" or "clone" designation can only be made after a careful analysis of the equipment, size, location, configuration, soil type, and cleaning chemistry. The "clone" circuits will require less CD field work because programmable recipe parameters will be copied from the unique circuit. It is important to note that a circuit considered to be a clone during CD may or may not be considered a clone when performing cleaning validation studies.

Generating a Schedule

A facility test matrix can then be developed to aid in the calculation of manpower requirements - *Table B*. This is necessary for generating a realistic Commissioning Schedule as required by the C&Q Guide.

CD consists of three distinct phases: water cycle testing, chemical (or cleaning agent) cycle testing, and soiled equipment testing. This incremental approach assures that chemicals are introduced into the systems only when it is safe to do so. The effectiveness of the pre-qualification soiled test runs can be measured by collecting rinse samples. The rinse sample data can be used to establish a cleaning data bank prior to starting the Cleaning Validation program. The manpower estimates per task (shown in man-days in Table B) represent the amount of time one member of the CD team will spend in the field running the CIP skid and process equipment. Each facility should use estimates that are particular to their site. The manpower requirements shown in Table B are estimates. The Buffer Department estimates are shown in full detail. Again, similar tables should be developed for the Media Prep, Fermentation and Purification Departments. We will assume that the overall Commissioning Plan designates a three month window in which the CD must be completed. Therefore, the following staffing estimates can be developed:

205 work-days / 20 work-days/month = 10 work-months

10 work-months / 3 months permitted by schedule ~
4 team members full time to satisfy the schedule.

The initial reaction to the required field execution time for Cycle Development is typically a surprise to those not familiar with the CD test procedures. The amount of time necessary for this effort often leads to multiple shift or around the clock testing. When scheduling the CD activities, it is critical to understand resource limitations that may negatively impact the effort. These limitations may include the capacity of water systems to meet demand and availability of QC laboratory coverage for testing. Most water systems are not designed to support continuous use of all CIP skids around the clock. Similarly, during the startup phase of a facility, QC laboratories rarely can support sustained around the clock testing of this nature. Equally important in scheduling the CD activities is to assess the impact of other plant or process commissioning. It is impossible to conduct cycle development on a media prep vessel while the batch software for the vessel is being commissioned. With a good understanding of these limitations, and the magnitude of the effort required, an accurate CD schedule can be integrated with the entire facility commissioning schedule.

CIP Cycle Development Test Procedures

The CD test procedure should define the amount of "regulation, adjustment, and performance testing" as required by the C&Q Guide. These procedures should be written to comply with the requirements of the FS for each unit operation. Their purpose is to control start-up/CD activities only and are not to be considered GMP documents. The FS must detail the recipe parameters for each piece of equipment to be cleaned. By using the incremental approach of water batch, chemical batch, and soiled batch testing, the CD team can efficiently and safely define these parameters for the Cleaning Validation effort.

Circuit Name	CIP Circuit Type	Unique/Clone	Work-days per Water Test Run	Work-days per Chemical Test Run	Work-days per Soiled Test Run	Total Work-days of CD Field Work
B-C05	Inlet Line	Clone	0.5	0.25	0.25	1
B-C02	Inlet Line	Unique	1	0.5	0.5	2
B-C09	Inlet Line	Unique	1	0.5	0.5	2
B-C07	Outlet Line	Clone	0.5	0.25	0.25	1
B-C15	Outlet Line	Clone	0.5	0.25	0.25	1
B-C03	Outlet Line	Unique	1	0.5	0.5	2
B-C10	Outlet Line	Unique	1	0.5	0.5	2
B-C12	Outlet Line	Unique	1	0.5	0.5	2
B-C13	Outlet Line	Unique	1	0.5	0.5	2
B-C17	Outlet Line	Unique	1	0.5	0.5	2
B-C04	Tank	Clone	1.5	0.5	0.5	2.5
B-C14	Tank	Clone	1.5	0.5	0.5	2.5
B-C01	Tank	Unique	3	1	1	5
B-C08	Tank	Unique	3	1	1	5
B-C11	Tank	Unique	3	1	1	5
B-C12	Tank	Unique	3	1	1	5
B-C16	Tank	Unique	3	1	1	5
Total Man-days of CD Field Work in Buffer Prep						**47**
Total Man-days of CD Field Work in Fermentation						**55**
Total Man-days of CD Field Work in Media Prep						**59**
Total Man-days of CD Field Work in Purification						**44**
Total Man-days for CIP Cycle Development						**205**

Table B. Biotech facility CIP cycle development work estimate.

Line Cleaning				
Department	**Contact Time(minutes)**	**Temperature**	**Supply Conductivity**	**Cleaning Action**
Buffer	3 minimum	Ambient rinse	WFI rinse	3-5x holdup volume turnover at 5ft/sec velocity minimum
		Ambient wash	WFI wash	
Media	3 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.6 mS	
Fermentation	5 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.6 mS	
Purification	5 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.3 mS	
Vessel Cleaning				
Department	**Contact Time(minutes)**	**Temperature**	**Supply Conductivity**	**Cleaning Action**
Buffer	3 minimum	Ambient rinse	WFI rinse	Achieve FAT sprayball ratings for flow and pressure. Visual confirmation that surfaces are residue free.
		Ambient wash	WFI wash	
Media	3 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.6 mS	
Fermentation	5 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.6 mS	
Purification	5 minimum	Ambient rinse	WFI rinse	
		60°C wash	0.3 mS	
TFF Cleaning				
Department	**Contact Time(minutes)**	**Temperature**	**SupplyConductivity**	**Cleaning Action**
All Departments	Rinse : 5 minimum	Rinse : Ambient	Rinse : WFI rinse	Rinse : Membrane pressure setpoint(s) and tangential velocity
	Soak : 30 minimum	Soak and Recirculate Wash : Membrane dependent	Soak and Recirculate Wash : Membrane dependent	Soak : Hold time
	Recirculate Wash : 10 minimum			Recirculate wash : Membrane pressure setpoint(s) and tangential velocity

Table C. Cleaning acceptance criteria.

The CD team must understand acceptance criteria for each cleaning circuit before proceeding with testing. The fundamental acceptance criteria should include:[6]

- ***Contact Time:*** defines the amount of time, usually in minutes, that the rinse and cleaning solution are in contact with soiled surfaces.
- ***Cleaning Temperature:*** the temperature of the solution supplied to the equipment from the skid. The temperatures required are unique to each cleaning circuit. Typically, rinses are conducted with ambient WFI.
- ***Solution Conductivity:*** the conductivity of the solution delivered to the equipment. The required value is a function of the detergent utilized.
- ***Cleaning Requirement:*** unique for each unit operation, but typically can be defined as the amount of fluid turbulence, fluid impingement, and/or soak time.
- ***Contaminent Solubility:*** it is important to ensure that the contaminent is soluble in the rinse solvent which is subsequently tested to demonstrate purity.

Table C defines the water and chemical batch cleaning acceptance criteria for three unit operations utilized during CD. The acceptance criteria for soiled equipment should be defined by the Validation Master Plan.

Now that the cleaning acceptance criteria are defined, the CD team must go about "setting the equipment to work" to meet the requirements. The regulation and adjustment is accomplished by configuring the programmable recipe parameters of the software. The recipe parameter names can be extracted from the Functional Specifications for each unit operation. The CIP skids also have their own set of parameters. The number of configurable parameters for each unit operation is on the order of 20-30. If Table A is completed for all four CIP skids, there would be six unique unit operations and a total of approximately 70 unique circuits. Therefore, the number of unique parameters that need to be tracked by the CD team is substantial, on the order of 2,000 unique numeric values. Utilizing a structured approach as defined in the C&Q Guide becomes the only way to manage the effort.

Tracking CIP Configurable Parameters During Cycle Development

The objective during CD is to identify and program configurable parameters for each CIP circuit that will be utilized during the formal CV testing. These parameters will

provide a high degree of assurance that the cleaning validation effort will be consistent and successful. Employing a database to document parameter values and test results is necessary.

The first step is to identify parameters that are unique to a CIP circuit from those that may be commonly used within a manufacturing department or grouping of equipment. For example, the wash volume required, air blow time, and gravity drain time are generally unique to each circuit. The wash conductivity, conductivity deviation allowance, and final rinse conductivity are generally common to multiple circuits. By separating the unique and common parameters within the database, a consistent approach to CV can be developed throughout the manufacturing facility. The database may take the following form and assumes that once the common values are defined, only the unique values will be tracked along with the test results. The Buffer Department database format is defined in Table D. Similar tables should be developed for each department.

Executing the Plan - Case Study 1 - Process Vessel

It should be noted, that the following "Case Studies" are general and should not be applied as a "rule" to all manufacturing situations. Each manufacturing site needs to apply the CD principals in a manner that is appropriate to the process, the equipment being cleaned, and the biological soil in question.

Phase 1 - Water Batch

The objective of the water cycle is to achieve rated flow and pressure for the rinse and wash sprayball(s) cycle times which ensures proper coverage. This may require the placement of a pressure indicator near the sprayball port on the tank. The flow measurement can be referenced from the CIP skid. Sprayball design parameters and the results of Factory Acceptance Test (FAT) sprayball testing should be referenced when determining the required flow rates and pressure. Tanks may have multiple inlet pathways that are within the cleaning boundary of the CIP circuit. The CD team will need to optimize the valve sequencing patterns to meet the cleaning acceptance criteria for lines as part of the vessel cycle.

CIP skid tanks and the overall CIP circuit have fixed hold-up volumes. The hold-up volume of the CIP rinse and wash tanks should be large enough to fill the circuit and provide enough extra volume to make-up for losses to drain during the rinse and wash steps. The typical CIP cycle consists of a series of rinse-wash steps with intermediate gravity drains and air blows to remove spent solution. The air blow time and gravity drain time are determined in the field by collecting real time data. In some cases, a CIP Return (CIPR) pump is utilized to deliver cleaning solution back to the CIP skid drain or wash tank. The pump must be turned on at the correct time to prevent excessive pooling in the vessel, but not before proper priming has been achieved. Likewise, the CIPR pump must be shut off after removing solution from the circuit, but prior to running dry for an excessive amount of time.

Water Batch Test Procedure

Determine the following recipe parameters: rinse time, wash time, CIP supply flow rate and pressure, CIP supply rinse and wash volumes, gravity drain and air blow time, vessel inlet pathway valve cycling time, valve to drain cycling time, CIPR pump start time delay, and CIPR pump stop time delay. The approximate total cleaning time for each circuit also may be calculated at this point in CD.

Phase 2 - Chemical Batch

Chemical testing can begin once water batch testing demonstrates the CIP skid and process equipment function as an integrated CIP circuit. Chemicals are added to solution at the CIP skid, typically into the wash tank during recirculation of the solution. The initial "bulk" charge of chemical will drive the solution conductivity to roughly 90% of the required value. Incremental additions are then made bringing the solution to the required conductivity. The wash solution is then recirculated and heated in the CIP skid to achieve homogeneity with respect to conductivity and temperature. Once temperature and conductivity set points are achieved, the solution is delivered to the vessel and returned to the skid. The hold-up mass of the equipment will "rob" the system of energy and the initial return temperature of solution will be less than required. Therefore, the wash timer will not start until the solution and equipment are "up to temperature." If valves are cycling to drain and creating losses, the hold-up volume of the wash tank must be large enough to compensate for the losses. Therefore, wash volumes can be greater than rinse volumes. Once the washes and intermediate rinses are complete, the final rinse should bring the return conductivity measurement to within specification, typically that of WFI.

		Unique Parameters					Test Results		
Circuit #	Water/ Chemical/ Soil Test	P-1(gpm)	P-2(sec)	P-3(min)	P-4(gal)	P-5(mS)	Rinse Sample (uS)	Swab Sample (ppm)	Date
B-01	Water					NA	NA	NA	
B-01	Chemical							NA	
B-01	Soil								
B-02	Water					NA	NA	NA	
B-02	Chemical							NA	
B-02	Soil								

Table D. Buffer department unique configurable parameter and test results database.

The purpose of the chemical test is to verify that cleaning agents are not trapped by "dead legs," all surfaces are "free draining," and to test the chemical delivery system on the CIP skid.

Chemical Batch Test Procedure

Determine the following recipe parameters: chemical pump bulk delivery time, chemical pump incremental delivery time, tuning parameters for wash heat-up, wash volume based on additional losses to drain, final rinse time.

Phase 3 - Soiled Batch Testing

Unfortunately, after all the previous cycle development, the CD team will not know whether the CIP cycle will satisfy the requirements of cleaning validation until tested on biologic soil. The difficulty of cleaning the soils is a function of the soil's fouling propensity, the hold up volume of the circuit, and its mechanical configuration. The soiled test procedure should include instructions on how to obtain rinse and swab samples. The rinse sample can be obtained by drawing from a sample port at the CIP skid on the CIPR line. Other locations can be determined as optimal. CIP skids often are not designed with these ports in mind so the CD team will need to figure out how to have a sample apparatus fabricated and draw the sample in a way that does not compromise the sample quality. The sample should be measured for conductivity and Total Organic Carbon (TOC). TOC limits are established by the Cleaning Validation group and reflect the maximum acceptable level in the final rinse. Difficult to clean areas of the circuit should be swabbed to measure the effectiveness of the cycle. Once the analytical results are obtained, the CD team must decide if the programmed recipe parameters need to be adjusted. If the circuit is still "dirty," the CD team can optimize the recipe parameters for better cleaning. If the circuit is "clean" the recipe parameters may be adjusted to decrease the overall CIP cycle time and thus increase plant throughput.

Soiled Batch Test Procedure

1. Run CIP cycle on soiled equipment.
2. Obtain rinse and swab samples.
3. Optimize recipe parameters to achieve required cleaning in minimal amount of time.
4. Determine if mechanical or software changes are required to achieve cleaning objectives and implement before the start of CV.

Executing the Plan - Case Study 2 - TFF Skid

Phase 1 - Water Batch

Cleaning circuits for TFF skids are configured in a variety of ways. In this case study, assume that cleaning solutions are delivered by the CIP skid to the process hold vessel utilized by the TFF unit during normal operations. All solutions are first charged to the vessel incrementally before a CIP cycle step begins. Rinse solutions are pumped from the hold vessel, by the process pump, through the TFF skid directly to a local drain. Wash solutions are recirculated through the membranes back to the hold tank before being sent to the same local drain. Therefore, the hold up volume of the process tank will determine the length of each wash and rinse step. Multiple rinse/wash steps may be needed to achieve desired contact time depending on the fluid throughput.

The cleaning action for a TFF unit is defined by the tangential flow velocity achieved across the membrane, the required trans-membrane pressure drop, and membrane soak time. The tangential velocity will "sweep" away biologic soils. The trans-membrane pressure differential will create flux flow through the membrane. Some membranes are sensitive to extreme temperatures and therefore will only accommodate ambient rinses and washes. The required tangential velocity, trans-membrane pressure drop and cleaning solution temperature should be referenced from manufacturers' recommendations or plant operating experience.

Water Batch Cycle Test Procedure

1. Determine required wash and rinse volumes.
2. Determine the TFF pump speed necessary to achieve tangential flow velocity.
3. Tune the flow and pressure drop control loops.
4. Adjust valve pathways to direct solutions to recycle and drain.

Phase 2 - Chemical Batch

The membrane material and biologic soil will determine the type and concentration of cleaning solutions required. In this example, the CIP skid will batch wash solutions to the hold vessel without CIPR flow. Therefore, the CIP skid recipe parameters must be adjusted accordingly. The chemical delivery algorithm at the CIP wash tank will be the same however. Soaking the membrane in wash solution is accomplished by closing isolation valves on the inlet and outlet ports of the membrane during the wash cycle.

Chemical Batch Cycle Test Procedure

1. Determine the required wash solution conductivity and temperature.
2. Adjust the valve pathways for a recirculation, drain, and soak step.
3. Ensure enough wash solution is delivered to hold tank.
4. Adjust CIP skid operating parameters for no CIPR flow.

Phase 3 - Soiled Batch Testing

The CIPR conductivity sensor cannot be utilized to determine if the final rinse has flushed all soil and cleaning solution from the equipment. The CD team must rely on rinse samples to confirm the rinse time and volume utilized by the TFF unit for a final rinse are adequate. Surface interactions at membrane fluid interfaces are a function of chemical absorption and typically cannot be cleaned purely by variation of the cross flow velocity. The main cleaning action for bio products is achieved by surface active agents as is the case for all sorptive processes. The circuit differs from the tank cleaning in that it will be validated based upon final rinse time and not

CIPR conductivity. A local conductivity sensor also might be utilized for this situation.

Soiled Batch Test Procedure

1. Run CIP cycle on soiled equipment.
2. Determine final rinse time and volume required by sampling.
3. Optimize recipe parameters to achieve required cleaning in minimal amount of time.
4. Determine if mechanical or software changes are required to achieve cleaning objectives and implement before the start of CV.

This series of procedural steps should be repeated for every type of unit operation concentrating first on the "unique" circuits. Cloned circuits may proceed directly to soiled testing. Each unit operation will have a unique set of recipe parameters to track. Typically, line and tank cleaning are the most straightforward while TFF skid, chromatography columns, and centrifuges present more difficult challenges. In every case; however, the Functional Specification will define the configurable parameters that must be incorporated into the CIP Cycle Development Test procedures for the CD team.

Summary

This approach to CIP Cycle Development requires implementation of the C&Q Guide, developing a detailed plan based on equipment functional specifications, accurately scheduling the activities, and implementing three phases of testing. When successfully implemented, CIP cycle development will promote a very successful cleaning validation effort, and ultimately minimize production losses related to insufficient cleaning cycles.

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This article presents drug discovery research trends and identifies the impact on laboratory facility design, construction, and operation.

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Planning and Operational Aspects of Robotics Laboratories

by Paul Leonard and Lou Angelus

Understanding Research Drivers Behind Robotics Laboratory Design

Under constant pressure to dramatically improve R&D productivity in a climate of rising R&D costs, shorter product lifecycles and limited sales growth, biotechnology researchers are turning to robotic processes and equipment to not only increase the quantity of compounds discovered, but also to enhance the quality of the leads created via the discovery process.

The profiling and screening portion of drug discovery is currently one of the best candidates to utilize automated research processes. This type of research typically occurs very early in the discovery process and its purpose is to identify compounds with specific biological activities required for potential use against a targeted disease. This high throughput type of compound profiling and screening process, its associated equipment, and the effects on the design of laboratory facilities are the topics of this article.

Profiling typically tests multiple biological activities within a prescribed class of compounds. This process can discover multiple benefits or detriments associated with the targeted disease. Profiling may also uncover additional biological activities that benefit multiple separate drug development projects. Screening tests one specific biological activity in a large number of compounds; therefore, testing multiple compounds for that one specific activity or for multiple activities.

Automation has led to faster and more cost-effective profiling and screening with more reliable results. The general benefits of automation are uniformity and the minimization of variables that leads to higher data quality, and therefore, allows the researcher more time to interpret the data. With known uniform input procedures, less analysis is typically required to be performed because the researcher can

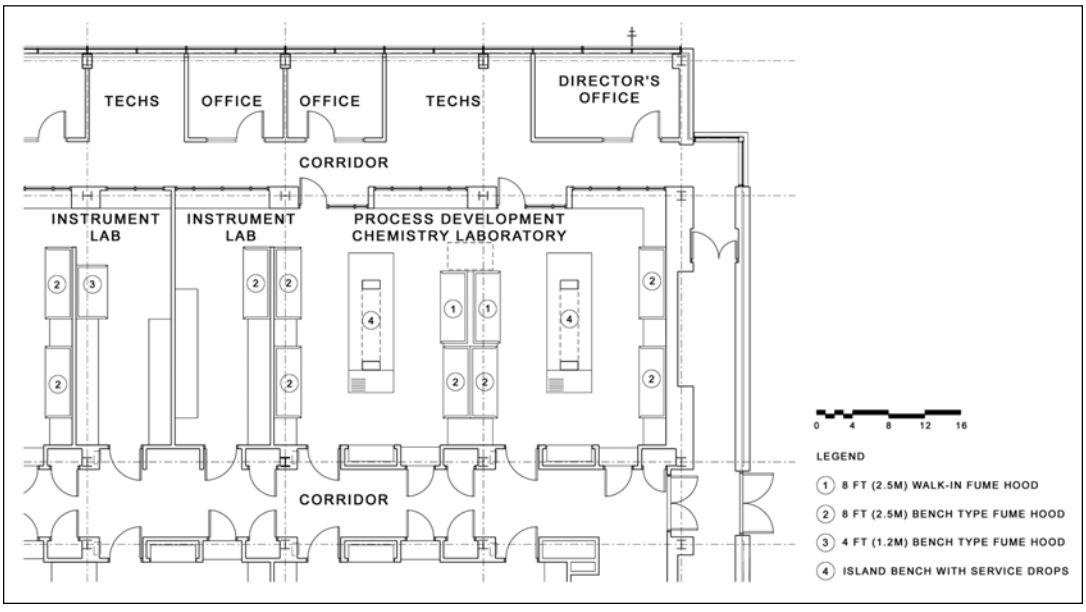

Figure 1. Traditional chemistry laboratory floor plan.

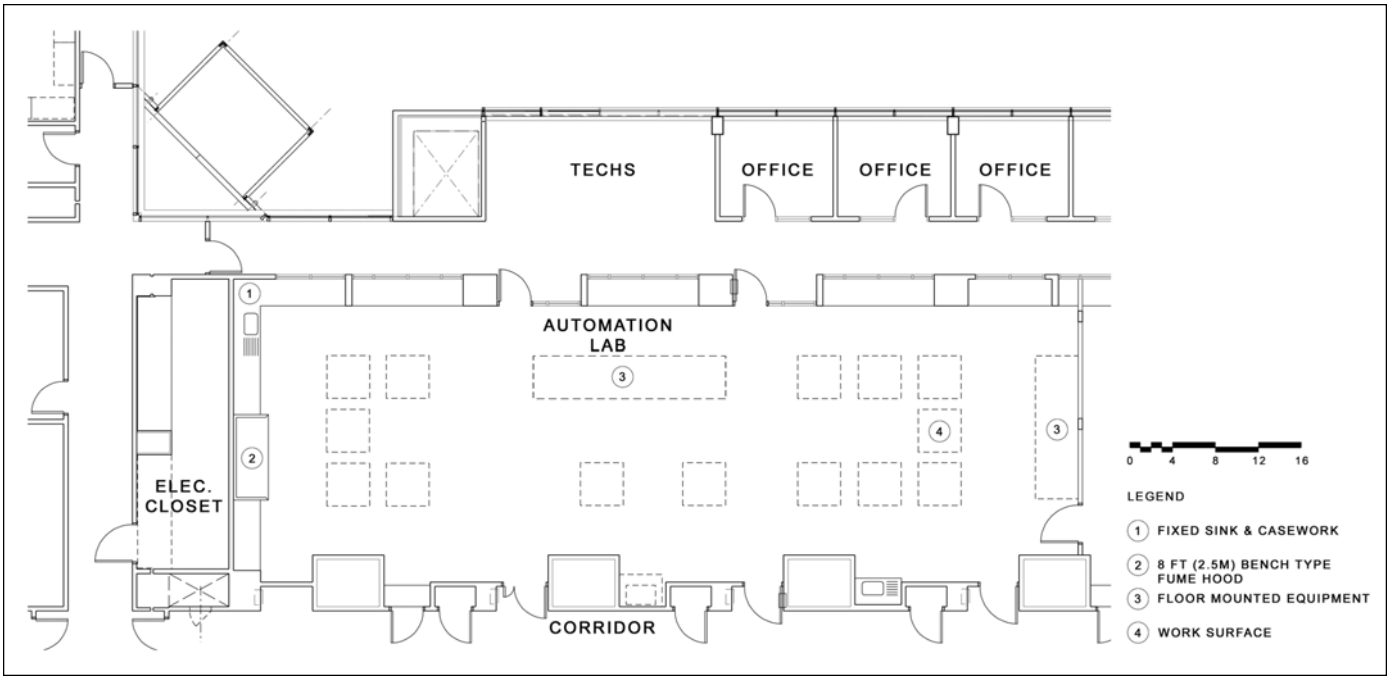

Figure 2. An open plan robotics oriented discovery laboratory.

concentrate on the particular reaction and not reactions from input error. This equipment evolution also is having an additional benefit by reducing the usage of solvents, compounds, and enzyme materials in the discovery process, thus reducing waste streams.

Even as little as 10 years ago, research for new compounds and the testing for interactions was typically conducted by a research chemist in a fume hood intensive lab. With today's combinatorial chemistry techniques, the same chemist has increased the speed of discovering and testing of compounds by as much as tenfold in the same fume hood intensive lab environment. The high throughput screening process is further accelerating the testing of compounds beyond the limits of combinatorial chemistry and has produced as much as a hundredfold increase in the amount of compounds that can be screened. The design of robotic laboratories is required to recognize how this trend will continue and how to anticipate the flexibility to allow for alternative equipment arrangements.

This mechanization of the drug discovery process will continue as the pressures of the industry continue to push for increased efficiency of discovery. Equipment technology is continuing to develop in a form that further minimizes the use of materials via micro-fluidics. Micro-fluidics and "Lab-on-a-Chip" technologies are evolutions of the current "well and plate" high throughput screening technology. This technology uses much less reagent than would be required for the equivalent plate-based assay. For example, for cell-based assays, it is possible that a 100 times fewer cells per data point are required compared to their equivalent plate-based assays. For scientists constrained by limited cell availability, e.g., those working with primary cell lines, this technology offers a way to perform more assays than would otherwise be possible.[1] With the continued drive to reduce R&D costs, it has been predicted that successful drug discovery efforts in the not so near future will depend on the further mechanization of the discovery process, greater reliance on affiliations between companies, more effective management of the data base of compounds that is being created, and continued movement to computer generated molecular libraries, bioinformatics, and virtual clinical trials. As today's typical 20-25 percent research completed via automated methods continues to grow, the role of chemistry research and associated facilities will need to change dramatically.[2,3]

Laboratory Facility Design Responses

The research trends described previously are driving new planning criteria and new process/utility/people integrated solutions to laboratory facility design. The requirements for equipment arrangement flexibility, unattended operation, and the critical nature of the data requires new multidisciplinary interactions in order to provide solutions that enhance and enable the overall process in the laboratory.

Adaptability in laboratory design denotes an ability to accept change. Typically, conventional laboratory design focused on establishing the parameters of a "laboratory planning module." Traditionally, the laboratory module was assigned an optimal square footage and provided fixed and/or specialized utilities. Significant cost driven HVAC infrastructure was provided for fixed fume hoods or more flexible point exhausts to support the scientific efforts targeted. Casework was fixed in place and walls became vehicles to support and isolate one function from the adjacent laboratories. A scientific investment was often measured in the quantity of planning modules assigned to support a specific research group.

In today's robotics oriented discovery laboratory, flexible open space is the driver in lieu of the traditional fixed fume

hood, casework, and utility service based laboratory layout. With the robotics oriented discovery laboratory, the most common criteria usually drives an open space environment without restrictive floor service penetrations and one that has that the ability to support moveable casework/tables that accommodate highly variable equipment layouts and successive technology platforms. This in turn shifts the investment from initial fixed equipment and casework to mobile research equipment and the supportive flexible facility infrastructure to serve this equipment.

Figure 1 is a diagram of a traditional chemistry laboratory floor plan. It illustrates the fixed equipment and casework approach described previously.

Figure 2 is a diagram of an open plan robotics oriented discovery laboratory within the same modular floor plan. This figure illustrates the potential locations of movable equipment and the inherent flexibility of the design.

In new construction of drug discovery facilities, a greater percentage of space that would normally be fume hood intensive chemistry laboratory is being redefined to accommodate automated processes. In a recent discovery laboratory project, a full 30 percent of a 140,000 square foot building was devoted to automated research and its associated support spaces. These support spaces typically consist of Plate Storage Libraries, Chemical Processing Rooms, Cell Reagent Banking Spaces, Cell Culture Areas, Autoclave Rooms, and Cold Storage Rooms. In this recent project, these support spaces represented 33 percent of the automated research area. Depending on the customization of the equipment required on the site, additional shop areas beyond this example may be required to construct custom equipment trains. Figure 3 identifies a typical orientation of an automated research lab with associated support spaces.

As laboratories are physically placed higher in buildings, national building codes limit flammable solvent use and its storage via the use of control areas. In the past, this has required that chemistry laboratories be placed on lower floors or designated with a higher hazard classification, which requires greater cost and separation from the remainder of the facility. Since automated research is typically less solvent and waste stream intensive, it can typically be placed higher in the building while maintaining conformance with solvent limitations. In the project illustrated above, all chemical synthesis functions were limited to the first and second floors while automated discovery laboratories were located on the third floor.

The researcher population densities of these facilities are generally less compared to traditional facilities. Typically, traditional research chemistry buildings are planned at approximately 750 square feet per person. A traditional biology research building generally has a denser population at approximately 600 square feet per person. However, a mechanized discovery laboratory is usually planned at 1,100-1,200 square feet per person.

Operations with fewer researchers supporting an automated process makes the spatial relationship between the laboratory and the researcher's office less critical. The laboratory can be located internal to the building and the data collected, managed, and supported from remote offices. As the laboratories can be an unattended operation, spill containment and security are elevated issues. Floor penetrations are generally not desired, and in the limited cases where

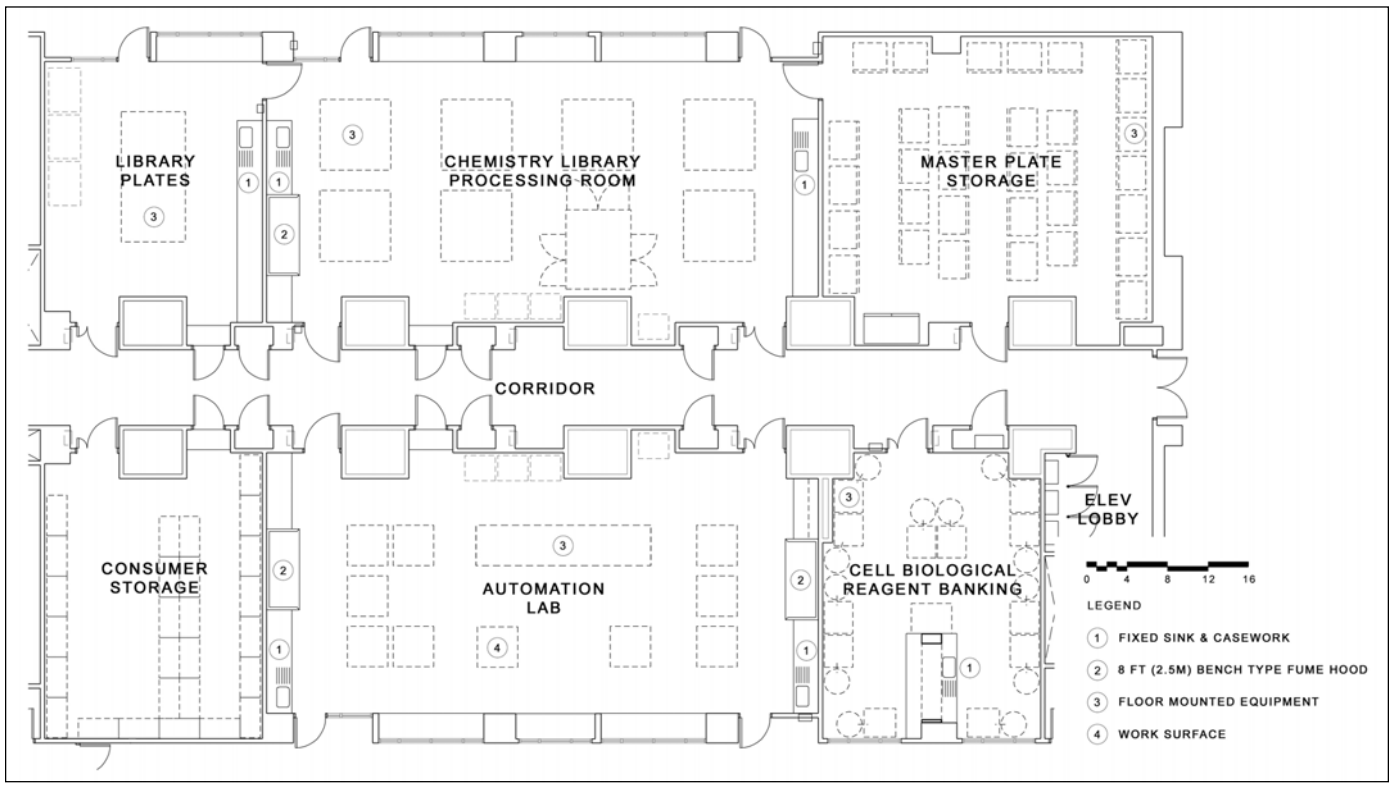

Figure 3. A typical automated research laboratory and associated support spaces.

Figure 4. Mobile laboratory table example.[4]

they are required, they are typically curbed and sealed. Past experience has shown that even when floor penetrations are kept to a minimum they hinder future equipment flexibility. Multiple level card access systems are generally provided to the laboratory area and supporting sample storage spaces to provide required security.

The robotics laboratory thrives on open floor plates, where a limited amount of fixed casework is provided along the periphery of the laboratory. Optimally, all fixed items such as sinks and other equipment are located along perimeter walls. The emphasis has shifted to have the ability to move to other technology platforms or alternative equipment arrangements without a major infrastructure modification. Mobile, either with or without wheels, refers to something that can be moved without significant expense, time, or effort. Researchers will often arrange tables and equipment to best suit the robotic equipment array.

Important to the flexibility of the moveable table concept is the stability of the equipment once it is in place. Concepts to achieve space flexibility should thoroughly be tested and proven to achieve the equipment stability required. For example, the use of telescoping legs provides flexible bench height, but may not provide the stability of solid legs. Alternative mobile casework designs that provide additional stability have been developed. One of these approaches is illustrated in Figure 4[4], which is a design that uses a solid leg normally resting on the floor, but by lowering the wheel mechanisms, the table can be fully mobile. Vibration and floor slab flatness are also prime concerns especially as the assay well count technology continues to rise.

Motorized options also exist to change the height of the work surface in response to individual researcher's needs. The goal is to take away any barriers that inhibit the science and provide an environment that improves productivity. In this lab environment, the researchers can make laboratory equipment, service, and work surface modifications independently of traditional facilities staff to further increase efficient day-to-day operations.

The overall arrangement and size of the HVAC system (as well as structural floor-to-floor heights and percentage of mechanical space) in a traditional discovery chemistry building is generally driven by the size, quantity, and simultaneous usage of fume hoods. The resulting 100 percent outdoor air HVAC system is not only a major first cost driver for the project, but also an energy consumption driver for the building's operation. The following HVAC system sizing comparison can be made for the traditional laboratory design and the automated discovery laboratory design to illustrate the impact of the robotic laboratory trend. The resulting cost impacts are presented at the conclusion of this article.

The typical discovery chemistry laboratory used in this example with its associated instrumentation support spaces (Figure 1) required a combination of fume hood types (three bench and one walk in hood was the standard of this particular design). In this laboratory building with 150 of these hoods, the HVAC system was exhaust driven. From a system sizing point of view, it is not generally practical to consider all fume hoods open simultaneously as researchers also have support spaces and offices in the same facility. HVAC system sizing was based on an assumed diversified simultaneous operation of these exhaust hoods to determine a proper and cost-effective HVAC system size. Agreements during design of this discovery chemistry laboratory also limited the working face area of the hood when open, therefore limiting the design exhaust airflow required. The floor plan diagram in Figure 1, limiting the working open sash area to 18" in height and utilizing a room level operating diversity of three out of four hoods open simultaneously, resulted in a maximum room air change rate of 45 Air Changes Per Hour (ACPH). A minimum room air change rate of 20 ACPH is required with all hoods closed. Assigning an 80 percent simultaneous operation of these labs across the building at design airflows, the total HVAC system is 144,600 cubic feet per minute (CFM) (68.25 m^3/sec.). Even with these substantial reductions in exhaust airflow, this equates to 5.15 CFM per square foot of lab area (0.026 m^3/sec./square meters). In order to reduce this substantial flow to meet actual needs, variable air volume controls are typically designed for each fume hood and the overall laboratory to maintain pressurization under the combination of the variable fume hood sash positions. These control systems have been optimized and refined in recent years to track actual used airflow based on fume hood sash positions and limit the system's outdoor air usage and operating cost.

The typical automation discovery laboratory illustrated in Figure 2 requires one fume hood in an open 10-module lab. Therefore, the laboratory is not exhaust driven, but cooling load or minimum air change driven. The good engineering practice criteria that was applied to these spaces was 10-12 ACPH of outdoor air (as solvents and other materials are still utilized in the lab) and a cooling load of 7-10 watts per square foot of cooling load (lights and equipment). These parameters produce nearly equal design airflows for the space and can reduce the control functions for the space level HVAC system to a two-position operation. Considering the same area for discovery as above, this design produces a system that is

53,300 CFM (25.16 m^3/sec.) and translates to a 1.90 CFM per square foot (0.0096 m^3/sec./square meter) of lab area.

Without the need for fume hood make-up air, adjacent offices can become an opportunity to return uncontaminated air to the HVAC system as opposed to providing fume hood exhaust make-up air. This further reduces the energy cost of the laboratory HVAC system.

In addition, more vertical building height is required in the traditional chemistry laboratory if shafts remain centralized or alternatively more local vertical shafts are required to be able to route the required supply and exhaust ductwork and coordinate with other services while maintaining a typical laboratory building structural floor-to-floor height of 15-16 feet (4.57 - 4.88 m). With the automated discovery laboratory, a more centralized shaft arrangement with more typical building heights can be realized due to reduced airflow. Therefore, the automated discovery laboratory function can offer a substantial building first cost reduction based on the support systems required.

Given the criticality of the research, the associated operations, the potential for unattended operation, the reliability of research equipment, and the associated support systems, supporting utilities are critical. Supporting systems' design must begin with this criteria, evaluate all potential modes of operation, provide required reliability via redundancy and elimination of single points of failure, and identify monitoring requirements to provide reports of upsets to the proper personnel for prompt response and correction.

With the evolution of laboratory room level control systems and the education of the user in using those systems, there are new opportunities to link the overall HVAC system operation to the actual room occupancy. This creates an HVAC system that tracks actual space airflow requirements based on actual process usage. The goal is to utilize the building automation system at a user level to minimize the amount of outdoor air that the HVAC system conditions and thus minimize energy costs. When fume hood exhaust volume setbacks (achieved either through variable or constant volume equipment) were implemented previously, facility personnel typically started awareness programs to make laboratory users conscious of the costs of leaving fume hoods open when not in use. With the focus on reducing energy costs and the variable use of the laboratory spaces, this same type of user control can be applied to placing the laboratory in the occupied or full airflow mode only when automation processes are in use. The HVAC system serving automated discovery laboratories is a conventional variable air volume system; however, it is the quantity of spaces occupied simultaneously that creates the system dynamics that tracks the use of the building. This effort takes the cooperation of the user, but significant energy savings can be realized. Further airflow reductions also can be realized with the enclosing of the process equipment and ventilating the enclosed area although consideration always must be given to any open bench work that is required to be completed. The facility can thereby optimize its energy utilization by actually tracking spaces in full operation and only conditioning the amount of outdoor air required to serve those spaces.

As stated previously, the laboratory spaces are to be flexible in equipment configuration. Therefore, modularity and uniformity in the distribution of piped and electrical utilities is required. One solution that provides flexibility is an overhead service grid as shown in Figure 5.[5] Typical piped services are compressed air, nitrogen, laboratory vacuum, and carbon dioxide. Service connections are usually quick disconnects. With the use of adjustable height benches and the researchers' ability to make equipment revisions, providing quick disconnects on the overhead service carrier as well as on the adjustable bench and connecting the services via flexible hoses allows adjustment of the work surface height without disconnecting the service. It also allows the user to plug-in services as required. Fume hoods also can be mobile. Supply and exhaust trunks also can be thought of as "piped" services.

Power and communications outlets also can be provided on a modular basis in this pre-manufactured service grid to suite equipment arrangements. The units are accessible to run additional cabling and piping in the future. Floor penetrations should be eliminated from the open floor plan as they limit future equipment layout options. Not only do floor penetrations limit the open work area, but also these penetrations can only accommodate a finite number of utility lines. Additionally, the disruption to the area below the

Figure 5. Overhead service carrier example.[5]

Figure 6. Service columns in areas of larger equipment.

laboratory for future renovation work also adds a further degree of cost and complication. If the floor penetrations cannot be avoided, the opening should be curbed and sealed. The quality of the gas services requires consideration in applying modular solutions such as cast aluminum manifold piped distribution systems. In most applications, these systems provide a flexible solution without impacting the service quality. However, in some high quality applications, these systems should be investigated for their impacts on service quality. Alternative field constructed service distribution drops also can be provided. As seen in Figure 6[6], service drop columns can be provided in areas of larger equipment. Alternatively, a system of cable tray and electrical raceway systems can be utilized for even lower cost solutions.

Cost Impacts

Using representative current projects in the Northeastern United States, the traditional chemistry laboratory facility as illustrated herein, has a construction cost range of $300-$325/gross square foot of area. Robotic laboratories in the same circumstances have a construction cost range of $250-$275/gross square foot of area. These ranges reflect building and support systems cost only. Laboratory equipment costs are not included as part of these estimates. As stated previously, with a robotics laboratory, cost shifts from infrastructure to laboratory equipment.

Ongoing renovation costs of a traditional laboratory facility include continued relocating of fixed casework. In a robotics discovery laboratory, these renovation costs are primarily equipment upgrade costs as the spaces are open, the utilities are distributed in a modular organized fashion and generally allow required equipment rearrangements without substantial investment in utility reconfigurations. These arrangements of equipment, casework, and utilities also allows for more direct researcher adjustment.

With the yearly cost of conditioning 100 percent outdoor air HVAC systems (in the Northeastern United States) at $4.65/CFM ($9,856/m^3/hr.), and the difference in airflow density of 3.25 CFM/sq.ft. (0.0164 m^3/sec./sq.meter), the system serving the automated research space will cost $15.11 per square foot less to operate per year than the chemistry laboratory example described previously. As general air quantities are reduced, the requirements to heat, cool, humidify, and reheat make-up air to laboratories (only to be exhausted via a fume hood) also are reduced. A planned unoccupied mode to reduce air changes when the lab is not occupied (4 - 6 ACPH) is typically incorporated into the robotics lab HVAC design. This compares with the minimum 20 ACPH rate for the example chemistry lab with all hoods closed.

Smaller infrastructure systems installed to support the building program result in less maintenance over the life of the building. Also control systems serving robotics laboratories have fewer dynamic operations, therefore require less commissioning and overall maintenance.

Conclusion

The use of robotics in pharmaceutical research is driving substantial and rapid changes in the design of the research environment. These changes range from those associated with the provision of flexible furniture and utility systems, to those involved with the sizing of building engineered systems, and ultimately to the relationship of the laboratory to support spaces and researcher offices.

The process of creating laboratory building designs responsive to these changing needs has created a byproduct of presenting additional challenges to traditional laboratory designs. These challenges are driven by life cycle, not just first costs of research laboratories, and require holistic, integrated architectural and engineering approaches utilizing state-of-the-art equipment and designs. They enable researchers to minimize the limitations of facilities by providing far more direct researcher interaction with supporting systems and more inherent flexibility in the design. Although a continuation of trends originating in the past, recent advances in research, equipment, and supporting systems promises to provide rapid progress in meeting these long sought after goals.

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4. Figure 4 photo courtesy of Technical Manufacturing Corporation (TMC) Peabody, MA.

5. Figure 5 photo courtesy of CASE Systems Inc., Midland MI.

6. Figure 6 photo courtesy of Aventis, Bridgewater Research Facility, Bridgewater, NJ.

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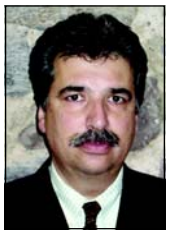

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This article describes the design criteria and a containment evaluation for bulk manufacturing facilities with closed isolation systems.

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Design Criteria and Evaluation of Pharmaceutical Containment Systems

Evaluation for Closed Isolation Systems

by Osamu Suzuki, PhD, Morihiko Takeda, Koji Tanaka, and Mamoru Numata

Background

This article is the sequel to "Design Criteria and Evaluation of Pharmaceutical Containment Systems -Evaluation for Open Isolation Systems" published in the March/April 2003 issue of Pharmaceutical Engineering. This article describes the design criteria and a containment evaluation for bulk manufacturing facilities with closed isolation systems, designed to allow manipulations at levels of containment below 1 [μg/m^3] categorized as Exposure Control Limit (ECL) of 4. The results of the containment evaluation under the manufacturing processes were complemented by a mock-up test to understand the containment performances as well as the previous open isolation systems.

Introduction

Pharmaceutical containment systems (isolation systems) allow pharmaceutical manufacturers to meet chemical hazardous materials exposure limits and are a fundamental part of pharmaceutical current Good Manufacturing Practice (cGMP).[1,2] This technology provides unique pharmaceutical containment facilities, including closed and open isolation systems at the aseptic[1-7] or non-aseptic[1,4-7,9,10] environments.

Pharmaceutical companies, engineering contractors, and equipment suppliers have recently, but independently, made an effort to establish the exposure control limit, through conceptual classification or case studies with various surrogate materials.[8,11-15] Design criteria for such containment systems in pharmaceutical facilities was proposed originally in 1999.[16-19] Since this proposal, the evaluation of the containment of potent compounds has been investigated during the design and construction of several types of pharmaceutical facilities with these isolation systems,[20-26] including:

- bulk Active Pharmaceutical Ingredient (API) manufacturing facilities
- aseptic dosage form facilities
- solid dosage form facilities
- multi-purpose facilities

Containment evaluation data using actual potent compounds was collected to redress the balance of:

1. insufficient potent compound containment evaluation data compared with an abundance of surrogate evaluation data
2. insufficient whole facility evaluation data in comparison with an abundance of specific equipment containment data

The purpose of the evaluation of the containment systems is to:

1. investigate quantitatively the containment level of the potent compounds to confirm whether the containment performances meet the design criteria proposed
2. establish conclusively the quantitative design criteria based on the analyses of the behavior of the airborne dust from potent compounds during manufacturing processes. The previous article described the containment performances in **open** containment isolation system that can be categorized as a Performance-Based Exposure Control Limit (PB-ECL)[11] of 3. In contrast, the present study investigated the containment performances of the **closed** isolation systems in bulk API pharmaceutical facilities, designed

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

Table A. Performance-Based Exposure Control Limit (PB-ECL) used for pharmaceutical drug manufacturing.

to allow manipulations at levels of containment below 1 $\mu g/m^3$ confirming that the performances met the assumed design criteria.

Design Criteria for Pharmaceutical Facilities

The strategy for the design of pharmaceutical containment systems is:[16,17]

1. Classification of bulk or finished pharmaceutical products into five hazard categories according to their inherent toxicological and pharmacological properties, PB-ECL - *Table A*. This PB-ECL classification was made on the basis of a previous report[11] and previous practices of the pharmaceutical facilities to contain the various potent compounds.
2. Classification of the barrier level into classes from 0 to 2.0, at 0.5 intervals, by integrating various containment systems, including personal protection - *Table B*. The protection systems for the external environment, such as the layout for zoning, a HVAC system, and building construction also are considered in the containment facilities.
3. Selection of the barrier level to maintain the required environment for processing with potent compounds. The barrier level should be selected according to the amount of dust generation depending on the state, such as water content and handling volume - *Table C*.

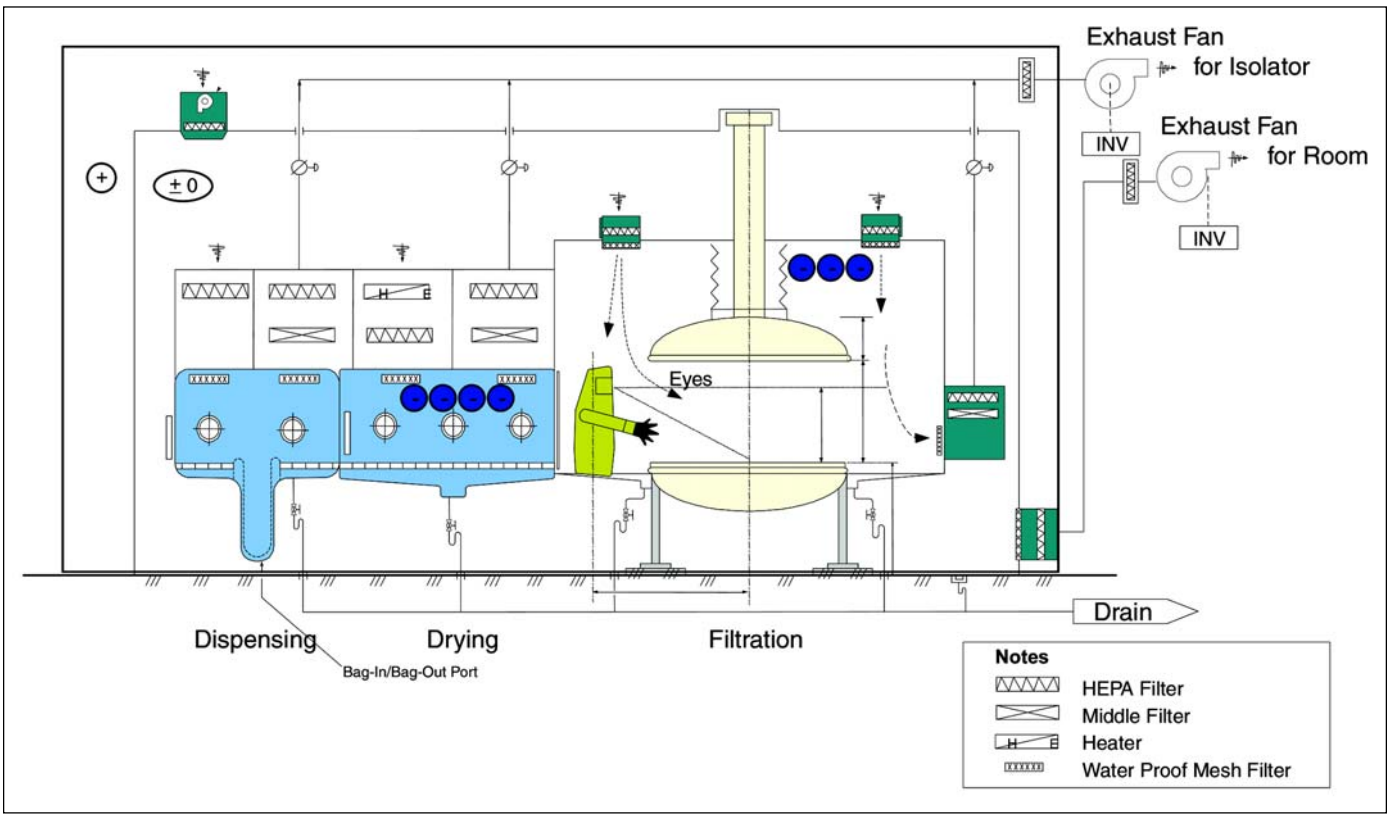

Figure 1. Negative pressurized isolators consisting of filtration isolator with half suits, drying isolator, and dispensing isolator.

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

Table B. Barrier level setting for worker protection.

4. Integrated study to satisfy the selected barrier level and reflect this in the facility design, together with several factors including the conventional barrier technologies, gowning regulation, and layout of building facilities.

Containment Strategy and Description of Processes for Potent Compound Handling in Bulk Manufacturing Facilities

Pharmacological Properties of the Drug

Pharmacological properties of the finished product are summarized in Table D. Both acute and chronic toxicity are estimated to show severe systemic effect. The pharmaceutical potency is 70 to 150 mg/day. The finished product shows no mutagenic properties, but does demonstrate potentially carcinogenic and partially sensitive properties. The finished product can be classified into an ECL category of 1 to 2 (Table A) with respect to the potency and the toxicity, but was placed into ECL category 4, from the point of view of being potentially carcinogenic.

State	Barrier level				
	Exposure control limit				
	1	2	3	4	5
Large amount of powder	0.5	1.0	1.5	2.0	≧ 2.0
Small amount of powder				1.5	
Liquid/wet powder		0.5		1.0	1.0
Very small amount of powder/liquid				0.5	0.5
Powder/liquid enclosed	0	0	0	0	0.5
No hazardous substances	0	0	0	0	0

Table C. Barrier level setting for state of hazard chemicals under ECL.

Barrier Level Setting for each Manufacturing Process

Table E shows the required barrier level for each process of the potent compound handling. The processes include general procedures in the handling from suspending raw material, crystallization and filtration, and dispensing for packaging. Except for the cake receiving process when wet powder is handled, level 2.0 was selected as the barrier level for handling the potent compound.

Description of Powder Handling

The potent compounds were totally processed within the closed system isolation systems. The processes included the following manual operations:

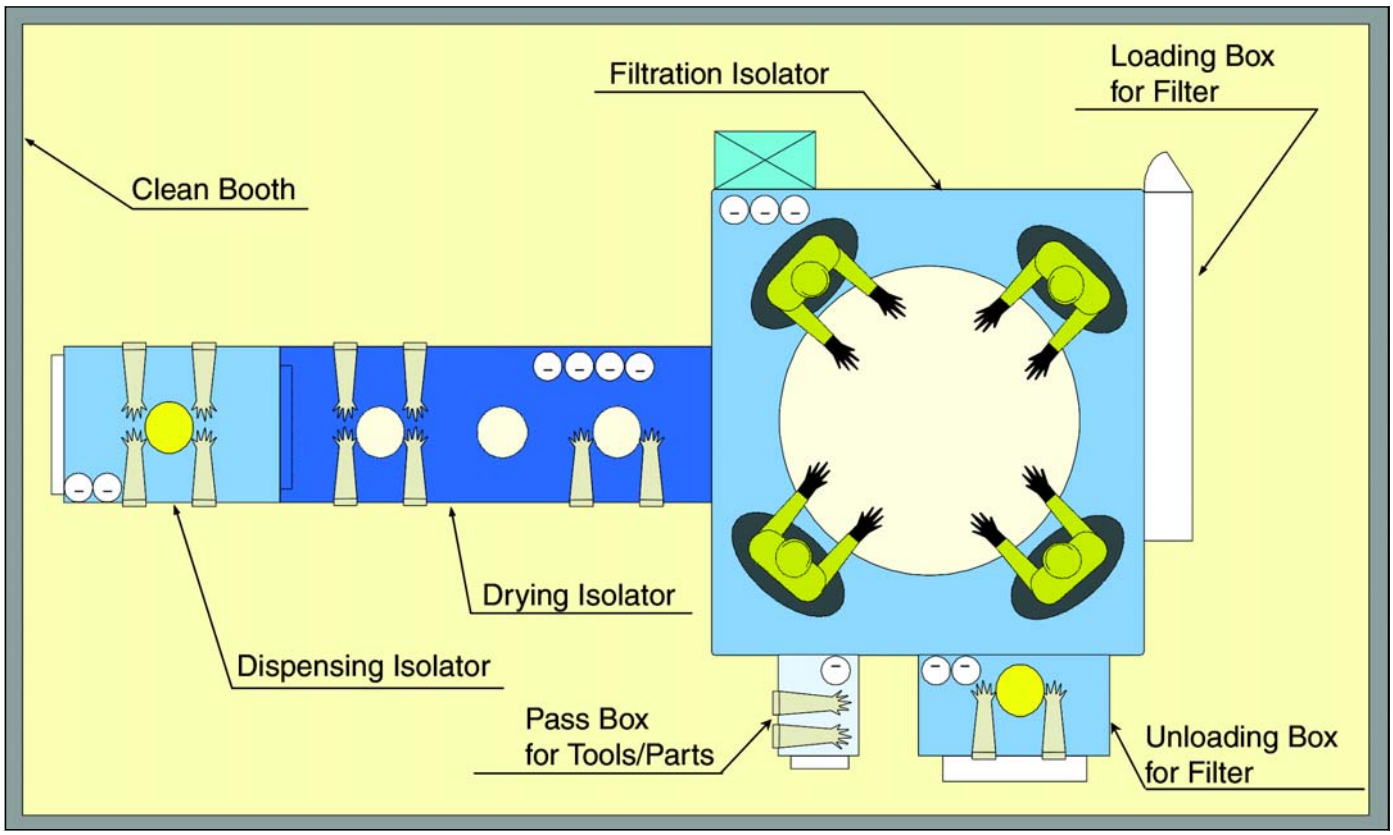

Figure 2. Plan view of negative pressurized isolators.

Properties	Description
Acute toxicity	Severe systemic effect
Chronic toxicity	Severe systemic effect
Pharmaceutical potency	70-100mg/day
Mutagenic	No
Carcinogenic	Potentially carcinogenic
Sensitization	Partially sensitive

Table D. Pharmacological properties of the finished product processed.

1. weighing the raw material within the glove box
2. loading the weighed raw material into a reaction vessel through the inlet which is directly installed within the glove box
3. wet cake filtration on circular pan filter with a 1.2 m diameter
4. fragmentation of the cake into small pieces and transfer into the neighboring drying vessel
5. dispensing into container and bag-out from the isolation system

Details of the isolation system required to maintain the barrier level of 2.0 are summarized in Table F. The isolation systems consist of a glove box for loading the material, a negatively pressurized isolator with half suits for the cake filtration, and isolators with gloves for drying and dispensing.

Containment Evaluation of the Isolation Systems

In the present study, the containment performances were evaluated in the glove box for loading and the isolators that consist of the filtration isolator with half suits, the drying isolator, and the dispensing isolator. The raw material was taken into the glove box via the pass box, weighed, and then charged into the inlet of the reaction vessel, which is directly installed within the glove box to crystallize. The slurry resulting from crystallization was transferred to the isolators for a series of powder handling processes including filtration for cake receiving, drying, and dispensing. Figure 1 illustrates the negatively pressurized isolators. The isolators were installed within a prefabricated room where the room

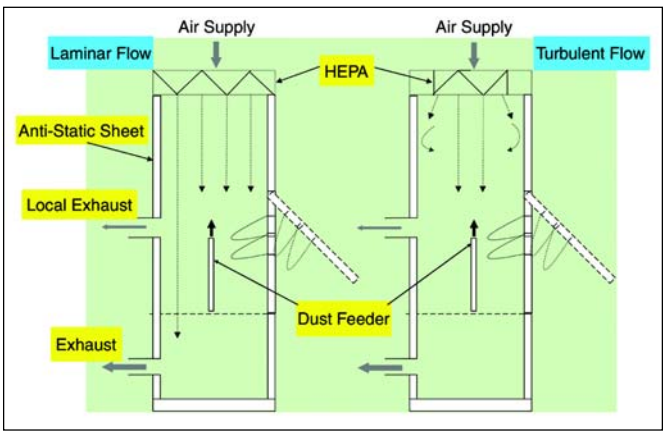

Figure 3. Schematic view of mock-up booths representing laminar and turbulent flow booths.

Process Flow	Barrier Level Set
Suspending of raw material	2.0
Crystallization	
Filtration	
Cake receiving	1.5
Drying	2.0
Dispensing	
Packaging	

Table E. Process flow and barrier level set.

pressure was controlled to be positive with respect to the isolator and negative with respect to the outside environment. This arrangement of the pressure differentials ensures the prevention of release of the potent compound from the working room in unforeseen circumstances. Figure 2 shows a plan view of the isolators. After filtration, the wet cake is fragmented into small pieces manually on the filter by workers wearing half-suits in the filtration isolator, and then transferred to a neighboring drying isolator which is designed to be negatively pressurized with respect to the filtration isolator. The dried powder is dispensed into the containers and unloaded using a bag-out system.

Evaluation Methods

a. Evaluation Methods Used

The evaluation methods used included air sampling of the atmosphere during working and swab testing of various surfaces related to the manufacturing processes. A standardized method of testing the containment efficiency of solids handling equipment has been proposed by a working group of occupational hygienists and engineers from Europe, the US, and Japan, and is scheduled to be published as an ISPE Good Practice Guide.[27] (The outline of this guide has been published previously.[27]) The main purpose of the guidelines is to allow direct comparison of test results both for similar and different types of equipment. However, the guidelines focus on the containment efficiency of equipment using surrogate materials, rather than the containment performances of equipment and facilities for actual potent compounds. Therefore, this study referred to the guidelines for the use of the measurement equipment, but developed the evaluation methods for the containment performances of the installed equipment and the facilities.[20-26]

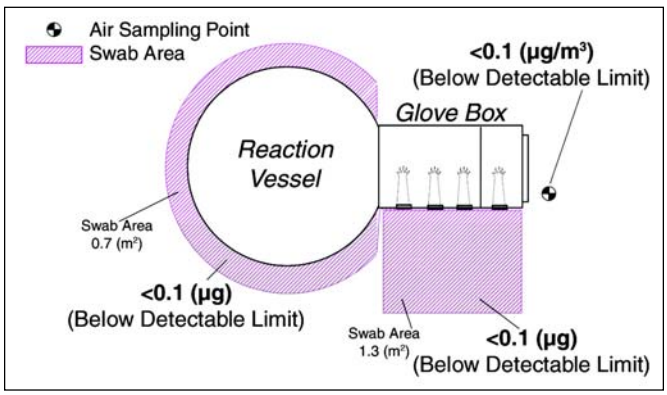

Figure 4. Containment evaluation in glove box after raw material charging.

b. Sampling Methods for Containment Evaluation

Air Sampling

The static monitoring of airborne concentrations in the working environment was performed using air samplers with constant flow. Airflow volume was calibrated for each air sampler before measurement. A 37 mmΦ-cassette type closed head was used with a PTFE filter. The cassette head is one of sampler heads recommended by the *Guidelines for Assessing the Particulate Containment Performance of Pharmaceutical Equipment* in addition to an Institute for the Occupational Medicine (IOM) sampler head.[27] Monitoring was started just before working and completed just after working. The working times at each process were generally within one hour. Therefore, the airborne concentration was expressed as Short-Term Particulate Airborne Concentration (STPAC), rather than long-term PAC by unit of amount collected per unit volume.

Swab Tests

Swab tests were performed for interior and/or exterior surfaces of some of the equipment and floors of the work areas to determine the degree of surface contamination. A previously reported[28] standardized swab procedure was used with minor modifications. Commercially available cellulose cloth, 10 cm square, was dipped in purified water, squeezed, and then used for swabbing. The swabbing was performed by the same person throughout. Surfaces such as the interior and/or exterior of isolator, floors around isolators, and the degowning room were included in the swab tests. The concentration was expressed either as total amount recovered or as amount per unit surface area.

Measuring Points

Measuring points for air sampling and swab tests were selected to incorporate:

1. interfaces between containment equipment and working environment
2. final points where the airborne dust collected, namely, in front of exhaust
3. floor surfaces traversed by the workers to account for carry over of potent compounds

These points take into consideration both the evaluation of equipment efficiency and the overall facility containment performance.

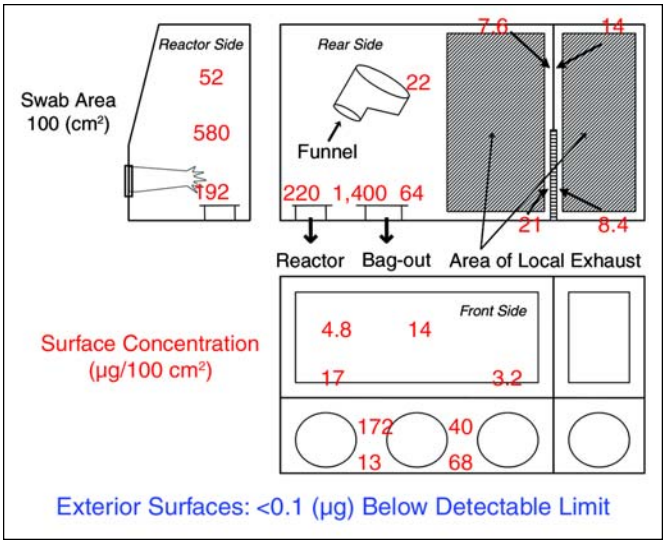

Figure 5. Interior surface contaminant concentrations of glove box after raw material charging.

Analytical Method

The concentrations of airborne and surface-contaminated particulate were analyzed by chemical analysis using HPLC. The recovery rates from both the filter and the cloth were validated and reflected in the analytical results. While the recovery rate from the surface was not determined, the surface was visually checked to confirm that no powder remained after swabbing. A previous study using this swab method[28] confirmed the recovery rate of 95% confidence of the test material from the surface although an organic solvent was used for dipping swab cloths in this earlier study.

Containment Facilities with Processing	Containment Facilities Description
Glove box Raw material loading into the reaction vessel (Highly potent raw material to be loaded into the reaction vessel)	Box pressure to be controlled negative 1. Raw material containers to be loaded through the pass box 2. Raw material to be loaded into the reaction vessel in this isolator 3. HEPA filter to be amounted for air supply/exhaust line 4. Waste matter to be unloaded from the isolator by means of bag-out system
Isolator with half suites Filtration (Wet cake to be collected by half-suite operators)	Chamber pressure to be controlled negative 1. New parts/filter/containers to be loaded through the pass box 2. Intermediate products to be transported into the drying/dispensing isolator directly 3. HEPA filter to be amounted for air supply and exhaust 4. Waste matter to be loaded from the isolator by means of bag-out system.
Isolator with gloves Drying/dispensing (Dried powder is dispensed into the containers)	Chamber pressure to be controlled negative 1. Containers to be unloaded with bag-out system 2. HEPA filter to be amounted for air supply and exhaust 3. Waste matter to be unloaded from the isolator by means of bag-out system

Table F. Containment facilities used in the facilities.

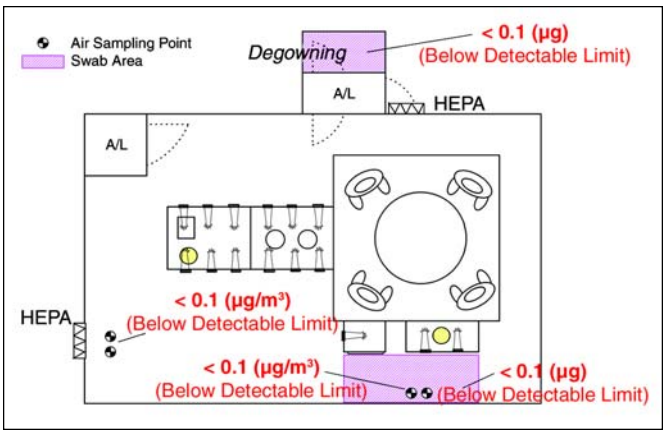

Figure 6. Containment evaluation in negative pressurized isolators after filtration and drying processes.

c. Mock-Up Test

Parameters for the Mock-Up Test and Description of the Mock-Up Booth

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

Figure 3 shows a schematic view of the mock-up booth representing laminar down flow and turbulent flow booths with local exhaust. A dust feeder was used to secure constant feeding of the surrogate material. In this study, the comparison between open and closed booths with laminar flow as a parameter was performed using a surrogate material. The cassette type closed head was used for air sampling.

Surrogate Material

Acetaminophen was used as surrogate material with a particle size range of below 75µm by weight ratio of 66% (provided by the manufacturers and determined by sieving number).

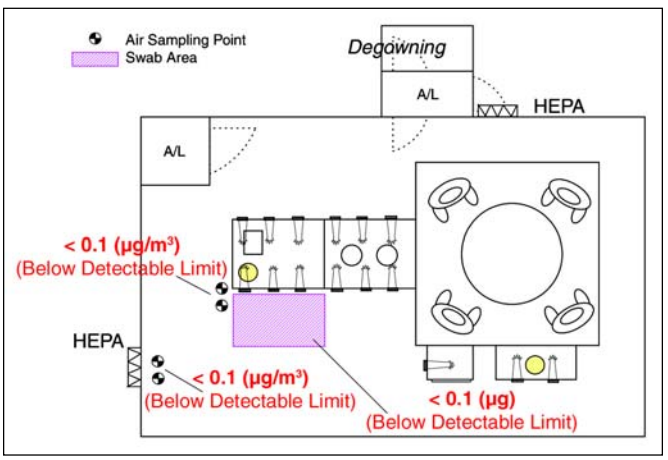

Figure 7. Containment evaluation in negative pressurized isolators after dispensing process.

Results and Discussion

Evaluation of Containment Performances of the Bulk Manufacturing Facilities

Glove Box Interior and Exterior Surfaces, and Floors around Glove Box

Figure 4 shows the sampling points and the analytical results for both air sampling and swab test. This figure is illustrated in plan view. Air sampling was performed out in front of the pass box where the potent compounds were collected. Swab points included floors in front of the glove box and around the reaction vessel that covers areas of work with swab areas of 1.3 m^2 and 0.7 m^2, respectively. The results in both analyses for air sampling and swab test indicated that concentrations of the potent compounds recovered were below the detectable limit of the chemical analysis used. Figure 5 shows the results for the interior surface concentrations of the glove box after the raw material weighing and charging processes. The concentration of the interior surface contaminations are presented, expressed by a unit of amount recovered per 100 cm^2 that corresponds to the swab area. The funnel was used when charging raw material into the reaction vessel. The shaded areas correspond to the areas where local exhausts were installed. The results indicated that surface concentrations generally increased downward, which may reflect airborne concentration distribution inside of the glove box. The flow within the glove box of the airborne dust could typically be controlled by the airflow. The major part of airborne dust could be collected by the HEPA filter of the exhaust. However, the large particles within the airborne dust seem to drop down within the glove box. In contrast, the exterior surface concentration from all front surfaces that were swabbed was below the detectable limit (<1µg/m^3). These results demonstrated that the potent compound was fully contained at a level below the detectable limit of the chemical analysis used.

Isolators for Filtration, Drying, and Dispensing

Figure 6 shows the sampling points and the analytical results for the isolators. Air monitoring was performed:

- in front of the filtration isolator between the unloading box for the filter and the pass box for tools and parts
- in front of the bag-out port of the dispensing isolator
- in front of exhaust in the room

The areas swabbed included floors in front of the filtration isolator and the dispensing isolator and the floor of the degowning room. These sites cover areas traversed by workers.

The dispensing process was performed the day after the filtration and the drying processes. The swabbing in front of isolators was performed after each process was completed. The swabbing of the degowning room was performed after the filtration and drying processes. These sites covered areas traversed by workers both during and after working.

The results revealed that the analytical concentrations were below the detectable limit (<1[µg/m^3]) for both air sampling and swab tests during the filtration and the drying

processes. Figure 7 shows that the containment performances achieved analytical concentrations below the detectable limit (<1[μg/m³]) for both air sampling and swab tests during the dispensing process.

These results demonstrated that the potent compounds processed in the isolators were fully contained at a level below the detectable limit of the chemical analysis used. In addition to the results obtained with the glove box, the containment performance was shown to meet assumed design criteria for both the isolation equipment and the whole facility, including the isolators.

A Study of Containment Evaluation

It is important to confirm that the containment performances of equipment and facilities meet the design criteria. This study demonstrated that the containment performances examined achieved analytical concentrations below the detectable limit of the chemical analysis used. However, it should be noted that the containment performance is influenced by the operational procedure. Previous studies suggested that a contaminated gown may be one source for carrying any powder handled outside the working area although in this case, the facilities evaluated included open isolation systems and were classified as ECL 3, which allows an exposure level between 1 and 100 [μg/m³].[20-26] The manufacturing processes along with standard operating procedures would be recommended from the point of view of total security of containment for the potent compound handling, even where the closed isolation systems are used.

Containment Performance Evaluation by Mock-Up Test

Figure 8 shows the STPAC of airborne acetaminophen for a base case (no airflow case), a local exhaust working case, and for closed system with laminar flow in the mock-booth. The numerical values are shown for both inside and outside the booths. The results demonstrated the quantitative efficacy of the local exhaust to reduce the STPAC (from 7,000 [μg/m³] to 1,000 [μg/m³] for inside and 1,000 [μg/m³] to 10 [μg/m³] for outside the booths) and the containment performance of the isolation system to contain the surrogate material fully (66 [μg/m³] for inside and below detectable limits for outside the booth). These results also could provide a theoretical background to understand the containment performances of the bulk APIs manufacturing facilities evaluated in the present study. Recent Computational Fluid Dynamics (CFDs) studies suggested that the exhaust has an important role to contain the compound by design of the airflow in the transfer vessel having a local exhaust system.[2] In such an open isolation system, it appears that understanding the airflow is critical to ensure the containment performance. On the other hand, it has been shown that particle size distributions of airborne dusts were different depending on the state of the powders despite using the same materials,[29] suggesting the different behavior of airborne distribution. Further study at the various conditions with different surrogate materials is required to fully understand the containment performances of the closed and open isolation systems.

Conclusion

From the measurement of containment performances of the glove box and the isolators, the present study can be summarized as follows:

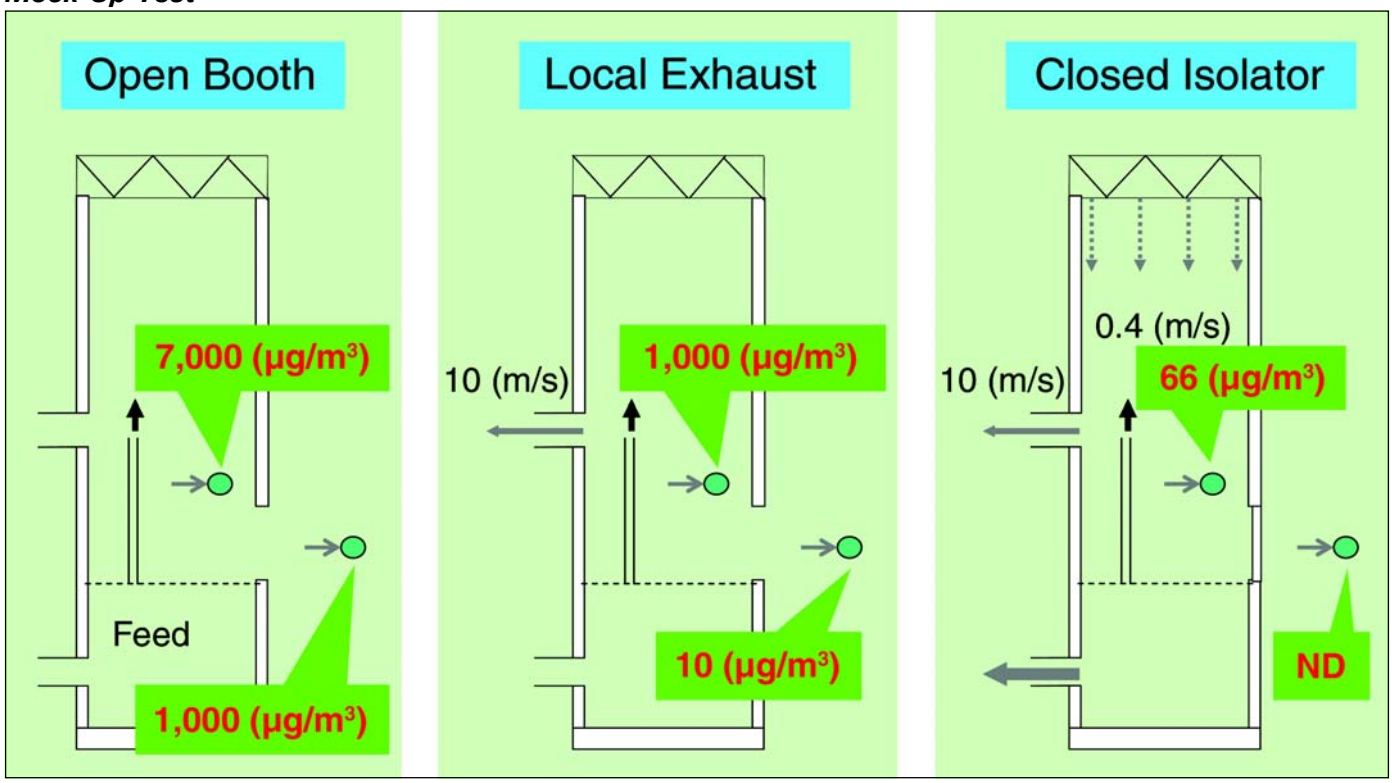

Figure 8. Containment evaluation in mock-up booth for open and closed isolation systems.

1. The containment performances of bulk APIs manufacturing facilities, designed to allow manipulations at level of containment below 1 [µg/m^3], were confirmed to meet assumed design criteria.
2. The closed system was compared to the open system using the mock-up booth to complement the performances of the bulk manufacturing facilities, demonstrating quantitative containment performances with non-detectable levels.
3. The influences of airflow and local exhaust on containment performances were delineated, and although fragmentary, they were quantitative.

Further studies are under way to understand systematic containment performances in different kinds of control system, such as type of airflow, using the mock-up system.

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This article presents ways in which Clinical Interactive Voice Response (IVR) Systems are used to enhance trial communications, request trial supplies for investigational sites, provide instant updates for trial sponsors, and save money in the process.

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An Introduction to Clinical IVR Systems

by Anthony Chow

Overview

Extremely reliable, cost-effective, and easy to use, Clinical Interactive Voice Response (IVR) Systems provide a wide range of services from just about any telephone worldwide. Successful integration of an IVR system with a clinical trial involves an understanding of the capabilities of the telephone as a data collection device, and being able to utilize secondary systems, such as fax, e-mail, and web portals, to post and route important information. This article will explore some of the many ways in which IVR is being used to enhance trial communications, request trial supplies for investigational sites, provide instant updates for trial sponsors, and save money in the process.

A Brief History of Clinical IVR

During the last decade of the 20th century, the use of IVR systems for clinical trials grew, not just in number, but also in variety. Most clinical teams are familiar with using IVR systems to capture patient diary data or to randomize trial subjects. Due to the many capabilities of IVR systems, and the fact that almost everyone has a telephone these days, IVR systems have been developed to automate more and more of the clinical trials process. IVR systems have been developed for investigators to order study drugs and trial supplies. Sponsors can place toll free numbers in radio and newspaper ads that permit callers to enroll in upcoming trials via IVR. Some systems even serve as information centers telling callers about particular trials and drugs.

As IVR systems took on more responsibilities, the capabilities of Clinical IVR Systems had to be expanded to meet the demand. Statistics and reports detailing IVR activity may be automatically faxed or e-mailed to clinical team members. Compliance reports assist investigational sites in reminding trial subjects to make diary entries. IVR randomization systems can send faxes to drug shipment facilities. Potential trial subjects can enter a fax number into an IVR Subject Recruitment System and receive study details. Data collected by IVR systems can be made available to most anyone needing such information.

The reach of IVR for clinical trials has become global with the addition of foreign languages. Many language translation vendors now provide recording services for IVR systems. Some are even familiar with the pharmaceutical/biotech industry and can assist with validation of IVR systems.

The potential power and reach of any Clinical IVR System is as vast as the global telecommunications network in existence today. In addition to voice recognition, newer IVR systems hardware can even decode digits from the old rotary-dial telephones. All of this evidence proves that Clinical IVR Systems are the most reliable form of electronic data capture in existence today for the pharmaceutical/biotech industry.

How does it Work?

When gathering information on IVR systems, many people are curious as to how the systems function. Most IVR systems are hosted on ordinary PC workstations outfitted with special telephone circuit boards, or add-on cards. (There is support for hosting IVR on multiple platforms such as Windows, Unix/Linux, and Solaris.) The telephone cards can accept two or more telephone lines, and in function, are different than fax/modem cards. Some telephone cards can accept an entire T-1 ISDN PRI network interface containing 24 lines. With modern PCs getting more powerful each year, it is

Basic Clinical IVR Custom Programming Requirements

If your company or facility is interested in hosting a Clinical IVR System, and you have access to a programmer, there is a very economical way to get started. Here are some basic hardware and software requirements.

1. PC Workstation (Windows 2000 or later preferred)
2. 2 or 4-line Dialogic Card
3. CallSuite software (2 or 4-line license)
4. Microsoft Visual Basic (Version 6 or .NET)
5. Microsoft Access, SQL Server, or Oracle database

Using very simple logic, and basic database access routines, a very useable Clinical IVR System can be designed and developed. In fact, the most difficult part of the process for most first-time programmers is getting the drivers installed for the Dialogic[1] hardware. Once the system is "talking," and can answer incoming calls, the hard part is mostly over.

Getting Started
The first routine to develop will be a utility to permit recording of voice prompt files. With a little ingenuity, a simple scripting system can be designed to read voice prompt filenames from a table in your database. The basic functionality needed for a recorder routine can be seen in the following menu prompt, which will be the first file you need to record.

"To record a file, press 1. To playback, press 2. To move to the next file, press 3. To move to the previous file, press 4. When finished, you may hang up."

Therefore, you will need to record a file, play a file, and move up or down through a list of voice files. Just coding this simple routine will give you valuable experience in how all IVR systems function. For example, using similar logic, a function can be written to permit Investigators to leave a voice message for someone on the sponsor's clinical team.

To improve on the functionality of this routine, error checking can be added to prevent playback of files that do not yet exist. You can also add checking to assure the caller does not move the index beyond the bounds of the record object, or array, of filenames being used. The experience gained with this simple exercise can lead to development of a fairly sophisticated scripting engine to handle Clinical IVR scripts.

Error Handling
Probably the most important aspect of a Clinical IVR Visual Basic program is to incorporate extensive error handling in each function and/or subroutine. The system must detect when a caller hangs up. By default, in Visual Basic, this generates an error. This error must be trapped and handled so you can finish writing any data to your database. If the error is not trapped, program control may otherwise bypass the database write routines resulting in incomplete or inaccurate information.

Reference
There are many computer telephony vendors that can provide IVR workstations with telephony hardware preinstalled and configured, ready for use with most telephony software systems.

not unusual to find more than one phone card in any given workstation. Being able to handle many simultaneous callers, e.g., 64 lines, in a single box makes IVR a very economical investment.

Touch-Tones

The main job of a telephone card is to translate the touch "tones" into numeric digits. When a key is pressed on a touch-tone telephone, a sound is generated comprised of two tones. One tone represents the key's row; the other represents the key's column. Together they represent digits 0 through 9, *, and #.

Voice Files

The second job of the telephone card is to "play" prerecorded prompt files to the caller. The caller "interacts" with these voice prompts, which is how this system got its acronym, Interactive Voice Response, or IVR. For example, when calling an IVR system, you may first hear a greeting followed by a request for your user ID and password. Your "response" is to enter the ID and password. Each of these prompts may be a separately recorded voice file on the IVR workstation. Voice files may be stored as WAV[1] files, or more commonly, as VOX[2] files.

IVR Scripts

The two basic functions described above, playing prompt files and receiving touch-tone responses, are controlled by one or more IVR scripts or call flow. The scripts are processed by the main IVR program and contain the business logic of the application. An IVR scripting language may take many forms including XML. Basically, the IVR script contains the necessary information to prompt callers for information and store their responses.

IVR scripts are often role-based by design. For example, when a site investigator logs in, the IVR system may present the caller with administrative options, such as patient withdrawal and activating/de-activating an investigational site. Whereas, when a patient calls, the IVR system may only allow access to the patient diary options.

To improve data integrity and reliability, IVR scripts usually include repeating the data entered so that callers can hear and confirm their selections. For example, a patient from the UK calls in, whose birthday is August 1, 1946:

IVR plays the prompt: Please enter your birthday using 2-digit month, 2-digit day, and 4-digit year. For example, January 9th, 1950, will be 01091950.

Caller punches in: 01081946

IVR repeats: You have entered January 8th, 1946. If it is correct, press 1. Otherwise, press 2 to enter again.

Caller hears the mistake and punches in: 2

IVR plays the prompt: Please enter your birthday using 2-digit month, 2-digit day, and 4-year year. For example, January 9th, 1950, will be 01091950.

Caller punches in: 08011946

IVR repeats: You have entered August 1st, 1946. If it is correct, press 1. Otherwise, press 2 to enter again.

Caller confirms the entry and punches in: 1

Database

Working in conjunction with the IVR script will be some type of database. The IVR system database is used to store and retrieve scripts, user ID and password information, and data collected from the callers. Additional information on IVR users may be stored in the database, such as contact information and reports preference.

More important, the database stores electronic records for audit trails per FDA 21 CFR Part 11, capturing each user's events and actions along with user ID and timestamps.

The same IVR system database, or perhaps a separate database, can serve as version control to track the design of voice files and IVR scripts.

IVR Packages

There are many software packages on the market that permit you to generate IVR scripts, record voice files for prompts, and capture data. Some IVR packages allow you to build an IVR script visually and interactively using icons and flow connectors.

Custom Programming

To custom build a Clinical IVR System, there are several third party programming libraries, or toolkits, available for many computer languages. One of the more common libraries encountered is CallSuite, which is a set of commercial ActiveX controls with computer telephony features. CallSuite may be used with Visual Basic, Visual C++, or Delphi.

These programming libraries provide transparent access to the telephony hardware. They give you control over what files are played and how they are played, and the ability to capture digits entered by callers into program variables. You also can write code to record a voice message from the caller, change the length of time the system will wait for a caller's response, and also put the caller on hold and forward them to another extension or another telephone number. Basically, you can duplicate just about any type of telephone system using these routines. As an example, many cable TV companies use computer telephony hardware with Visual Basic programs to process calls from customers wanting to purchase "pay per view" movies. These systems are able to read the Caller ID information sent between the first and second rings and activate the selected movie for the customer automatically.

In addition to the advantages above, it is possible to code extra functionality into your IVR system. For instance, you can easily build a transaction log of all caller activity and then save or "publish" the information. You can code routines to send faxes or e-mails to staff members. If a caller is having trouble, you can give them an option to talk to a live operator. The real power of Clinical IVR Systems is in these auxiliary systems that provide people easy access to information.

A Survey of Clinical IVR Systems

Subject Diaries

One of the more common types of Clinical IVR Systems, subject diary, is used by many drug companies to corroborate the study results collected from investigational sites. Drug efficacy, alone, is no indication that a drug will succeed in the market place. The patient's "quality of life" while on study medication must be at acceptable levels as well.

Clinical IVR diaries have been hugely successful for many reasons, but mostly because of the excellent quality of the data collected. This is mainly due to the fact that most IVR diaries do not permit subjects to make entries for past days. In other words, subjects only have 24 hours in which to enter their "daily diary." This prevents subjects from cheating. Many investigators have observed trial subjects filling out their "daily diaries" on paper for the past two weeks while sitting in their waiting room. And, just recently, one investigator caught a subject *pre-filling* in their diary data for the *next two weeks*! Unlike paper diaries, which are held in the same regard as homework, Clinical IVR Systems provide simple constraints that drastically improve data quality and value.

Another major factor that can impact data quality is taking some extra time to design the diary script expressly for an IVR[3] System. IVR systems are live 24 hours a day. Therefore, subjects can be instructed to make diary entries at the onset of a significant event. For example, when a headache is starting, or pain relief is indicated, subjects can call the system and enter data on how they are feeling "right now." This fact alone makes IVR diaries superior to all other formats, especially paper. Having immediate access from virtually any telephone, plus the constraints on entering information only for "today," combine to produce accurate and timely diary data.

Randomization Systems

Clinical IVR Systems have been used to randomize subjects for blind, double blind, open-label, and virtually any other type of clinical trial. A true central randomization can be achieved by using a central computer to select the appropriate treatment, which is a feature most statisticians find very attractive. The randomization number, as well as the treatment name, can be played to the caller over the telephone so they can act on the information immediately. Once the randomization is completed, a confirmation report can be generated and either faxed or e-mailed to the investigational site to file with their records.

Trial/Drug Supplies, Inventory, and Randomization Systems

Using another very popular type of Clinical IVR System, investigational sites can call and request study drug and/or trial supplies while permitting the sponsor's clinical team to monitor inventory and supplies. When combined with a randomization feature, such IVR systems function as the heart of a clinical trial. Reports and statistics on active sites, enrolled/randomized subjects, and supply usage can easily be generated and automatically sent to the appropriate clinical team members. The easy addition of a Completion/Withdraw script completes the system and provides pertinent details on the trial.

Common Auxiliary Services

Merely collecting such information does little to enhance a trial. The real power and value of Clinical IVR Systems is in how such information is presented and distributed.

Fax/E-mail

A successful Clinical IVR System must include reports and statistics and an easy method for users to receive and view them. Most people have e-mail addresses these days. But, not all biopharmaceutical companies are permitting information to be sent in this way. For Clinical IVR Systems, the main venue for reports, confirmations, and summary statistics is still the fax.

The following is a partial list of the many reports that can be produced from Clinical IVR Systems:

1. Active Sites
2. Global Subject Enrollment
3. Subject Enrollment by Site
4. Subject Enrollment by Treatment (unblinded only)
5. Completed Subjects
6. Discontinued Subjects
7. Summary of Completed/Discontinued Subjects
8. Trial Supplies Inventory
9. Trial Supplies Alerts (when to order new supplies)
10. Trial Supplies Usage by Site
11. Study Drug Shipments
12. Unused Study Drugs

Keep in mind that, for information to be reported, it must be collected. Fortunately, Clinical IVR Systems make collecting such information a very easy task.

As with the information itself, the reports are of little use unless they can be distributed to the right people in a timely fashion. Incorporating faxing and e-mail capabilities into report generation systems is not uncommon for most programmers these days. Once a report has been generated as a result of a pre-defined event such as a randomization event, scheduled report generation, or a direct request from an Investigator, it is a simple matter to call the appropriate function to fax or e-mail the report to the appropriate recipient. Some Clinical IVR Systems can even publish reports and summary statistics on report usage, which provides useful metrics for future trials.

Web Portal

Web portals, or interfaces, usually reserved for clinical team members, can permit fast access to all Clinical IVR data and provide forms for initializing new investigational sites, or updating fax/e-mail information. In addition to providing access to information, a web portal can allow users to manage more of the project.

For example, when activating accounts for a site for a large trial, the site administrator may need to provide the IVR system administrator a long list of site user's names, fax numbers, and e-mail addresses via paper, fax, and/or e-mail so the IVR system administrator can enter the information. Instead of this manual paper-handling process, a web portal can provide clinical team members with the ability to enter and update information to save time and effort.

Web portals also can provide the clinical team with administrative capabilities for managing key events in a clinical trial such as granting waivers, or exceptions. For example, some patients may not be eligible for randomization into the trial due to multiple entrance criteria based on the number of diary entries made, as well as the number of clinically significant events occurring in a given period. A clinical team may use the IVR system administrative capabilities to grant waivers, thus allowing these subjects to be randomized into the trial.

Hand-Held Computer Devices

The emergence of hand-held computer devices as a means of data capture is noticeable in clinical trials today. Working in conjunction with IVR systems, hand-held computer devices are useful to capture sensitive, text-based patient data. However, distributing these devices to all study subjects can be costly. Also, they can easily be misplaced and lost. Therefore, hand-held computer devices by no means should replace IVR systems, but may improve data reliability if they are both available.

Saving Money on Trial Supplies and Study Medication

One of the more recent developments in Clinical IVR Systems is the ability to manage delivery of trial supplies and study medications. While the ability to request delivery of these items via IVR has been around for some time, the *management* of the delivery is causing some sponsors to take a closer look.

Traditionally, the sponsor sends investigational sites packets, or kits, for trial subjects. Each kit is outfitted with all of the supplies and materials, sometimes including study medication, for the duration of the trial. For lengthy trials, trial costs can increase dramatically when subjects withdraw early and the content of the kit is wasted, especially when keeping subjects enrolled is difficult, or for drugs that are very costly to manufacture.

To remedy this situation, and potentially save hundreds of thousands of dollars in the process, some Clinical IVR Systems are providing "just-in-time delivery." This is a cooperative effort between the IVR vendor and the sponsor. The IVR system requires the sites to enter study participation data on each subject, and the sponsor breaks up kits into separate deliverables for each visit.

After each visit, the sites make a very quick call to the IVR system and record the visit in the database. After verifying the subject is still in the study, a report is sent to the drug shipment facility, and/or the trial supplies facility, and materials are shipped to the site for the subject's next visit. If a subject is lost to follow-up, or withdraws consent, etc., the sponsor saves the cost of the drug, the materials, and also the

shipping. The cost savings, in addition to the minimal additional effort required, is more than enough to make such drug and supplies management a *necessity* for all clinical trials.

Potential Drawbacks

In the aforementioned scenario of granting waivers, which actually happened repeatedly to a real-life trial during Visit 2, the IVR help desk would receive a call from the Investigator saying, "the subject is in the waiting room, and the IVR system says the subject does not qualify to be randomized. What do I do?" Unfortunately, the IVR help desk could not resolve this particular problem because it required a clinical decision. A member from the clinical team had to review the data and make a decision to withdraw or randomize the subject, which could potentially lead to a high level of frustration for the investigational sites.

Such scenario also reflected negatively on the IVR system itself, even though the IVR system was doing its job *perfectly*. To prevent this from happening, a careful evaluation at the business processes is crucial during the requirement phase of the IVR system so that developers can implement proper controls and functionalities to handle anticipated scenarios. For example, the frustration could have been eliminated by adding a web portal where investigators can make clinical decisions on-line or by sending them automated alerts when the IVR system detects a low randomization rate.

It is a potential downside that using "off the shelf" solutions; that is, most of them require you to do things *their* way, which can be quite peculiar sometimes. In addition, some of these solutions may not be specialized for the biopharmaceutical industry. For any IVR system with regulatory impact, you can expect to add functionality and documentation to make them compliant with FDA 21 CFR Part 11.

Conclusion

IVR systems for the biopharmaceutical industry are still growing in size, complexity, and functionality. The number of companies taking advantage of Clinical IVR Systems is slowly growing, but is still far from a majority. However, there are a variety of clinical applications for IVR systems, such as those related to neuropsychopharmacology and psychiatry.

More people should be aware of the capabilities, time savings, and potential cost savings of Clinical IVR. Considering the myriad of tasks that can now be accomplished over the telephone, integrating an IVR system to a clinical trial will certainly allow biopharmaceutical companies to produce robust and reliable results.

References

1. Wave files are a Windows standard sound file format. Many, but not all, telephony cards support one or more Wave file types like mono, stereo, etc.

2. Refers to Dialogic VOX, a proprietary voice file format using adaptive differential pulse-code modulation (ADPCM)

3. Paper diaries rarely translate into useable IVR scripts without some kind of alteration. For example, diaries that require date and time entries have much greater success when the diary script is changed to an event-based format. The IVR system, not the subject, then records the time and date of each event.

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Anthony Chow recently joined Octagon Research Solutions' Clinical IT Department to research and develop IT solutions for all lines of business. His work at Octagon has been related to Electronic Data Capture (EDC) using Interactive Voice Response (IVR) systems. He also is responsible for developing CDISC-compliant solutions for regulatory submissions. Prior to joining Octagon, he was a senior consultant with BearingPoint, a global IT consulting company formerly known as KPMG Consulting, where he held leadership positions at several high-profile projects with Fortune 50 companies and government agencies. Chow holds a BA in computer science from Northeastern University. He can be contacted by tel: 1-610/265-8300 or by e-mail: achow@octagonresearch.com.

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This article compares the benefits and potential difficulties involved in either renovating an existing facility or building a new facility.

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Renovation Versus New Build

by Werner Seiferlein

Introduction

The decision to improve a plant may be prompted by changes either in internal (technology/business/company) or external (regulatory/governmental/environmental/political) environments. Choosing between renovating an existing facility or building a new one is rarely simple and is frequently based on a balance of many factors, such as total cost of ownership, production requirements, and regulatory aspects, all of which require thorough consideration.

Reasons for Improving a Pharmaceutical Plant

The reasons behind a decision to improve an existing plant may be both external and internal. External reasons, initiated by authorities or market forces outside the company, may require that a facility be modernized. Changes to regulatory requirements, local Environmental, Health and Safety (EHS) requirements, or energy saving may require that a facility be enhanced to maintain compliance with those requirements. A facility that is not in compliance with current GMP requirements may require Renovation to realize compliant status.

There are several reasons from within an organization that may prompt an improvement in a plant. If the production performance of the plant deteriorates (or plateaus), a business decision may be taken to invest in/improve that plant to increase performances in production. It may be that the company wants to expand or reduce production of a product which requires some form of modernization.

Maintenance of the plant also may be a deciding factor. Where production units are not reliable, Operational Equipment Effectiveness (OEE) deteriorates, and may indicate the incorporation of alternative machinery. Unreliable units may no longer be reparable, or are simply too costly to repair and require replacement. It may be that the company decides that it is time to introduce innovative technology to boost their production and cost effectiveness and the

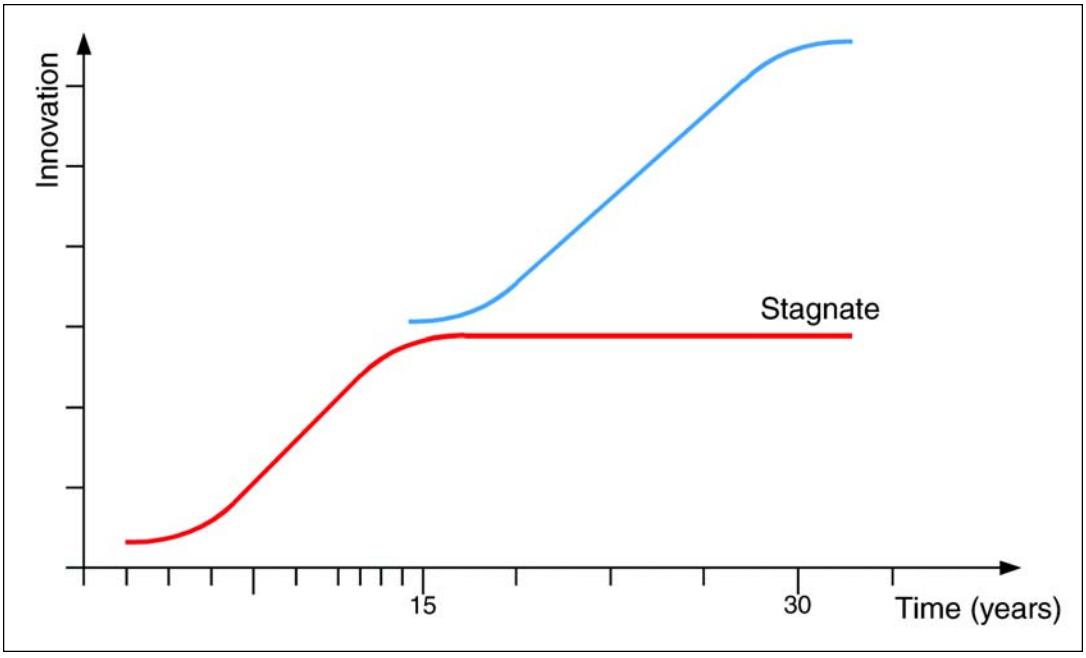

Figure 1. Increasing innovation by deciding a New Build.

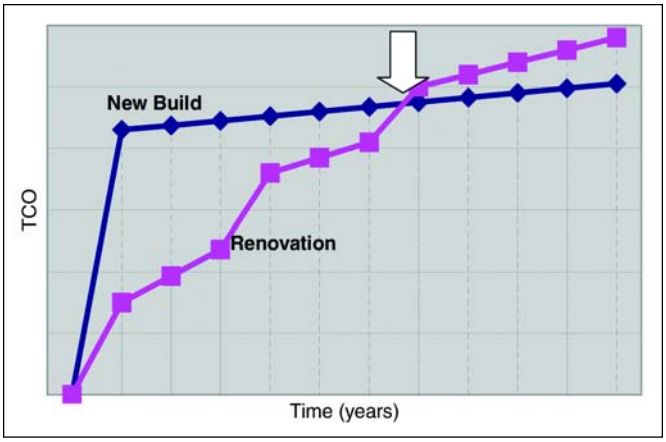

Figure 2. Total cost of ownership over time.

existing facility design may restrict this policy.

Political or strategic decisions within a company also may determine improvements to a plant. The local tax conditions may change, or the company's relation to a particular country or market may modify. The company 'vision' and strategy may alter, particularly where there has been a merger. The capital expenditure situation, cash flow, and market forces may require that the time to market for a particular product be altered.

All such decisions may prompt a determination of whether the plant needs some form of improvement. Once this is decided, the question of "Renovation versus New Build" has to be considered.

The outcome of a 2003 study[1] showed that approximately 90% of investment projects are in the "Renovation" category. In contrast, approximately 40% of the investment was spent for the remaining 10% of 'New Builds.'

User Requirements Follow Site Strategic

The success of a project[2] depends on several factors.[3,4] One of these factors is to know the goal and the requirement of a project. Applied to "Renovation versus New Build," answers to the following questions should provide clear goals and clarity for future steps:

- How might business change over time?
- What is the required product volume and capacity?
- How much space will be needed?
- What kind of influence is infrastructure likely to have?
- How will the space support the technology?
- What are the future personnel needs?
- What are the tax liabilities likely to include?
- Will depreciation limitations prevent efficient renewal?

Building - Layers

The concept of "Renovation or New Build" needs to consider the different levels of that Renovation or "New Build." One way to achieve this could be to look at a building as a six-layered system with each layer having distinct implications in time.[5]

The construction sequence or six-layered system follows a strict order:

> *"Site preparation, then foundation and framing the structure, followed by skin to keep out the weather, installation of services, and finally space plan or layout. Then the tenants truck in their stuff."*

The six layers are indicated by:

- skin
- structure
- services
- space plan (or layout)
- stuff
- site

The exterior surface, known as 'skin', has to be changed every 20 years, in accordance to aesthetic technology or maintenance needs. 'Structure' denotes the foundation and load-bearing elements with a lifetime of 30 to 300 years, which are expensive to change. The interior elements of a building, such as communication cabling, electrical wiring, and HVAC are known as 'services'. These have a lifetime of about 15 years. The fourth layer is named 'space plan' and includes the interior elements such as walls, ceilings, and doors. The 'stuff' (trucked in by the tenants) includes furnishings. The last layer is 'site'; compared with the other layers, this layer has probably the most timeless and enduring attributes.

As one looks at reclaiming older buildings for modern use, in most cases, three or four of the six layers have to be altered or dramatically revamped. Engineers and architects must reach beyond the skin, the space plan, and deep into the services layer to fully update and reclaim outdated buildings.

How Space Can Affect Work

All six attributes combined create the efficiency of a building. The space exists only as the forum in which the pharmaceutical processes and infrastructure are performed. However, space can have a tremendous impact on the quality, function, and speed of the work. It also can have a significant impact on the costs of supporting the work performed.

Building design can influence new ways of working, support user control and comfort, and supports the functionality of technology.

Renovation

The Renovation of existing buildings can yield flexibility, timing, and cost advantages over new construction.

In *How Buildings Learn*, author Stewart Brand[5] argues that buildings shape, and are shaped by, both space and time. Intelligent Renovation is as much an art as original design. Antiquated services, environmental hazards, and inadequate accessibility often plague older buildings. Poor lighting, insufficient cabling infrastructure, and inadequate Heating, Ventilation, Air Conditioning (HVAC) systems are common afflictions in such structures, even those less than 10 years of age. While the structural grids of some existing buildings may prevent cost-effective Renovation, many "obsolete" buildings can be successfully upgraded for contemporary use.

Renovation may afford certain advantages over the alternative of a New Build. Use of an existing site or a new 'greenfield' site both have distinct pros and cons, such as time out of production during demolition and 'New Build,' or acquiring and training of staff.

Renovation of an existing facility may be the faster option, improving the time to the market for any products affected by the decision to renovate or rebuild, and present less risk to realize the extended product manufacturing. For a Renovation the infrastructure is already in place:

- energy (e.g., waste, water, gas, electricity)
- utilities (e.g., power-gas supply, steam, IS)
- transport connection (e.g., road, rail, air)
- real estate (e.g., climate, ground-water)
- adjacent residential areas
- legal position and development regulations

During a Renovation, staff is already present and any extension to their training is likely to be less time consuming. The financial feasibility of Renovation depends on the existing investment in a building. Depreciation schedules, debt ratios, operating costs, revenues, and tax liabilities are all part of the equation.

Contrary to the decision to renovate is the need to free sufficient space to realize the Renovation (interim manufacturing, space area) along with constraints in terms of layout and building design, and the possible limitations in applying new technology. Renovation may need to continue during running production or manufacturing and the potential consequences need consideration. Existing facilities may need to be demolished to make room for the Renovation in advance, and this could impact current production. A step-by-step Renovation under ongoing production requires adequate sub steps or even provisional relocation of manufacturing which could extend the required timeline. Alternatively, establishing a stock of product can bridge the time of Renovation. Another solution could be to relay prefabricated modules, which can "push" in the plant where this is possible.

New Build

New Builds allow for a quantum leap within technology (and knowledge). Such building allows for the creation of future orientated building design, in which a long-term view may be accommodated. The entire build may be performed according to current EHS ergonomic and GMP requirements. Studies have shown that ultimately this option will lead to a lower Total Cost of Ownership (TCO).

With continuous Renovation and adaptation to new technology, the limits of improvement eventually will be reached - *Figure 1.* However, if planning and design take account of available and appropriate new technology, it is possible to 'achieve' the so-called 'quantum leap' in innovation - *Figure 1.* Innovation in this regard is a process involving multiple activities, performed by multiple persons from one or several organizations, who develop an extraordinary and extreme

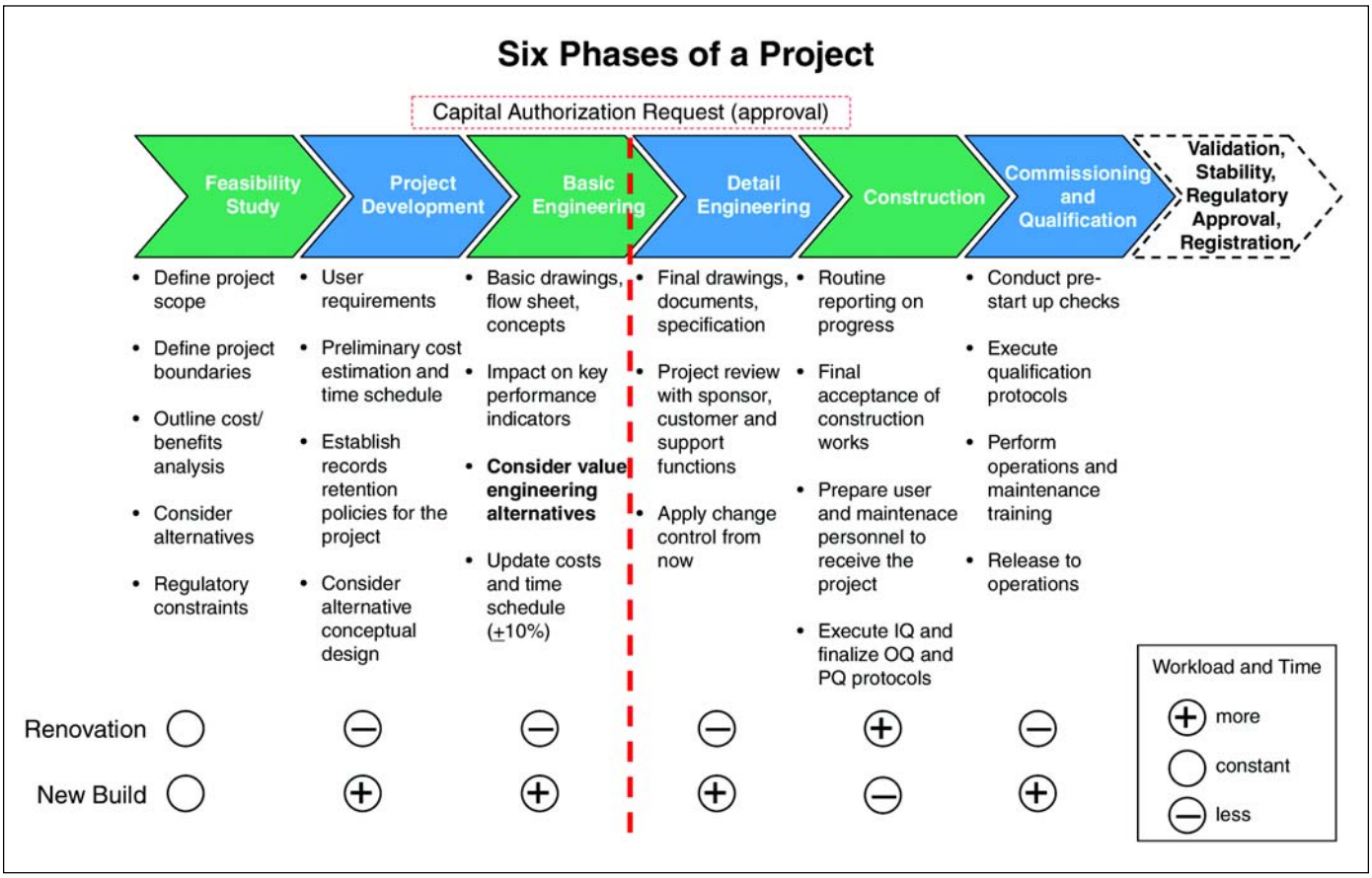

Figure 3. The evaluation of workload and time during the project phases for Renovation and New Build.

new process, equipment, and/or technology.[6]

The implementation of new technologies may carry a high risk because these technologies are not proven by regular business use and may not provide the necessary function or reliability, so this needs to be assessed and defined. Time and resources are also factors to be considered and may count against a New Build. It may take some time to locate and acquire an appropriate site, and staff will need to be hired and trained.

It may be cheaper to have a New Build, rather than to invest in "stop gap" solutions, but a New Build also requires a high immediate investment.

Cost and Time

In order to ascertain whether Renovation or New Build is the best way forward, innovative technology business drivers, such as cost and time, need consideration.

Cost

When referring to cost, the complete picture of cost, i.e., the Total Cost of Ownership (TCO), should be considered.

The total cost of a facility is the sum of:

- one time capital cost (initial cost)
- initial cost includes the purchase price, first set of spare parts, plus engineering, installation, commissioning, validation, and training
- operating costs of the facility throughout its lifetime
- operating costs may include raw materials, energy and other utilities, manpower, and environmental factors
- maintenance costs of the facility throughout its lifetime
- maintenance costs are cost of Predictive and Preventive maintenance, plus cost of repairs
- other operating costs where a failure of the facility leads to plant shutdown
- failure costs include wasted raw materials cost, off-spec cost, clean-up cost, disposal cost, profit loss, etc. resulting from non-availability of the facility
- dismantling/disposal costs or residual value
- dismantling/disposal cost is the cost to get rid of the facility, clean the area, and make it available for the next user. If the facility can be sold, it is a value.

The goal must be to choose facilities which minimizes the lifetime cost of ownership; this minimum is often a balance between initial cost of the plant and lifetime operation and maintenance costs. This implies that the project manager should utilize the know-how and expertise of various functions, such as engineering, purchasing, operations, quality control and assurance, process development, as well as of plant personnel and suppliers.

In all cases, a Net Present Value (NPV) evaluation should be made. The other indicators must be applied independently of the type of project and the decision that has to be supported by the evaluation.

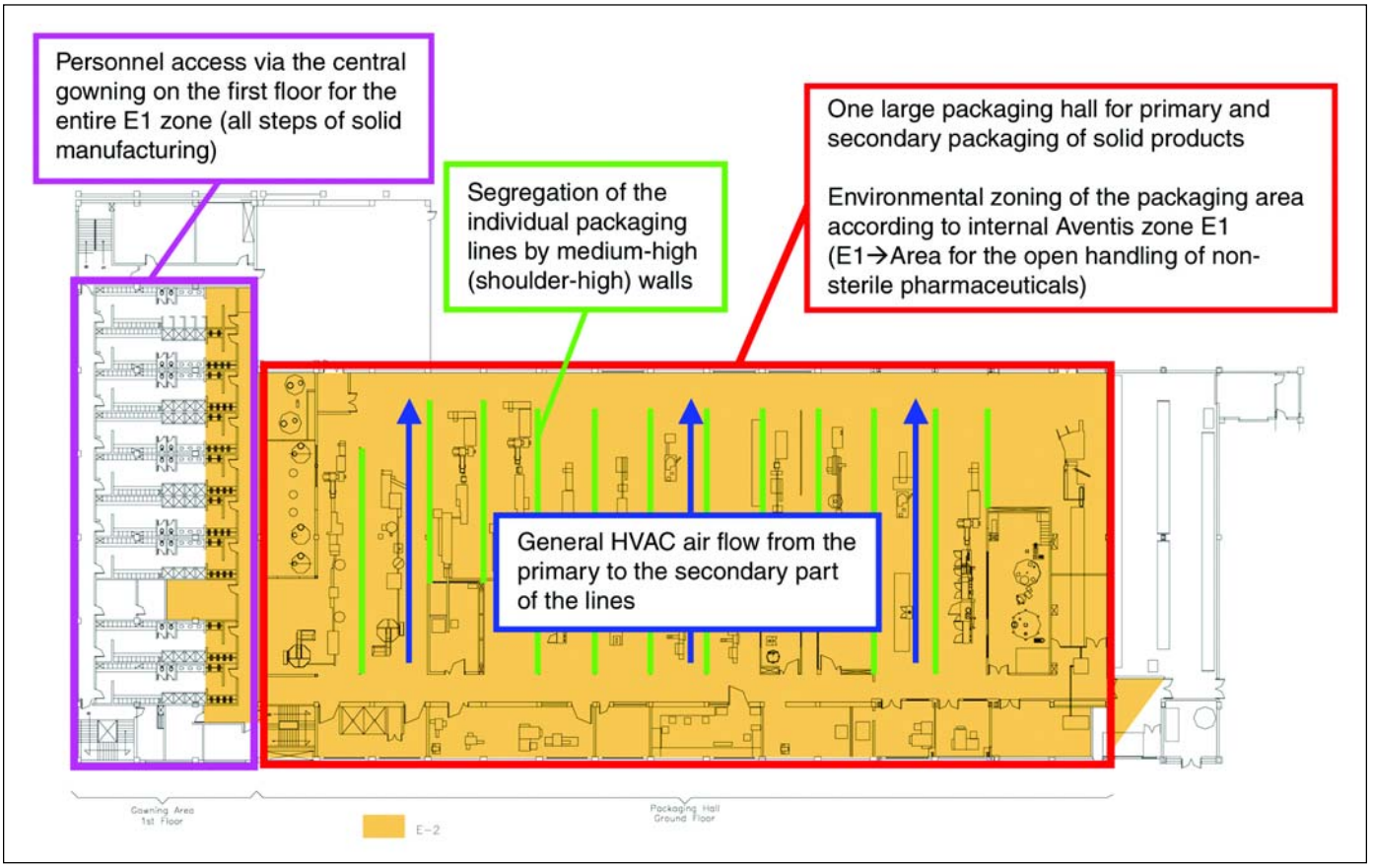

Figure 4. Original layout of the packaging area.

For the NPV calculation, any available system may be used, and the methodology presented in this article applied.

Value engineering should be performed in order to optimize projects with a structured methodology in addition to current project best practices. This is a structured method to optimize the project's value, starting with the challenge of project objectives, assuring consistency between needs, functionalities, and technical solutions with minimum TCO or maximum NPV as the target.

At some point in the lifecycle of a pharmaceutical plant, the cost of Renovation exceeds that of a New Build. Although Renovation may seem a less costly option initially, overall it may be more expensive than building a new plant - *Figure 2.*

In the case of Renovation (Figure 2), investment is step by step in relation to requirements, e.g., compliance or other requirements of plant improvements. The total cost of ownership will increase in regard to time.

In the case of a New Build (Figure 2), there is a major investment at the beginning of the project, but subsequently more efficient equipment processes and appropriate layouts, which need less space. The total cost of ownership will be lower.

The white arrow (Figure 2) shows the break-even-point when it is possible to take advantage of the New Build scenario. The time when the break-even-point occurs depends on specific circumstances.

Time

To answer whether the Renovation of a plant or a New Build would take more time, the specific parameters of a project are needed. This method is an attempt to undertake a comparison of the relationship between project phases.

A project consists of several phases.[7] In the case described, six phases are defined - *Figure 3:*

1. feasibility study with the key activities:
   - define project scope, project boundaries, regulatory constraints, etc.

2. project development with the following key activities:
   - start to set up user requirements, preliminary cost estimation, and time schedules, consider alternatives in conceptual design, etc.

3. basic engineering with the following key activities:
   - basic drawings, cost estimation for capital authorization request. This is the step where total cost of ownership and value engineering should be applied and investigated.

4. detail engineering with the following key activities:
   - final drawings and document specification, etc.

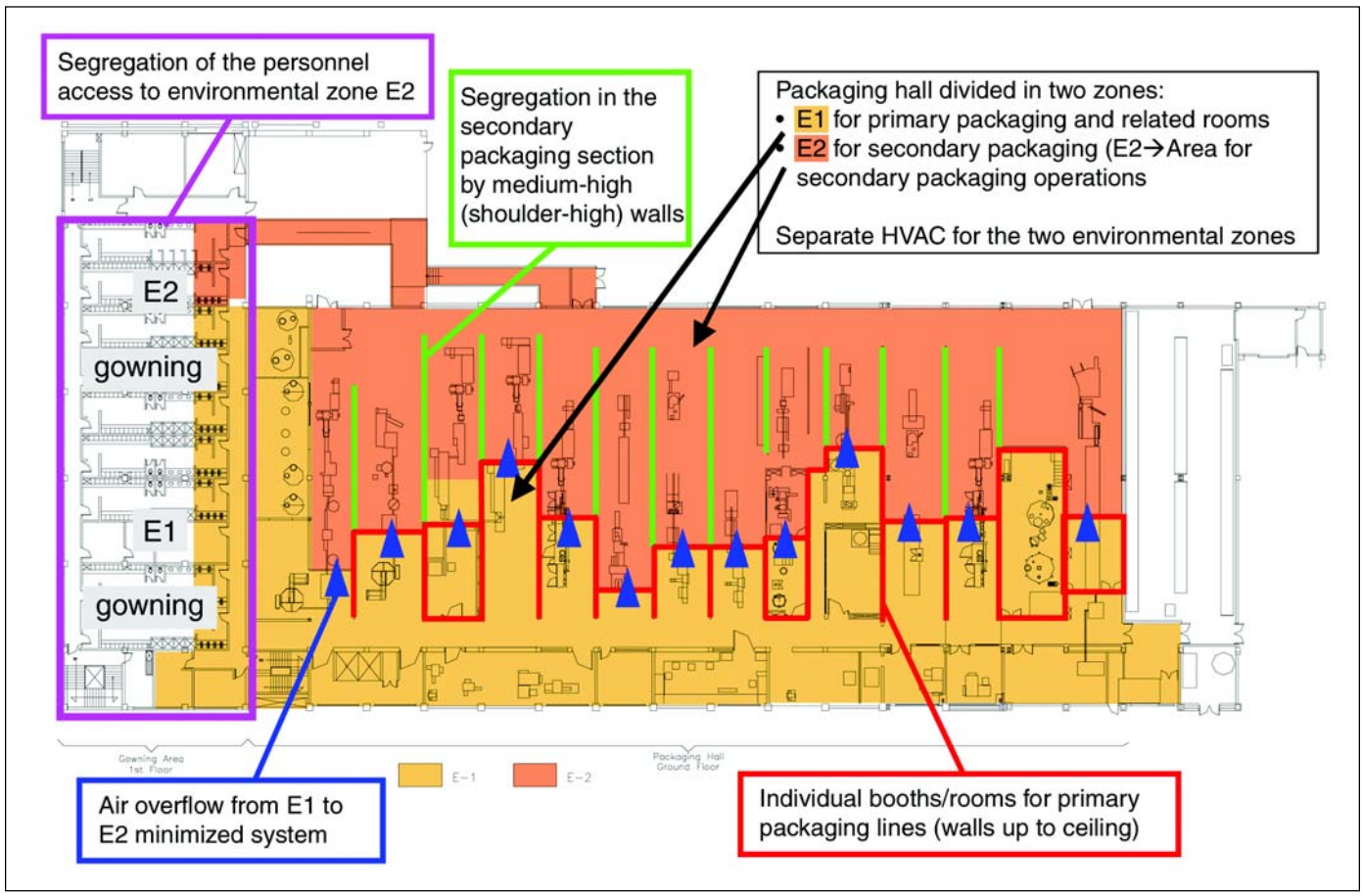

Figure 5. Renovated layout of the packaging area - adapted concept to requirements.

Renovation Pros	Renovation Cons
• Faster in Realization • Less Risk to realize the extended production manufacturing • Infrastructure is given - Energy (Waste, water, gas, current, etc.) - Utilities (Power-gas supply, Steam, IS, etc.) - Transport connection (Road, Rail, Air, etc.) - Real estate (Climate, Groundwater, etc.) - Adjacent residential areas - Legal position and development regulations • Staff is available	• Demolishing of existing facilities and equipment in advance • Need sufficient free space to realize Renovation (interim manufacturing, space area) • Renovation during running production or manufacturing • Constraints in terms of layout and building design • Limited in applying of new Technology

Table A. Pros and cons of Renovation.

5. construction with the following key activities:
   - final acceptance of construction work, execute IQ and OQ protocols, etc.

6. commissioning and qualification with the following key activities:
   - conduct pre start-up checks, execute qualification protocols, release to operation, etc.

Figure 3 shows the evaluation of workload and time during the project phases for Renovation and New Build.

In the first phase, Feasibility Study Renovation and New Build are likely to have the same time and workload requirements.

In Phases 2, 3, and 4, you should need more workload and time for New Build to establish documents like drawings, layouts, and specifications for equipment and devices. In the case of Renovation, existing documents may be utilized.

In the case of construction, more time is required for Renovation, as production needs must be met, so construction work continues in parallel to production and a kind of interim manufacturing space.

Hence, both Renovation and New Build have factors which cause increases in the time needed.

In case of Phase 6, "Commissioning and Qualification," the same argument given for Phases 3-5 could be applied; existing documentation and work may be relied upon.

This is a very rudimentary judgment, as different time periods are required for each project phase. Nevertheless, by counting the "**+**" and "-" it seems that Renovation could be faster than a New Build.

Example for Renovation

Packaging Area Renovation

A packaging area required a new layout to facilitate a change in company philosophy. This change required that the open handling of non-sterile pharmaceuticals in the packaging area must be performed in a separately controlled environmental zone. The decision to renovate rather than rebuild this packaging area caused several difficulties, which required specific solutions, while minimizing disruption to production. Figure 4 shows the original layout of the packaging area. Figure 5 shows the renovated layout of the packaging area.

The Renovation could be achieved by segregation of primary and secondary packaging or by local protection of the filling section of the primary packaging machine. Difficulties in implementing local protection on existing packaging machinery compelled the segregation of primary and secondary packaging areas.

This required the packaging area to be divided into two distinct environmental zones, classified as E1 and E2, where E1 was the more stringently controlled environment for the open handling of non-sterile pharmaceuticals. Consequently, the gowning areas required segregation and separate HVAC systems had to be constructed to provide for the two distinct environments.

Several difficulties arose with the decision to renovate, including:

- finding an acceptable location for the segregation wall between primary and secondary packaging
- implementing a separate personnel access route for the secondary packaging area
- rearranging the entire HVAC system
- realization without unacceptable manufacturing interruptions
- reorganization of the operation and maintenance activities, required by the segregation

The example shows a remodeling project initiated by compliance issues, the solution to which demonstrates the difficulties that arose, and the compromises necessary to remedy those difficulties.

The initial investment required may be considered as the initial step - shown on the red curve in Figure 2. A single

New Build Pros	New Build Cons
• Quantum leap within Technology and Knowledge • Create future orientated building design • According to current EHS, ergonomic and GMP requirements • Less Total Cost of ownership	• High Risk with implementation of New Technologies • Probably needs time for Site Selection • Hire and train new staff
Cheaper than to invest in "stop gap solutions"	**but** **High investment at once**

Table B. Pros and cons of New Build.

investment such as this is unlikely to justify a New Build. However, where further investment is required (as signified by the stepwise investments indicated in Figure 2), any investment made after the position indicated by the white arrow could be considered squandered.

Since the investment for Renovation occurs step-by-step over a long timeframe, it may be difficult to predict future investment. A better approach could be to establish a site strategy to define and identify the potential triggers and requirements that lead to Renovation. This allows the calculation of the cost of these investments for a clear period of time, and a comparison to the cost of a New Build to be made.

Conclusions

Renovation of existing areas seems to be faster compared with a New Build - *Tables A and B.*

This occurs because during the project phases Project Development, Basic-and Detail-Engineering, and Commissioning and Qualification, a significantly higher workload and more time is needed to establish drawings, layouts, and specifications for equipment and devices.

Despite this consideration, a general decision to select between the Renovation of existing space or a New Build space is not feasible.

The decision strongly relies on the conditions and circumstances related to the specific goal and content of a project.

Existing tools and methods, such as Site Master Planning, Total Cost of Ownership, and Value Engineering which cover well-known calculations, e.g., Net Present Values (NPV) can help support such decisions.

Decisions for a New Build depend on economical reasons, but also may require top management to have the courage of their convictions to initiate such projects.

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About the Author

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This article discusses the recent trend of Campaigning sterile drug batches in conjunction with the installation of isolator technology for aseptic fill/finish operations. The article was based on a presentation that was held at the 11th Annual Barrier Isolation Technology Forum in Arlington, VA, June 2002.

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Isolator Campaigning - An Industry Survey and Discussion of Operational Practices

by Douglas Stockdale

Introduction

Campaigning, the manufacturing of multiple batches of parenteral fill/finish products between complete sanitization/sterilization processes may be an economic necessity with the implementation of isolator technology for high speed aseptic filling operations. This was one of the key points that came out of a recent independent isolator technology survey.[1]

The purpose of the Isolator Campaign survey was to provide the industry with operational and compliance information regarding the implementation of a Campaign process in conjunction with Isolator Technology. This was a subject that Mike Winter, Director Form-Finish, Baxter Biosciences, and I, President, Stockdale Associates, Inc., had personally noted that kept reoccurring in a number of side discussions at ISPE Isolator Technology conferences in the late 1990s. At the 2001 ISPE Barrier Isolation Conference, "Isolator Campaigning" was a largely attended break-out discussion group meeting. Subsequently, Mike Winter, and I initiated an independent industry survey on the use of Campaigning within the Isolator user community. Jack Lysfjord, Vice President, Valicare division of Bosch Packaging and Co-Chair of the ISPE Barrier Isolation Conference, provided us with valuable guidance during the entire survey process.

The isolator technology community is in a transitional period. It has overcome the technical development hurdles of the Isolator process as applied to the Life Science Industry. Most have come to recognize the ability of isolator technology to further reduce the risk of microbial contamination of aseptically filled products. Isolator fill lines are now facing the intense and tough operational economic requirements.

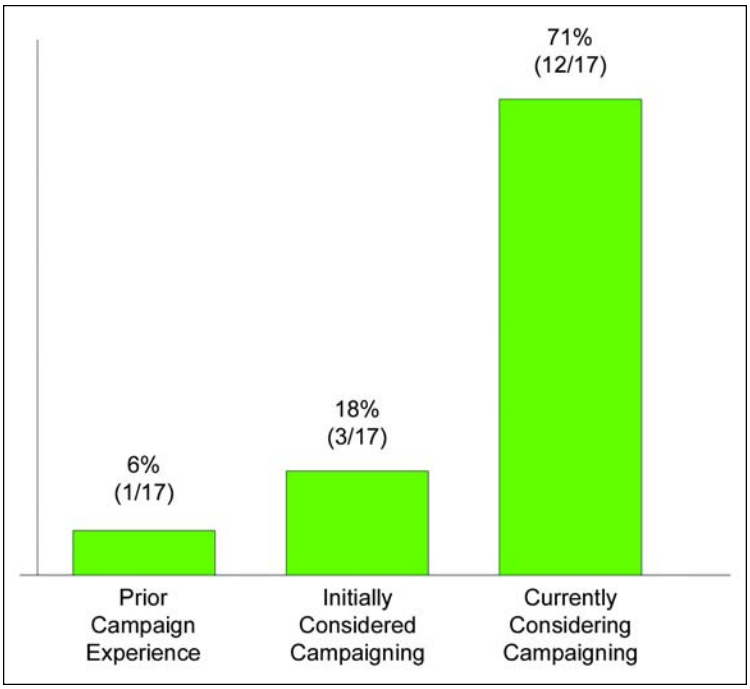

Figure 1. Campaign trends.

The high-speed, large production volume isolator fill-lines are faced with the commercial reality of production schedules, throughput, return on managed assets, and standard cost. A big concern with the implementation of isolator technology is the extended durations required for the sanitization cycle of an isolator with Vaporized Hydrogen Peroxide, which is becoming the industry de facto

standard. One way that organizations could possibly leverage their isolator investment is to utilize the process of Campaigning, which is to produce multiple batches of product between sanitization/cleaning cycles.

The Isolator Campaigning survey was developed to understand the current industry thinking about the implementation of Campaigning in conjunction with isolator technology. The survey results were expected to be used to benchmark the industry on how the use of Campaigning could impact the continuing implementation of Isolator Technology.

The concept of Campaigning was already being considered as an operational tactic with Isolator Technology by a number of early innovator companies. Many pharmaceutical companies had a history with Campaigning for batches of Active Pharmaceutical Ingredients (APIs) produced between cleaning cycles. Biotechnology companies also were gaining some operational experience with Campaigning when the concept is applied to the use of chromatography columns.

The Isolator Campaigning Survey

In a preliminary meeting about this survey, it was decided that Campaigning would be really relevant to large-volume, commercial users of isolator technology. Small scale isolator users would probably not be under the same scheduling and throughput constraints, therefore Campaigning would probably not be an issue that would need to be addressed. It was recognized that the resulting survey would then be limited to a very small and restricted distribution (22 companies survey), but would be a very focused and relevant survey.

The importance of keeping this survey confidential and reporting the results anonymously also was recognized as the issue of how to implement a Campaign process is becoming a sensitive issue. The survey respondents had an opportunity to return their survey to either Winter (Baxter) or me (Consultant). This concern did prove true, as we received two non-responses due to "management objections to discuss a critical operational strategy." Otherwise, a very high response rate of more than 80% was received (22 surveys distributed, four non-response); which reflects the industry's desire to share information and further improve the safety of patients who will be utilizing the sterile products. The data and graphs presented in this article will not add up to a full 100% as the survey data is effected by partial survey responses, where some questions have purposefully omitted answers, and where there were multiple isolator installations, with operational variance between geographies and installations. We sincerely appreciate all the time that was spent by all of those who invested their time and shared their information with us.

The interim study report was presented at the 2001 ISPE European Isolator Technology Conference in Zurich. The final survey results were presented at the 11th Annual Barrier Isolation Technology Forum in Arlington, VA, June 2002.

Survey Results

First, more than 70% of the operating companies, which are now considering an investment in high-speed isolator tech-

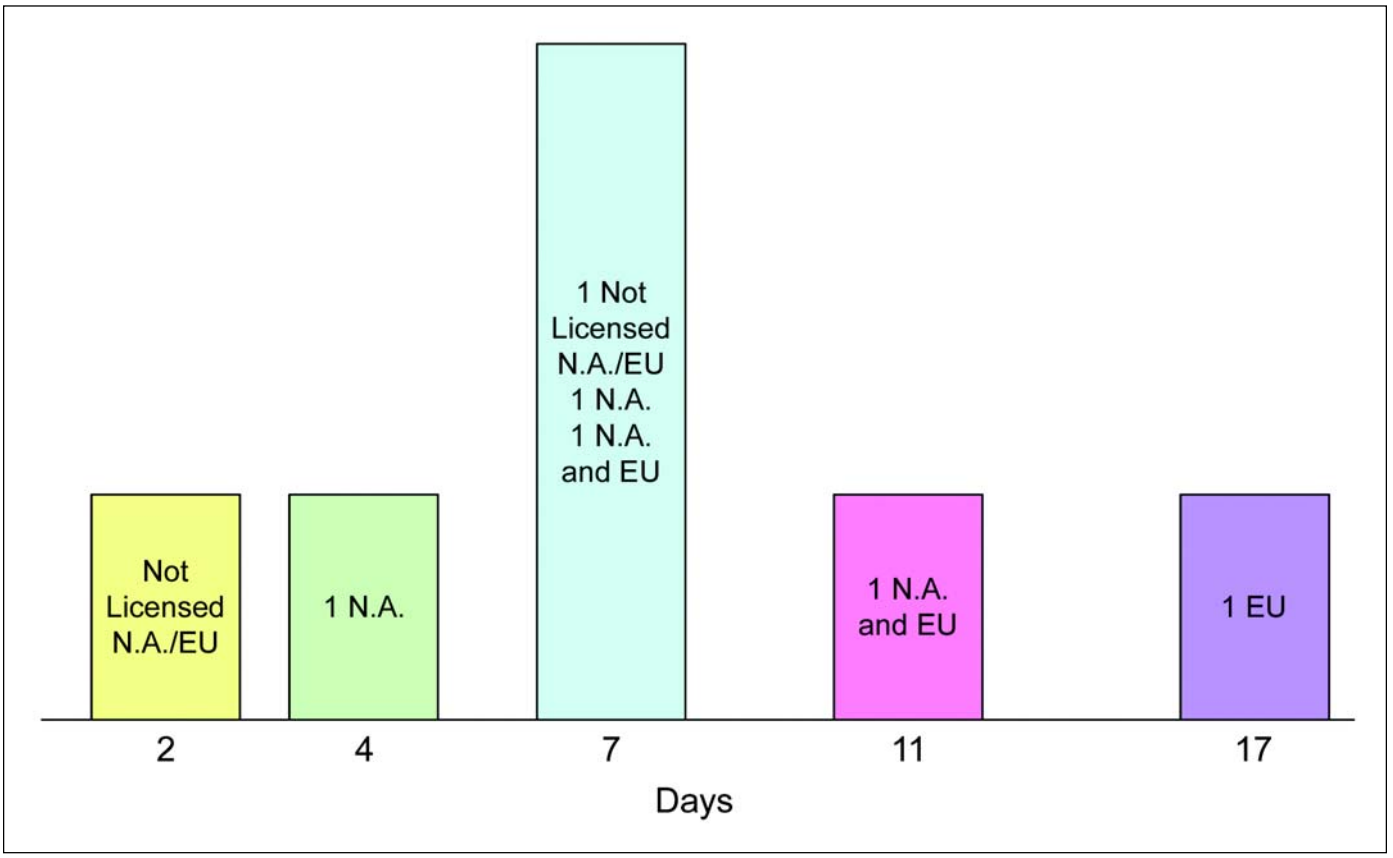

Figure 2. Campaign durations – current.

nology, also are evaluating a Campaign process – *Figure 1*. When isolator technology was being initially developed, less than 20% of the companies had considered the use of Campaigning as an operational option. Comments were received that early high-speed Isolator lines did not have many of the current options available that would easily facilitate a Campaign process.

All the comments about reasons for implementing isolators were related to the increased ability to control microbial contamination by eliminating personnel. The principal reason to implement a Campaign process was economics: reduced down time. Companies commented on the increased loss of production time with isolators for sanitization between batches versus their traditional barrier aseptic fill lines. Without Campaigning, they were not getting the same volume of production per fill line, which was compounded by the increased investment for the isolator technology, thus increasing the manufacturing standard cost per vial. To improve their economics, e.g. reduce their manufacturing standard cost per vial, they needed to implement Campaigning and reduce downtime.

A comment from a number of organizations, which have already made an isolator technology investment, is the additional investment required to modify their equipment to permit Campaigning. Others may not consider the implementation of Campaigning now, they would consider Campaigning with future isolator technology investments.

Of those companies that are not considering Campaigning, half cited United States Food and Drug Administration (FDA) regulatory concerns. The others either produced very large batches now and Campaigning would not provide an advantage or there were other product issues that would preclude Campaigning.

Second, there was an initial large difference in the use of isolator Campaigning for products manufactured and distributed in the European Union (EU) versus North America (NA)/United States. At the time of this survey, there is now more of a balance in Campaigning between the two geographies – *Figure 2*. The majority of the European isolator organizations are Campaigning products exclusively for European distribution. The European isolator organizations stated that they are cautious about Campaigning products intended for export and commercial distribution within the United States. Many of the United States/North American isolators are not Campaigning, but were very interested in the process and considering the potential implementation. Every comment regarding the implementation of Campaigning in the United States/North America was directed at the uncertainty of the FDA's position on Campaigning, the requirements that would need to be met to validate a Campaign, and the potential of regulatory approval.

Third, organizations focused on the duration of the Campaign, versus the number of batches processed, but recognized there was a finite limit of batches that could be processed in that duration. There is no consensus on the number of batches or durations of a Campaign process – *Figure 2*. But there is a consensus that the number of batches or the duration of the Campaign could be greater than was initially thought, and more than 70% of those Campaigning are considering a longer Campaign duration. Figure 3 highlights the responses to the survey that provided target durations for extending their Campaigns.

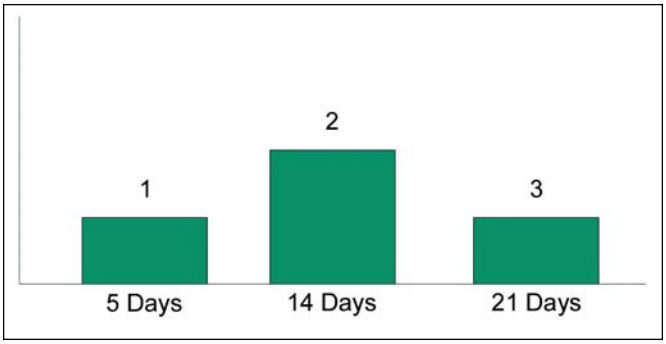

Figure 3. Campaign durations – potential.

The comments about Campaign duration indicated that decisions were determined by either compliance/operational/finance risk about by a potential "failure" or the amount of revalidation time required to support an extended duration. Most organizations did not want to comment about failure modes at this time.

Fourth, there was a 100% consensus by all organizations that only products of the same family would be Campaigned with variations occurring only in potency within the same product family.

Fifth, all of the organizations were requiring the use of Clean-In-Place (CIP) and Steam-In-Place (SIP) on the fluid path of the product between batches during a Campaign.

Sixth, there was a consensus (80% of those who answered this question) that the media fill would simulate the maximum lot size of the Campaign – *Figure 4*. Most of the organizations indicated that the media fill for validation was a concern, and very few organizations provided detailed information about their media fill strategy.

Discussion

Early high-speed isolator lines were not designed to easily facilitate a Campaign process, such as the inclusion of CIP/SIP for the product fluid path. The possible reason for not considering Campaigning in conjunction with early isolator technology development was two fold: aseptic filling operations are traditionally a single batch process as dictated by regulatory guidance, and second, the amount of clock time that was going to be required for Vaporized Hydrogen Peroxide sanitization was not well understood.

The commercial implementation of isolator technology was adopted quicker in the EU, and likewise the use of Campaign processing also is being quickly adopted for isolator technology by EU, but not for products to be commercially distributed in the United States.

Even though there is stated FDA support for the implementation of isolator technology as an improvement on aseptic fill/finish, most organizations are cautious about seeking FDA approval for Campaigning of aseptic production in

conjunction with isolators.

Prior to our presentation in June 2002, an extensive literature search was conducted of the FDA guidance documents regarding Campaigning. The only Campaign guidance that we presented then, as it is now, is within the International Conference on Harmonisation (ICH) Q7A, "Guidance of Industry; Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," dated August 2001. ICH Q7, Section 5.2, Equipment Maintenance and Cleaning states:

> *"When equipment is assigned to continuous production or Campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over contaminants (e.g., degradants or objectionable levels of microorganisms)."*

A problem for the Campaigning practice is that the scope (section 1.3) of the Q7A, states: "The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but shall be performed in accordance with Good Manufacturing Practices (GMP) guidance for drug (medicinal) products as defined by local authorities." Even so, during the Questions and Answer discussion following the June 2002 presentation,[1] Richard Friedman, FDA, stated that Q7A did help establish guidance for Campaigning with isolator technology. It was still necessary for an operating company to validate what would be an "appropriate interval" for a Campaign production.

A review of the *Draft Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice*, August 2003, does make two statements that address the process of Campaigning of Aseptic filled drugs.

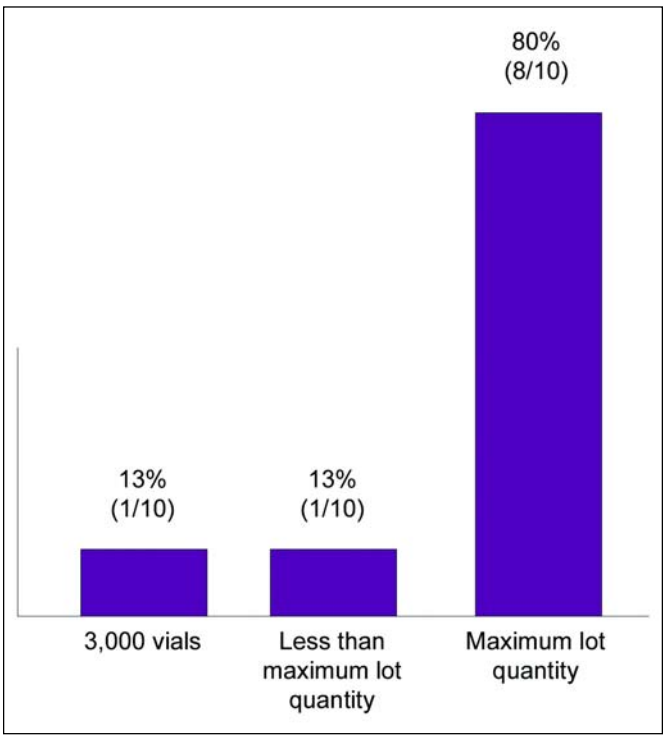

Figure 4. Campaign media qualifications.

First, Section IX, Validation of Aseptic Processing and Sterilization, Section C (line 042) states "Sterility of aseptic processing equipment should be maintained by batch-by-batch sterilization." The challenge to the operating company is how to work within the language of this statement to perform a Campaign process.

Second, in Appendix 1, Aseptic Processing Isolators, section D3, Decontamination Frequency, states: "When an isolator is used for multiple days between decontamination cycles, the frequency adopted should include a built-in safety margin and be well justified." This statement does not provide the full resolution with isolator technology processes for the batch-by-batch statement in Section C, above.

It also could be argued that this draft document does not explicitly prohibit Campaigning of multiple batches either. Reference is made in Section E, Design, to 21 CFR 211.67(a) that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug beyond the official or other established requirements." The use of the term "appropriate intervals" is the same terminology as noted in Q7A section 5.2 and could permit an operating company to validate what an appropriate interval is for their production process, which includes the process of Campaigning.

Section VIII, Time Limitations, of the Draft Guidance requires only that "time limits should be established for each phase of aseptic processing," which does not prohibit the validation of multiple batches as Campaign production process.

Some Campaign validation guidance is provided in Section IX, Validation of Aseptic Processing and Sterilization, section A.1 Size of Runs. The Draft guidance states: "Some batches are produced over multiple shifts or yield an unusually large number of units, and media fill size and durations are especially important considerations in the media fill protocol. These factors should be carefully considered when designing the simulation to adequately encompass conditions and any potential risks associated with the larger operation."

One issue that may concern the FDA is the challenge to the long tradition of single batches of aseptic filled products and the potential Pandora's box that may now open with the approval of Campaigning for isolator operations.

If Campaigning is a viable compliance practice with isolator technology, why could it not also be applicable to a well controlled "Restricted Access" aseptic operation? Or could Campaigning be a validated and acceptable process for a very well controlled traditional barrier aseptic filling operation?

Or extend the application of Campaigning to the sterile lyophilization process, even without the use of isolator technology. Couldn't a sterile lyophilizer be considered a restricted access process if all of the production operations were completed through its "pizza" door? The pending application of a Campaign process to a tradition sterile lyophilization process was just confirmed during a discussion with a European aseptic manufacturing manager at a recent sterile

lyophilization conference in Brussels.

There are no explicit regulatory guidance's being provided to assist an operating company with developing and validating a Campaign process for an aseptic filled drug. It would be helpful if industry organizations and operating companies provided a consensus input to the isolator section of the *Draft Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* regarding the validation of Campaign operations.

The industry has now embraced isolator technology and the process of aseptic Campaigning is both feasible and a reality.

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This article explores the need for a more strategic approach to outsourcing decisions in clinical materials management.

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Strategic Value of Clinical Supplies

by Colin Andrews

Background

A previous article in *Pharmaceutical Engineering*[1] described the dynamic and changing business environment for drug discovery and development. This article concluded that – due to a potential step increase in drug discovery – execution processes such as Clinical Materials Management (CMM) are becoming more critical to competitiveness than ever before.

A key area of focus in CMM has been about the development of outsourcing in this area of activity.[2,3] For some firms, this may be the only viable option for effective CMM. For others, outsourcing may be appropriate in selective cases. Indeed, the growth of CROs in the last three years[2] demonstrates the growing demand for this service.

However, it is equally clear that the decision to outsource is frequently taken *arbitrarily* rather than for *strategic / tactical* reasons, for example,*"we haven't the capacity to do 'this', 'now.'"* Given the increasingly central position of CMM in determining a company's competitive capability, too many short-term decisions can weaken its overall competitive performance. The discussion is too often *"We don't have the capacity so we'll have to outsource…"* The discussion should be *"What are our strategic priorities?" Are these reflected in our core competencies and capabilities? What must we do ourselves and what therefore should we outsource?"*

The growth of the outsourcing of execution activities has been a feature of many other industries. There are lessons to be learned and shared. Equally, there are distinctive features of the pharmaceutical development industry that must be taken into account.

This article develops a framework for understanding where the firm is deriving *strategic* value from its clinical materials processes in order to help organizations formulate appropriate strategies for developing their CMM capability.

Supply Chain Learning from Other Industries

Other industries, such as the electronics industry, have followed a development path that is analogous to the pharmaceutical industry, albeit with relatively more compressed market life cycles. In the early growth stages of the industry, firms were strong innovators. As no one could provide them with the specialist skills and services they required, they were developed in-house. Many organizations became highly vertically integrated.

As the industry developed, more and more specialist suppliers emerged, or were spun off. Original Equipment Manufacturers (OEMs) began to focus on core competences in areas such as design, assembly, and marketing. The specific competencies developed depended on the OEMs' particular competitive strategies. Some organizations pursued a strategy of *differentiation* where design and new product introduction capabilities were core. Others pursued a strategy of *lowest-cost producer* where

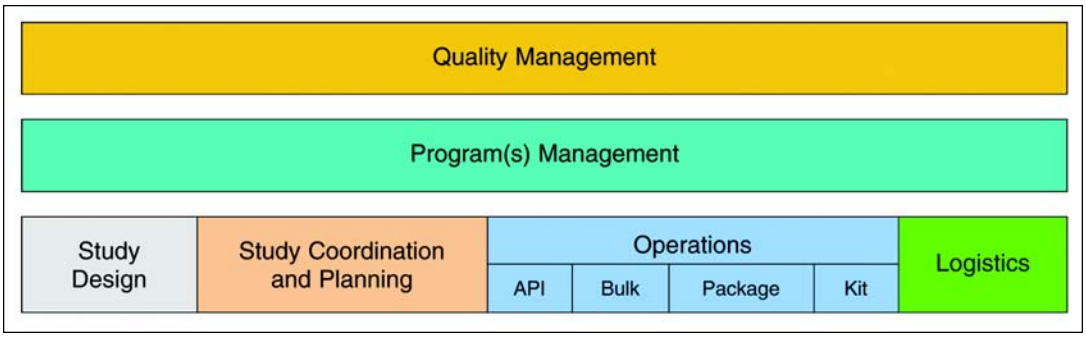

Figure 1. Clinical Materials Management competencies.

design competencies were about following trends and core competencies for competitive advantage were in manufacturing and distribution.

Toward the end of the growth phase, the typical electronics producer would have a number of design 'centers of excellence.' Production/execution would be via regionally based manufacturing centers focused on assembly operations with core expertise in managing the supply chain. Relationships were established with Tier One suppliers who shared the OEMs global reach. Each Tier One supplier would have a network of secondary suppliers in each region for the provision of required materials.

With the market essentially mature in many areas of electronics products (VCRs, television, personal stereos, computers), the OEMs are stepping back from supply chain operations. Their competitive area of focus is now on product design and marketing.

The automotive industry has followed a similar although less extreme pattern. The OEMs still tend to assemble the vehicles, but this is not exclusively their preserve. Major components and sub-assemblies such as engines, gearboxes, and even body shells are produced by partner organizations. These may be suppliers. They may actually include other OEMs, for example, sharing engines and gearboxes.

In both these industries, close involvement with many aspects of the suppliers' operations is seen as critical to maintaining and developing competitive advantage for the OEM.

Make or Buy in CMM

The decision to outsource Clinical Supplies can be seen as a classic 'make or buy' issue. For some businesses, such as 'virtual' corporations or bio-technology start-ups, there may be no other way to access the necessary expertise. For other firms, the complete outsourcing of CMM is a dangerously simplistic option that ignores the many linkages between CMM and other development activities such as study design, formulation development, and manufacturing process specification. It is a common complaint within CMM organizations that the trial's personnel assume that materials are available 'off the shelf' to meet any trial requirement at any time.

One of the unique features of clinical materials is that they come in many forms. Not all of these forms are equally 'valuable.' By the time a drug development program has reached Phase III, clinical supplies can include:

- the 'drug' being trialed - likely to be in short supply and highly valuable
- a suitable comparator - possibly difficult to source, but of lesser value than the drug
- a placebo - simple to produce and low in value

Issues of blinding in the study will restrict how differently these groups of materials can be managed.

It is also necessary to consider sub-divisions of the whole supply process. Figure 1 describes a simplified supply chain for CMM.

Any one of the above supply chain steps can be outsourced. It also is possible that only parts of each step may be outsourced, for example, bulk production of placebo. These are important decisions with implications for business performance, and such decisions are not to be taken arbitrarily.

Another dimension of complexity in CMM is the phase of clinical trial being considered, i.e., Phase I – IV. The different phases have very different requirements both for the volumes of clinical supplies required, and in terms of the level and types of controls required. The clinical phase also has a significant impact on the nature of the manufacturing capability required.

With this complexity, it can be challenging for firms to manage CMM processes clearly and consistently. It is unusual to find a consistent approach across multiple clinical trials within a single organization. Clearly, some form of strategic reference-point for these activities is essential.

The issue is less of a simple and often (capacity determined) arbitrary choice between in-house operation and outsourcing. The real issue is where most benefit can be derived from outsourcing and what competencies provide greatest benefit to the company if developed and maintained 'in-house.'

Value in the Clinical Materials Supply Chain

It is generally easy for organizations to see the costs involved in the supply chain for clinical materials. Equally, there is an inherent logic that any facility within a single company set up to cope with a peak of large Phase III trials will be underutilized at other times. Similarly, the complexity described above suggests that any company aiming to maintain a broad capability in CMM, for its own competitive advantage, must retain a significant level of redundancy in its Clinical Materials supply chain.

A focus on costs tends to push any outsourcing activity into a price sensitive transaction-by-transaction equation. There is anecdotal evidence that this is the case within CMM.[4]

Counter-balancing the positive financial attractions in outsourcing are concerns about the reliability of supply from contractors, and worries over assuring the quality of those supplies. These concerns are often based on personalized experiences of specific projects and often lack appropriate review of the causes of 'wrong' outcomes. The end result of this is a tendency to frequently move suppliers, and to impose significant levels of intervention in the outsourced processes.

The costs of outsourced clinical materials supply tend to make up only a small proportion of a typical Phase III trial's budget. While significant differences in cost *between* suppliers may only change the overall budget by a few percent, different levels of performance *from* the supplier (quality, delivery, responsiveness) may negatively impact the whole study significantly. Therefore, there is a need to get back to basics and consider where the 'value' in the supply chain resides.

The following elements are suggested as potential areas of value-add for the development company. In turn, these should begin to form the framework for the *'make or buy'* decisions

referred to earlier. Figure 2 describes a 'virtuous circle' of added value from the elements described below.

Product Knowledge

Throughout the development process, there is 'learning' about how the 'end product' production scales-up. Benefiting from this 'learning' is an underlying driver for 'concurrent engineering' in other industries. The objective is that – by tackling production issues during the development stage – new products can be introduced to market more quickly and with better quality. As medicine becomes more 'niche' and personalized, and the development process more transparent with earlier 'me-too' products, well-managed product knowledge will be essential for sustained competitiveness.

This knowledge is of most value to the eventual producer of the drug product. Where arbitrary decisions are made about the production of clinical supplies, the producer of the drug during trials is not necessarily involved intimately enough in the later specifying of production processes. This makes it difficult to transfer any learning regarding the unique characteristics of the specific product.

It is a particular feature of pharmaceuticals that it is difficult to make changes to a production process once it has been validated for approval. Early optimization is not just a 'nice to have,' it is an essential in the new competitive environment. It is also too important to leave to chance.

In general, the management of knowledge regarding the end product can become critical at key stages in the development. Typical of the types of problems seen are difficulties with Methods Transfer. These difficulties can arise between the development organization and the contractor, or just within the development organization itself. Such difficulties can cause significant delay in the program. At their worst, they can jeopardize the whole program by introducing concerns over the robustness of the product that may or may not in fact be valid.

Problems with this knowledge management can lie undetected and may not be recognized until late in the development program – for example, if there are queries regarding submissions to regulatory authorities.

Supply/Lead-Time Flexibility

It is a fundamental of clinical trial experience that clinical materials supply is not a 'critical-path' activity for study start. Indeed, it has been identified that fewer than 5% of clinical studies are delayed by late clinical materials.[5]

However, there are still significant elements of value in *reliably* reducing the clinical materials lead-time. Research at the Tufts Centre for the Study of Drug Development has identified that reducing the development lead-time by half will reduce total costs by approximately 30%.[6] This reduction comes from a myriad of savings, but even from a restricted CMM viewpoint, the longer materials sit on the shelf, the more effort is required to maintain and coordinate expiry dates, the more resource required to identify and manage stability issues, and greater volumes of storage required (significant if refrigerated, or specialist storage is required).

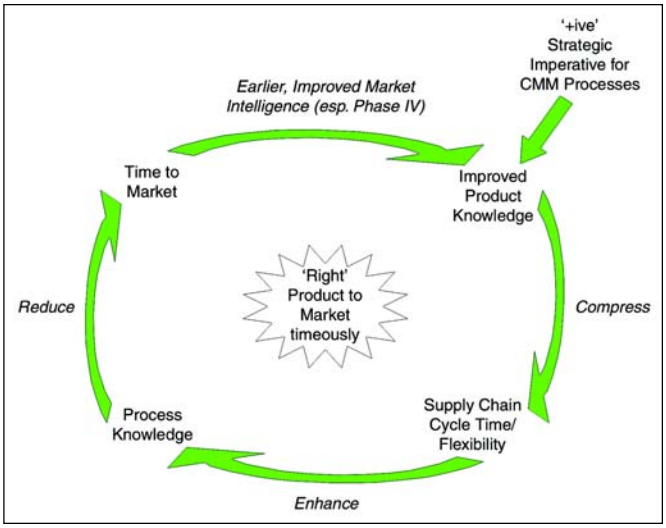

Figure 2. Added value in CMM.

Intangible benefits also can come from reducing supply lead-times. The shorter the lead-time, the greater the opportunity there is to fine-tune details of study protocol. Provided this is well managed, the end result will be a better study. An example of how this may work is allowing the study sites to have more input, or input closer to the study start, thereby improving investigator ownership of their tasks and reducing the number of issues to be addressed during the study operation.

Alternative Use

Active Pharmaceutical Ingredient (API) is often in very short supply during the development process. The ability to change the trial destination of API can be crucial to bringing the best product to market quickly.

One of the mantras often cited for efficient drug development is 'kill early, kill often.' Benefit will only be gained if the resources that are freed up can be redeployed in a timely and purposeful manner.

This may be simple in principle. However, in practice, the delays and potential for mistakes in retrieving a batch of material from one site and re-releasing and/or transferring to another can, and does, make this course of action impractical for some organizations in some cases. Enhancing product and process knowledge is essential to achieving these levels of organizational competence.

Responsiveness to Trial Results

Clinical trials often require 'fine tuning' during their run. Patient recruitment may be markedly different from expectations (country, demographics, quantity etc.). Patient retention may be better or worse than anticipated. Survival rates may be higher or lower. Results may show un-expected outcomes. Each of these can impact the nature of the clinical materials required, and the mechanisms used to manage existing supplies.

Extended, complex or poorly thought out supply chains can make change expensive and time consuming. In the worst case, CMM activities may influence decisions on the develop-

ment process. For example, as an extreme case, an otherwise promising drug program may fall into the 'kill early' category due to the failure of CMM processes to cope with difficulties in the running of the clinical trial.

Process Knowledge

Deriving value though process knowledge is an over-arching case of all the above elements. The automotive and electronics experience is that quality improvement over a multitude of projects comes from the active involvement of suppliers rather than from 'intervention' and policing.

Sometimes it is possible to look at a pattern of supply difficulties and make a single coordinated change to produce a step improvement in performance. Often, it is more practical to make many small, incremental improvements. Experience from other industries is that this can result in real performance benefits in the long term.

Patterns of Outsourcing

As indicated previously, other industries have had to address comparable issues with their own supply chains. There is a generally recognized hierarchy of outsourcing from transaction-based relationships to risk sharing partnerships - *Figure 3*.

Transactional

In a transactional relationship, it is assumed that all suppliers' offerings are comparable and so price dominates. The outsourcing process involves publishing invitations to tender, getting a number of quotes, and selecting the cheapest credible quote.

In this relationship, costs are believed to be closely controlled. The reality is that significant levels of negotiation are required, based on a contract document, to avoid creep in either costs or requirements.

Preferred Supplier

In preferred supplier relationships, it is recognized that some suppliers better fit the company's requirements than others. Suppliers are selected based on some form of pre-qualification, perhaps including some elements of 'unit pricing' for the services provided. Typically, a limited number of suppliers will be identified for a specified range of services.

This benefits both parties by reducing the cost of each transaction. The contracting company also benefits through shortened lead-times.

In this type of relationship, the costs of services for a single project are less tightly controlled. However, costs are well defined and predictable.

Partnering

Partnering relationships develop where it is recognized that the supplier has specific competencies that complement the contracting company's. Clearly, before any supplier competence can be described as 'complementary,' one must first understand one's own (required) competencies.

The partner supplier is likely to be closely involved in the specification of work required and in the planning of projects. The cost of service is secondary although it must be related to the value of the input. A partner supplier would typically be expected to share in the risks of the development in some way.

Alliances

This is appropriate where core competencies are mutually understood within a meaningful strategic framework.

Alliances tend to occur where the 'supplier' has key skills

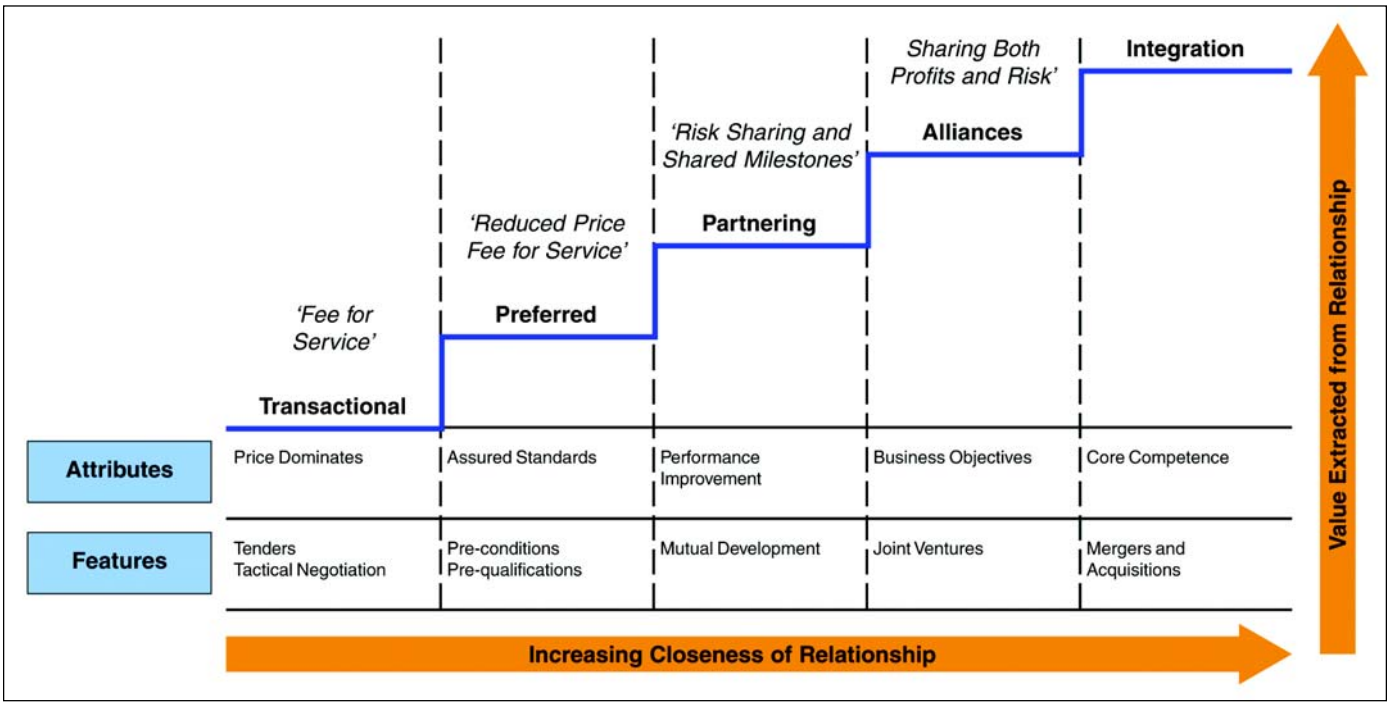

Figure 3. Development of customer – supplier relationships.

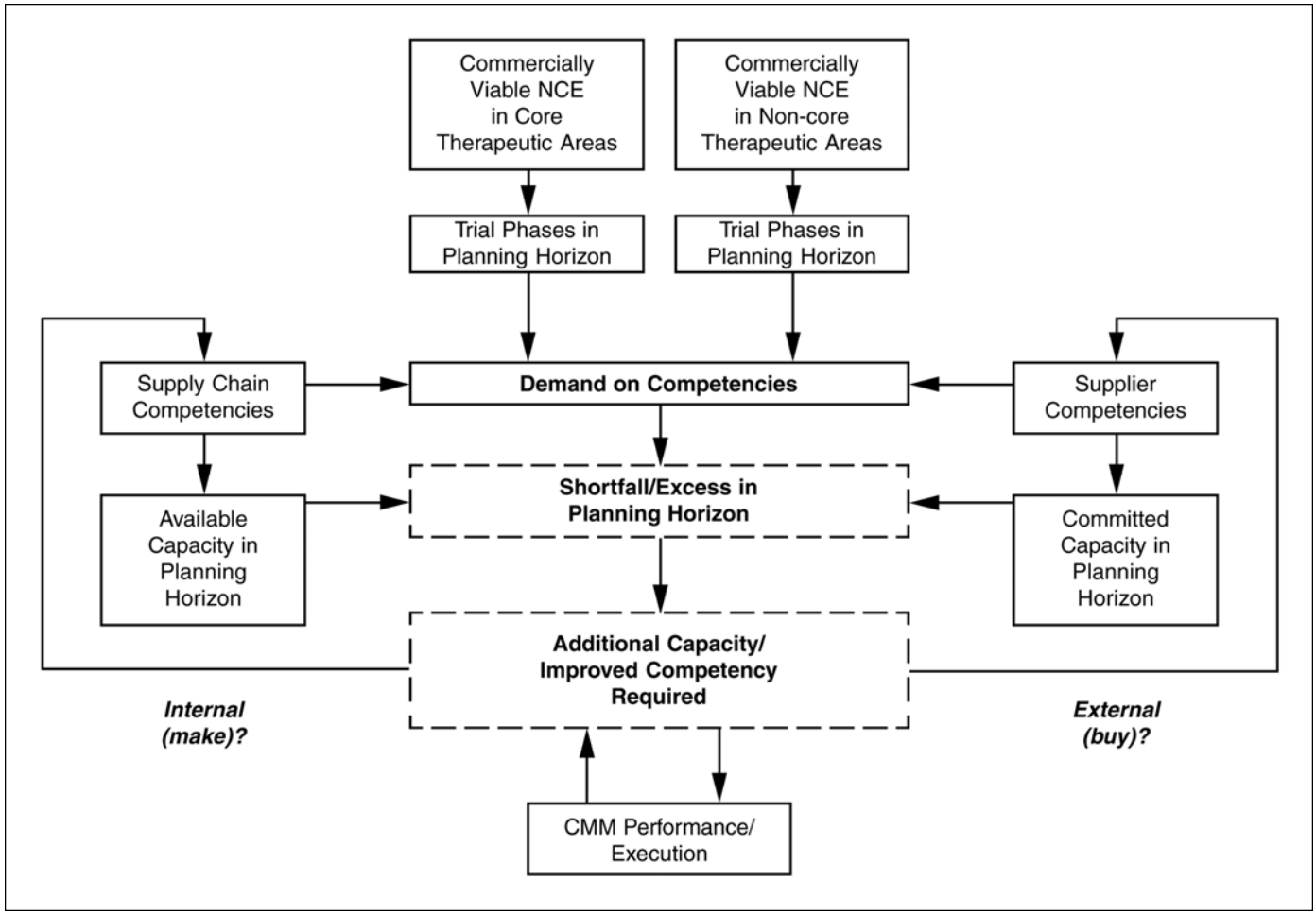

Figure 4. Influence map strategic choices in Clinical Materials Management.

that are required by the OEM. The supplier will be solely responsible for certain deliverables within the project.

It is not unusual for the companies involved in an Alliance relationship to be nominal competitors.

In Alliance relationships, the costs are a joint responsibility and liability. Any profits from the venture are split between the OEM and supplier according to pre-agreed arrangements.

Integration

This is the extreme of close customer-supplier relationships. The closeness of the relationship, and the mutual dependence of each party, means that it is appropriate that the supplier becomes part of the same organization as the customer. Logic determines mutual benefit from combining core competencies in a single business entity for compelling strategic reasons.

This development hierarchy is shown as a series of steps. In reality, it is more of a continuum and there can be significant friction between the customer and supplier when there is a mismatch of perceptions about where the relationship stands.

The most important consideration is to recognize that as the relationship gets closer, and the value invested in the relationship gets greater, so the core competencies that are required by both parties changes.

At the transactional level, the core focus for both organizations is to manage the contract. Procurement and sales departments are the main points of contact. In a partnering relationship, the focus has moved away from the contract to consider what performance improvements can be achieved by operational changes. Line management functions become the main point of contact.

Planning CMM Strategic Value

How then can companies make appropriate *strategic* and *tactical* decisions about the configuration of their CMM processes? The goal is to have a clearly defined framework that eliminates the arbitrary nature of outsourcing decisions. The objective is to ensure that the core competencies required internally are fully developed, and that qualified outsource capabilities are available when required.

Among the key dimensions that must be considered by this framework are:

- The market opportunity represented by an NCE. What annual sales value is projected for the end drug?
- The fit of the NCE to core therapeutic areas for the company. What level of risk does the development represent?
- the Phase of Clinical Trial being considered

These first three elements set the requirements necessary of CMM. The business also must consider the competencies and capabilities that are to be deployed to meet these requirements:

- Core CMM competencies. Where does the company add most value – managing the programs, designing studies, coordinating supplies, policing quality, producing pharmaceuticals etc?
- Available capabilities. Essentially, a combination of supplier management and internal performance management. In both cases, appropriate capabilities for different Clinical Trial situations must be available to the company.

The choices open can be illustrated on an influence map in Figure 4. The following statements describe how the influence-map (or framework) might be deployed:

'NCEs within the core therapeutic areas will have all active clinical materials produced and managed in-house for all Phase I, II, and III clinical work.

CMM operations for NCE opportunities in non-core therapeutic areas that become available to the company for development/exploitation will be outsourced from Phase III to our partner CRO supplier.

Our internal CMM competencies are:

- *supplier quality assurance*
- *program management*
- *study design*
- *bulk product production*

The following activities will always be outsourced to our Partner suppliers:

- *placebo and comparator production and material management*
- *end use packaging*
- *logistics*

The requirement for capacity in CMM will be assessed annually and any external capacity required will be placed with partner CROs.'

Establishing such a strategic framework places some practical demands on CMM organizations. They must:

- understand their core competences as determined strategically
- understand their effective operating capacities
- operate a Capacity Planning regime that is flexible enough to accommodate a variety of scenarios
- deploy appropriate Planning and Scheduling tools to manage processes tactically for optimum performance

Summary

This article describes the complex environment within which CMM processes operate. Outsourcing is a valid mechanism for reducing that complexity. However, any business intending to outsource such processes must understand where value in its CMM is derived. If outsourcing is used solely to drive down the cost of individual clinical trials, or to 'plug' short-term arbitrary capacity holes, competitive performance will, over time, be eroded.

Important areas of value that are embedded in the supply chain include:

- management of product and process knowledge
- increase responsiveness of the organization to clinical trials
- 'portfolio' management of new entity opportunities
- fundamental competitive strategy of the business

Organizations cannot now leave the configuration of CMM as an arbitrary decision taken on a project-by-project basis. There must be clear alignment to business strategies, and a focus on developing competencies and capabilities in the resultant 'execution' processes.

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This article describes a methodology and supporting tools focused on quantifying the cost-savings benefits of new system implementation.

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Estimating ROI for Automated Clinical Materials Management Systems

by Lee Anderson and Devar Burbage

Introduction

This article describes a methodology and supporting tools focused on quantifying the cost-savings benefits of new system implementation. The system of interest is an automated clinical trial supplies manufacturing management system. The methodology is designed to analyze a company's current operations for production of clinical supplies, identify those areas where an automated system will have an impact, and quantify the expected payback in each area from implementing the new system. Project leadership will use the quantitative output of this analysis to help justify the project with expected tangible results. Those tangible results will be expressed both in dollar value of the planned identifiable improvements and as process improvements to be implemented according to the project plan. Finally at project conclusion, project management will be able to compare actual vs. planned process improvements as well as actual vs. planned dollar returns.

Since the amount of paperwork to do this in detail is voluminous, presented below are the details for one functional area only and an overview of the results for all areas. For those interested readers, the complete set of spreadsheets is available from the authors.

The results of the analysis are very positive in the sense that a large organization in a regulated environment can benefit greatly from implementation of an automated materials management system. This is an environment with many relatively small batches that need to be checked just as thoroughly as large batches.

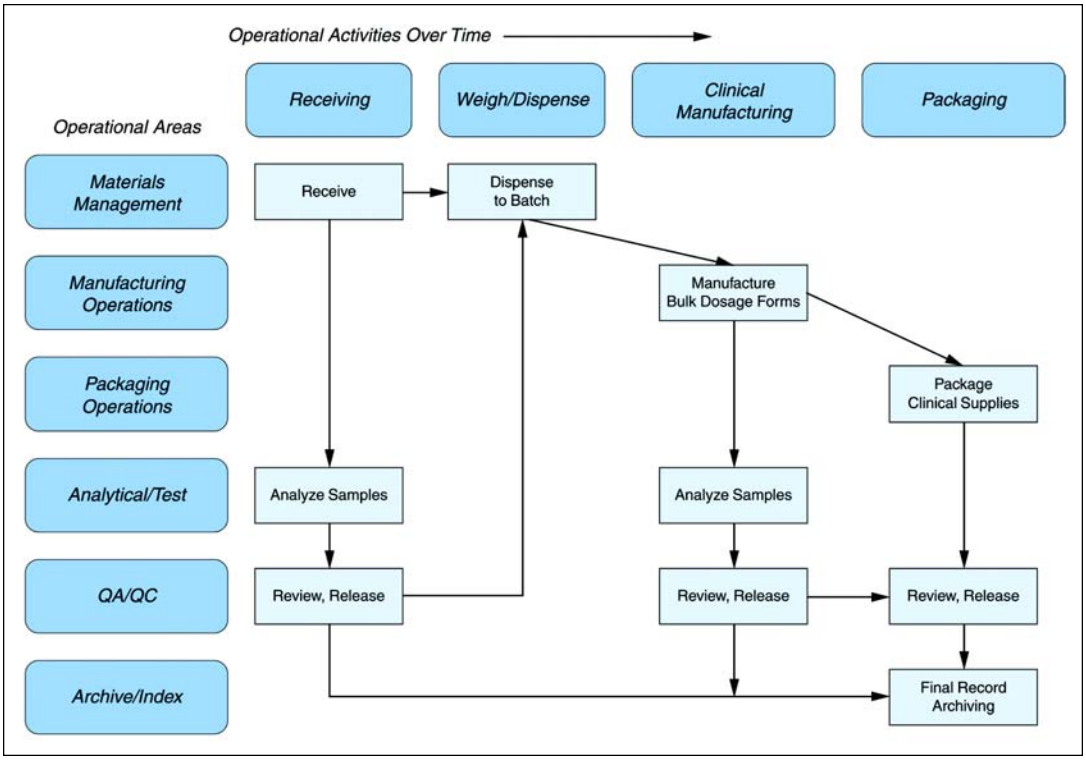

Figure 1. Process flow diagram for pharmaceutical research and development.

	Questions for Receiving Dept. #_____	
	Areas of Savings	Avg. Cost per Batch Record
1.	Central handling, duplication, storage, archival for this Dept.	$ 25
		Avg. Hrs/
2.	Time for QA to review completed Receiving Record for Release	2.0
		Avg. hrs to correct RR now
3.	Direct Processing Time to correct Simple errors	2.0
4.	Direct Processing Time to correct Serious errors	8.0
	Other Areas of Savings	Factor
		Avg. Ann. Value
5.		$ -
6.		0

Table A. Per unit questionnaire for receiving.

Although there may be small savings per batch, the large number of batches is the multiplier to ensure substantial savings for this part of the project. As can be seen from the example, we estimate cumulative net cash flow over the five-year period of this hypothetical project with an initial capital investment of $1.4 million to be $4.8 million. The estimates are very sensitive to assumptions about percent of work saved. Using figures reported from some new systems implementation projects; the estimated cumulative net cash flow could be as high as $24.6 million.

Methodology Overview

There are three main parts to the methodology:

1. analyze each operational area to determine the activities to be included in the new system
2. develop and apply a spreadsheet-based questionnaire to measure individual improvements in each area
3. aggregate the results in a spreadsheet to capture the value of improvements and a final expression of the net benefits of the project

The estimate of the net payback of the project will include the present value of benefits vs. expected costs over the appropriate time horizon and production load assumptions made by the project team.

We take a broad approach to clinical supply materials production and include drug synthesis as one of the operations. Then we consider the supply chain from drug synthesis to clinical shipping as the scope of our new system. For our purposes, the Drug Development Supply Chain consists of the operational areas: Chemical Process Development, Clinical Manufacturing, Packaging and Labeling, and finally, Clinical Supplies Shipping.

Assumptions

Estimates of an absolute amount of cost savings are determined by:

1. calculating current costs based on the volume of work units and effort or cost per unit, then
2. calculating expected future costs as those current costs times a work reduction factor which is an estimate

The value of the estimated reductions such as review time, archiving time, etc. that we include here is based on our experience with successful projects. Note: the basic value-added steps of physically receiving materials or manufacturing product cannot be directly impacted by an automated recordkeep-ing system.

ROI figures are likewise dependent on many estimates about future values of interest rates, inflation, and company specific figures such as real growth rates, and cost of capital. These will vary for each individual project and company.

Analyze Operational Areas

The implementor of a new system needs to do a detailed functional analysis of the activities in each operational area. The result of this is the guide to expected improvements in the area of interest. For purposes of analysis, we begin by dividing the activities of each area into discrete functional categories. Depending on organizational structures, these may need to be added to or revised to achieve the right level of detail. Assume we decide to deal with the Pharmaceutical R&D area as a unit. A sample process flow diagram of that area is shown in Figure 1. In brief, the major areas of functionality are:

- receiving
- weigh/dispense
- clinical manufacturing
- packaging

Develop Departmental Questionnaire

Per Unit Cost Savings Estimates - Receiving

We focus on a detailed analysis of receiving. For each activity, we prepare a questionnaire to perform a detailed analysis of the per-unit work to be done. An example of such a questionnaire is shown in Table A, Questionnaire for Receiving, with sample values. The areas in which a new automated system can have an impact are those areas where excess overhead is associated with processing records that would be electronically stored, or areas where errors persist in the current system. As examples, based on unit of work, consider the time or cost to:

- Archive, Process, and Duplicate Records for a Receipt - this activity is an artifact that arises because receiving records in a manual system are not self-duplicating, and are not archivable in an easy manner, etc. The work is not valued in itself, but is essential to orderly and compliant recordkeeping for a regulated activity.
- Time for QA to Review Completed Receiving Record for Release - the QA group has the responsibility to review all relevant records before releasing or approving a batch of material. This time will be reduced if the receiving records are available electronically in report form, and can be

reviewed for exceptions in a straightforward manner.
- Direct Processing Time to Correct Simple Errors - errors in receiving can occur for many reasons, mis-registered information, wrong material classification, missing documents, etc. Some errors can be classified as "simple" in that they can be easily repaired with some minor searching or review.
- Direct Processing Time to Correct Serious Errors - receiving errors that require detailed analysis to fix occur less often, but have an increased individual cost to fix.

Space is left in Table A for other areas where savings may be found – characterized as problem areas in current operations. An example is where personnel are assigned to take samples for analytical testing after receipt. If the sampler can't find the material and no receiving personnel are available to locate it, considerable time can be lost searching for the material.

Annualizing Factors for Activities - Receiving

Corresponding to the per unit costs described above, in order to state the values in an annualized manner, there must be estimates of the work load of the receiving department for the entire year. Consider a more or less common set of factors that needs to be applied to each area in Table B. The items to be measured are:

- Average Value of Raw Materials in the Receiving Department - needed to arrive at inventory carrying cost, the average value is an accounting number usually available from plant cost accounting.
- Number of Receiving Records in the Department prepared/Handled per Year - this is based on the number of lots received and the number of documents per lot, we assume 600 lots per year.
- Number of Receiving Record Errors per Year Detected - Simple
- Number of Receiving Record Errors per Year Detected - Serious
- Carrying Cost Percent for Inventory - the other part of the equation to determine inventory carrying cost, an imputed interest rate, times the average value of Raw Materials above.
- Cost per Receiving Record for Central Records Handling/ Archival - this is an estimate of overhead costs to properly process records in the existing system.

Lastly, to determine costs associated with time spent correcting record and processing paperwork, estimate average loaded personnel costs:

- Supervisor Correcting Receiving Records
- Analyst Reviewing/Correcting Receiving Records for Release
- Analyst Transcribing Data from Manual Receiving Records

Determine Departmental Expense Reductions

Record Handling, Storage, Archiving - Receiving

Moving from paper records to electronic records, we make the assumption that we can reduce expenses for record handling, storage, and archiving by 75%. This is mainly attributable to the fact that electronic records are by their nature easier to manipulate, store, and archive. Given the inputs above, we calculate the expected dollar savings for Record Handling to be 600 records × cost per record of $25 × reduction factor of .75 which turns out to be $11,250 per year.

Reduced Time to Assure Compliance (QA Release) - Receiving

We make a similar assumption that we receive 600 lots and we can reduce QA time to review a receiving record by 75%. The basis for this is that the receiving records and their logs can be examined on screen and they are presented in a uniform format, accompanied by any associated paper records. Then, if we assume the average loaded hourly wage is $37.00 per hour, the reduction in QA review time in the new environment would be 2 hours per record × 600 records × .75 × $37.00 = $33,300.

Replacing a system where much of the data is collected and stored on paper affords many opportunities for savings. A key capability of an electronic system is that many of the common data values can be predefined and when needed, the values can be chosen from a list. Particularly, in receiving, where physical lots of material from diverse suppliers and manufacturers are processed, any automation of data entry helps reduce errors. We estimate that 90% of the data entry errors can be eliminated by a system where many common values are predefined and only selection from a list can be done at processing (e.g., receiving) time. Referring to Tables A and B, we see of the 600 receiving records, 100 are estimated to contain simple errors to be fixed and 25 are expected to have serious errors that need to be fixed. Each fix requires time. We estimate the cost of a supervisor correcting the problems to be $40.00 per hour. Then the cost savings associated with better data entry and reduced errors can be calculated as the

Common Dept. Factors Needed for the Analysis:			
1	Name of Department		
2	Type of Dept (Receiving, Weigh/dispense, Mfg, Pack, and Other depts.	R	
3	Average Value of RM in Receiving Dept.	$	500,000
4	# Receiving Records in Dept. prepared/handled per year (lots)	$	600
5	# Receiving Record Errors/year detected - Simple (# errors)		100
6	# Receiving Record Errors/year detected - Serious (# errors)		25
7	Carrying Cost percent for inventory (percent)		20
8	Cost per receiving record for Central Records handling/archival	$	25
9	Average Loaded Hourly Personnel Cost:		
10	Supervisor correcting Receiving Records	$	40
11	Analyst reviewing/correcting Receiving Records for Release	$	37
12	Analyst transcribing data from manual Receiving Records	$	36

Table B. Annualizing questionnaire for receiving.

			Annual Savings			
	From Individual Workbooks	One Time Savings	Labor	Mat'l	Var OH	Other Dir Cost
1a.	Receiving Department 1*	$ 200,000	$ 11,925		$ 10,000	$ 2,813
2a.	Weigh/Dispense Department 1	$ -	$ 291,581	$ 16,250	$ -	$ 10,281
3a.	Manufacturing Department 1	$ 299,962	$ 187,780	$ 387,500	$ 23,058	$ 34,844
4a.	Packaging Department 1	$ 591,771	$ 637,300	$ 15,750	$ 52,023	$ 42,188
	Totals		**Labor**	**Mat'l**	**Var OH**	**Other Dir Cost**
	Annual Savings		$ 1,128,586	$ 419,500	$ 85,080	$ 90,125
	One Time Savings	$ 1,091,733				
	* = reduced expected labor savings			Annual Savings	Grand Total	$ 1,723,291

Table C. Aggregate savings across all departments.

cost savings associated with the simple errors ($7200 = 2 hours per fix × .90 savings × 100 records × $40 per hour) plus the cost savings associated with complex errors ($7200 calculated in a similar manner).

Reduced Inventory/Material Savings (Variable Overhead) - Receiving

The other main cost area in receiving is the value of inventory. We postulate that we can reduce the amount of inventory carried by taking advantage of the improved recordkeeping capabilities of the new system to:

- improve material throughput
- reduce loss of material due to obsolescence
- avoid retesting and time needed to expedite items

Then we expect we can reduce the average inventory over a year's time by 40%. In this case, where we expect the average inventory to be $500,000, that means a one-time savings of $200,000, followed by an annual cost savings of $40,000 (20% of that $200,000).

Departmental Financial Benefits - Aggregate the Above Benefits

If we add the savings from each source above, we get total annual savings for the receiving department calculated to be $98,950 and the one-time savings from a reduction in inventory is $200,000.

Overview of Aggregate Expense Reductions

Given assumptions similar in nature to the ones made for Receiving, we have calculated estimated savings for the other model areas in our business. Table C shows a summary of those savings.

- ***Weigh/Dispense -*** Of particular note are the labor savings of the Weigh/Dispense Area, estimated to be $291,581. The Weigh/Dispense area is assumed to carry a work load of 1500 dispense orders per year. The savings are obtained mainly by assuming 20% reductions in manual report preparation and duplicate data entry, and a 25% reduction of direct labor spent only on verification. A more aggressive assumption of 75% reduction in manual report preparation and 100% elimination of time spent on verification would yield savings of $1.2 million.

- ***Manufacturing -*** There is a large savings in materials in the Manufacturing Department, which we assume to be making 1500 batches of product a year. The savings are mainly attributable to reductions in throwaway due to Process Error and Incorrect or lost batch record paperwork, along with savings by reducing waste due to a too high overage allowance on weighing.

- ***Packaging -*** The Packaging Department is estimated to be saving $637,300 per year in labor. The workload is assumed to be 7800 packaging orders per year. A large part of the labor savings is based on the same assumption as in receiving that there is a 20% reduction in the time for QA review. Other savings come from 20% reduction in time spent locating material, elimination of time spent waiting for material delivery, etc., and lastly, a 25% reduction in packaging order preparation time estimated at 2 hours per order reduced to 90 minutes. As above, if we are more optimistic about the reductions in effort with the new system, we can project savings of up to $2.5 million.

Multi-Year ROI - Overview of Analysis

In Tables D and E, we present the final analysis sheets. In Table D, we present Capital Investment and Expense Reduction. The capital investment figures are straightforward. Expenses and Expense Reductions are based on a 10% real annual growth rate and a 3% inflation rate. Note that displaced costs of maintenance on existing systems also count as a saving. Taking a conservative approach to the savings to be expected over the 5-year period, and adding across, the total capital investment is $1.4 million and the Expense Reduction is $10.6 million.

Table E takes account of the extra expenses incurred due to the new system – software support, platform maintenance, etc. Net income is based on the project income and expense figures (pretax income) less taxes at an assumed 40% tax rate. Finally, we see cash flows from project operations goes from -$127,500 in year 0, when there is no savings to be had, to $1.5 million in year 5.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
I. CAPITAL INVESTMENT							
System Costs							
SOFTWARE	**-500,000**	0	0	0	0	0	-500,000
SERVICES	**-800,000**	0	0	0	0	0	-800,000
PLATFORM: HARDWARE/SOFTWARE	**-150,000**	0	0	0	0	0	-150,000
REDUCED WORKING CAPITAL	0	0	0	0	0	0	0
TOTAL	-1,450,000	0	0	0	0	0	-1,450,000
2. EXPENSE REDUCTION							
Assumed CAGR	**10%**						
From Dept. Spreadsheets							
Labor	0	1,128,586	1,241,445	1,365,589	1,502,148	1,652,363	6,890,130
Materials	0	419,500	461,450	507,595	558,355	614,190	2,561,089
Variable Overhead	0	85,080	93,588	102,947	113,241	124,566	519,422
Other Direct Costs	0	90,125	99,138	109,051	119,956	131,952	550,222
Displaced Costs of Current System Maint	0	**10,000**	11,000	12,100	13,310	14,641	61,051
TOTAL	0	1,733,291	1,906,620	2,097,282	2,307,010	2,537,711	10,581,915

Table D. Return on investment - 5 year view - capital investment and expense reduction.

Summary

To summarize the steps to follow, model a series of manufacturing activities to develop a solid estimate of the expected ROI for the implementation of an automated clinical supplies management system. First, determine the scope of the project – in this case, the drug development supply chain. Then, break down the supply chain to operational units that can be examined separately or are organizationally separate. Perform a detailed functional analysis of the activities and groups engaged in each functional area. On the basis of the detailed analysis, develop focused spreadsheet questionnaires, gathering information on per unit costs and effort; and on total number of units and effort. This is the basis for the estimate of current costs.

With the spreadsheets and assumptions about reduction of effort using the new system, and the work redefinition that accompanies that, one can estimate the new levels of costs and effort. The difference between the new and old figures is the amount of gross savings per year. Then one can project the gross savings per year along with estimated project costs, estimated tax rates, inflation rates, etc. to arrive at the final determination of ROI.

The actual ROI figures are one part of the total information requirements needed to decide if a project should be pursued. In a regulated environment, assessments must be made as to the validation effort required to put the system in place and the ability to maintain demonstrable control over the functioning system once it is in place. A proper analysis for purpose of determining ROI can yield information that is applicable for many other purposes.

The assumptions about reductions in materials, reduced effort for QA review, and reduced errors while performing activities are key to what to expect from installation of a new system. Expectations for returns on a project, assuming no major changes in workload, are based on these assumptions. Since they are so critical to the decision making process, a

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
3.INCREASED EXPENSES							
Assumed Rate of Inflation	**3**						
POMS SW SUPPORT	-85,000	-87,550	-90,177	-92,882	-95,668	-98,538	-549,815
PLATFORM MAINTENANCE	-22,500	-23,175	-23,870	-24,586	-25,324	-26,084	-145,539
SYSTEM SUPPORT PERSONNEL	**-80,000**	**-25,000**	-25,750	-26,523	-27,318	-28,138	-212,728
INCREMENTAL CLIENT SERVICES	**-25,000**	**-25,000**	-25,750	-26,523	-27,318	-28,138	-157,728
TOTAL	-212,500	-160,725	-165,547	-170,513	-175,629	-180,897	1,065,811
DEPRECIATION EXPENSE	0	-290,000	-464,000	-278,400	-167,040	167,040	1,366,480
PRETAX INCOME	-212,500	1,282,566	1,277,073	1,648,369	1,964,342	2,189,774	8,149,624
COMBINED FED/STATE TAX RATE	**40%**						
INCOME TAXES	85,000	-513,026	-510,829	-659,348	-785,737	-875,910	-3,259,850
NET INCOME	**127,500**	**769,540**	**766,244**	**989,021**	**1,178,605**	**1,313,864**	4,889,774
DEPRECIATION ADD-BACK	0	290,000	464,000	278,400	167,040	167,040	1,366,480
CASH FLOWS FROM OPERATIONS	-127,500	1,059,540	1,230,244	1,267,421	1,345,645	1,480,904	6,256,254
CAPITAL INVESTMENT	-1,450,000	0	0	0	0	0	-1,450,000
NET CASH FLOWS	**-1,577,500**	**1,059,540**	**1,230,244**	**1,267,421**	**1,345,645**	**1,480,904**	**4,806,254**

Table E. Return on Investment - 5 year view - expenses, depreciation, taxes, and net income.

useful exercise is to identify each assumption, and carry the assumptions as entries in an "independent variables" spreadsheet where changes can be made easily, then by increasing or decreasing one or all of the assumptions, a sensitivity analysis can be made. If, when a key assumption is changed by 10%, the corresponding results change by 20% or some large amount, the assumption needs to be examined in detail to get the necessary level of assurance that it is correct. When offering an in-depth analysis of expected ROI, a range of expected values - high savings, expected savings, or low savings should be made.

Further Extensions

The discussion above focused on the analysis associated with cost savings, almost entirely from labor or materials. The model can be extended to consider changing workloads, scaling as appropriate. Other advantages from implementation of a new system are harder to quantify. If the QA group ascertains that the new system provides more visible compliance or reduced effort to determine that batches can be released or not, a real value exists, but may be hard to quantify in dollar terms. If the new system is part of an overall Business Process Re-engineering effort the total expected returns might be hard to separate from the expected returns from the system itself. The analysis that precedes implementation of a new system should consider all expected advantages and disadvantages, quantify wherever possible, and report any other items that should be considered.

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This article provides a current overview of the European Commission's (EC) Good Manufacturing Practices (GMPs) "Annex 13." Annex 13 is used for the manufacture of investigational medicinal products. This overview will include a brief history of the Annex, the relationship the Annex has with the Clinical Trials Directive, and a comparison of the 2003 version with the current (2002) version.

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Annex 13: An Update

by David Barnes

Background History

In the past, the European Union (EU) member states have had no legal requirements regarding the manufacture or packaging of medicinal supplies for clinical studies using GMP guidelines. The majority of companies have strived to achieve GMP guidelines in the clinical manufacturing and packaging areas. Many of the GMP guidelines used were from the commercial sectors of the company or were taken from the United States Code of Federal Regulations (CFR).

By the late 1980s, the EC drafted two directives using GMP guidelines for the manufacture, packaging, and storage of medicinal products. The first directive addressed medicines for human use (91/356/EEC). The second directive addressed veterinary products (91/412/EEC). While these directives covered commercial products, they also contained a clause that allowed countries in the EU member states to require that *"clinical study materials"* also be prepared according to GMP. This can be considered the origin of Annex 13.

The adherence to the GMP guidelines for clinical trials materials will become mandatory with the implementation of the Clinical Trials Directive (2001/20/EC). To facilitate organizations with guidance in preparing supplies for clinical studies, in accordance with the GMPs, an extra Annex to the document (entitled "The Rules Governing Medicinal Products in the European Union - Volume 4" or commonly called the "Orange Guide") was written. Annex 13, specifically addresses the differences in practices when making investigational products, as compared with commercial manufacture and packaging. It provides a guide against which facilities preparing clinical materials can be audited. GMPs not covered in Annex 13 can be found in other sections of the "Orange Guide."

Annex 13 was revised and published on 25 July 2003. It is available for review at the following Web site: http://pharmacos.eudra.org. The content of this article references the 2002 and 2003 versions of Annex 13. Each version contains 13 sections. However, the format for the two publications is different. The formatting in this document is organized to follow a typical workflow pattern.

Introduction

The "Introduction" section of the 2002 version provides the historical background to Annex 13 (similar to the "Background History" section provided above). In the 2003 version, this section is referred to as "Principle." The "Principle" section no longer provides historical details; however, it clarifies the status of products other than the test product used in a clinical trial, e.g., a diagnostic agent. These details should be an appropriate quality for the purposes of the trial. The reader is advised to obtain the advice of a Qualified Person (QP) to assist in the process. A new addition to the 2003 version is a useful glossary of terms.

Quality Management

Because investigational products are rarely validated to the standards required for marketed products (except as required for sterilization cycles) and these products have specifications and manufacturing processes that frequently change, Annex 13 requires both an effective and well-documented Quality Assurance system. The primary difference in the 2002 edition versus the 2003 edition is the notation that the packaging and labeling processes for clinical trial supplies are different when compared to those for commercial products. This invokes the EC Guideline on Good Clinical Practices (GCPs) requirement for self-inspection and independent audit. This notation is absent from the 2003 edition.

Personnel

The 2002 edition of Annex 13 does not specify

the need for the involvement of QPs in the release of investigational products. What it does state is that the people who are responsible for Quality Control/Release of investigational products should be trained in the appropriate GMPs and independent of the persons who manufactured the product. However, this omission was addressed in the 2003 edition. It clearly states in a comprehensive list the duties and responsibilities for the QP(s). The QP is responsible for ensuring that there are systems in place that meet Annex 13 requirements. Additionally, there must be a thorough understanding of clinical trial processes and drug development. The QP is responsible and legally obligated for the quality of the released products.

Premises and Equipment

Both versions of Annex 13 recognize the difficulties associated with validating aseptic processes for small batch sizes and suggest that environmental monitoring be enhanced in these cases to provide the necessary assurance. The 2003 version of Annex 13 suggests that the media fill runs of a batch size larger than the clinical trial materials batch be carried out "to provide greater confidence." However, no guidance is provided in determining the acceptable results for these media fill runs.

When working with sensitizing products such as 'penicillin' or 'toxic/highly potent' drugs, the current edition of Annex 13 removes the need for dedicated facilities. It does emphasize the need to thoroughly decontaminate the equipment and facilities used. There is no mention of this subject in the 2003 revision.

Documentation

Annex 13 reflects an understanding that the technical specifications for investigational products will be modified during the course of the product's development. Annex 13 requires that all changes made be recorded. Specific references to previous versions of the product specifications along with the rationale for the change must be recorded in the documentation.

Clear written instructions for manufacture and supply must be produced. Additionally, written records of the operations performed must be kept. The 2002 edition requires that these records must be kept at least two years after the end of the clinical trial. Unlike commercial manufacture, there is no requirement for master formulae and processing instructions. A written procedure that incorporates the modifications to the product as well as the authorization of the product must be established. The 2002 edition requires that particular attention be given to product stability and bioequivalence.

The sponsor of a study should provide an official written order or may transmit an electronic order to the manufacturer. It should be precise, and in the 2002 version, it is required to refer to the order as the 'Product Specification' file. The 2003 version acknowledges that the order may additionally need to be referenced to the 'Clinical Trial Protocol' if necessary. Both versions of Annex 13 require that investigational products have a 'Product Specification' file similar to that for commercial products. This should include formulation, processing, packaging, testing, storage, and shipping information. As suggested above, this document will need to be updated as changes occur and these changes need to reference previous versions. While the 2002 version provides little guidance in this matter, the 2003 revision provides a list of required documents and information. It also provides that where a number of sites are involved in the operation, each site can maintain a file pertaining to that site's operations.

Annex 13 recognizes that the packaging and labeling of investigational products is generally more complex than for commercial products especially when "blinded" labels are used. Therefore, it requires that processes such as label reconciliation and line clearance be appropriately enhanced and performed by an independent Quality Control staff.

Annex 13 provides allowances for batches of investigational products that may be packaged as a number of sub-lots over a period of time. The number of units to be packed each time must be specified beforehand allowing for quality control and reserve samples. Detailed reconciliation of the packaging and labeling processes must take place.

Labeling Instructions

Annex 13 provides detailed labeling requirements for both the outer and primary packaging of investigational products. It allows for the use of symbols and pictograms on the outer packaging. Copies of the labels should be retained in the packaging records.

There has been much discussion about the need to provide a 'period of use.' The 2002 version of Annex 13 addresses the need for 'in-use extensions' to 'expiry dates of investigational products' by requiring that expiry extensions should be on additional labels. These labels may be affixed over the original expiry labeling. The extra labels *must* include the material's batch number and when affixed to the container *must not* obscure the original label's batch number. Although not stated, this means that if multiple expiry updates are made, the labels should be designed to obscure previous expiry dates and leave all examples of the batch number clearly visible.

The 2002 version states that the clinical trial monitor or site pharmacist must apply these labels according to written SOPs. A second person must verify the application of the labels. This must be documented in the trial documentation and batch record. The 2003 version introduces the need to do this at the manufacturing site and provides some flexibility to be performed at other sites as required.

The 2003 revision has not addressed many of industry's concerns over labeling requirements. The original list of requirements remains, but the revision offers an opportunity for the contents of the labels to be reduced by stating (prior to the list of requirements) "The following information should be included on labels, unless the absence can be justified, e.g., use of a centralized electronic randomization system." Finally, the 2003 revision provides a useful summary of labeling details required for various sized containers.

Production

Annex 13 requires that the starting material qualities need to be defined and periodically reevaluated. The specifications for the active materials should be as comprehensive as possible. This information on material quality should be maintained to allow for variations in production.

Annex 13 recognizes that validating manufacturing processes to the standards required for marketed products is not appropriate for clinical trials supplies, and, because of this, quality control testing takes on more importance. Annex 13 requires that provisional parameters and in-process controls will be put in place, possibly based on experience with analogues. These processing procedures, parameters, and controls should be adapted in light of experience. There is a specific mention of reconciliation in Annex 13 with the requirement that it is carried out and that any abnormal results be investigated.

In recognizing the potential of a product's toxicity, Annex 13 specifically states that the cleaning procedures employed to decontaminate facilities and equipment should be stringent. Where biological materials are used, impurities must be removed with the same stringency as for marketed products.

Comparator Agents

Annex 13 requires that the quality and integrity of comparator agents should not be compromised. If significant changes are made to comparator agents, data must be available to demonstrate that these changes have no significant effect. The 2002 version states that the expiry date on the original pack of comparator is based upon the original packaging and that it may not be appropriate when repackaged. Therefore, the sponsor company has to provide data to support expiry date in any new packaging and specify that it cannot be later than the date of the original pack. If no data is available, the new expiry must be less than 25% of the period from repackaging to original expiry date, or six months, whichever is less. The 25% requirement is not listed in the 2003 version. The statement now reads as "there should be compatibility of expiry dating and clinical trial duration." The 2003 revision is less specific and more ambiguous.

A specific requirement in Annex 13 states that all aspects of the generation and subsequent handling of randomization codes must be in a procedure and that there needs to be a procedure to identify blinded products. This procedure and the randomization code must allow complete traceability of products to the original batch number of the product before blinding.

Quality Control

In the absence of full process validation, end product testing is very important. The testing should assess those characteristics affecting the product's medicinal efficacy, e.g., dose and uniformity, release of active ingredient, and estimation of stability. Where appropriate, these tests should cover the characteristics of blinded products.

Batch Release

The text in the 2002 version recognizes two processes: the release of bulk product and the final packaged product. It requires that bulk product testing demonstrate compliance with the specifications listed in the 'Product Specification' file. Finished (i.e., packaged) product testing should be compliant with the specifications and include a review of packaging documentation.

The 2003 version significantly expands this section, and in particular, provides detailed guidance on the duties of a QP in this matter. One interesting aspect of this is that a QP releasing materials from a non-EU country (referred to as a third country) will need to determine that standards of GMP equivalent to those in Annex 13 have been applied. One way of achieving this is participating in an audit of that manufacturer's quality systems. One consequence of this is that the QP of a EU-based Contract Research Organization (CRO) packaging materials for a customer manufactured at a third country site may audit that site to ensure that the quality systems are appropriate. So, not only will the customer audit the CRO, but quite probably, the CRO will have to audit the customer.

Free Movement

Annex 13 clearly states that once appropriate testing and release has occurred within the EU, there is no justification for any further testing as long as the correct control procedures have been followed and documented.

Contract Manufacture and Analysis

The 2002 edition of Annex 13 specifically references contract manufacture and analysis requiring the contracting parties put a contract in place clearly stating that the products are for 'clinical trial use only.' There is no reference to this in the 2003 revision.

Complaints

Annex 13 requires that all parties discuss conclusions of investigations from any complaints. This helps to assess the impact upon the clinical trial and product development. The 2003 version specifically requires the involvement of the QP in this process.

Recalls and Returns

Both versions of Annex 13 require procedures to obtain and document the retrieval of materials. The investigator must fully understand and monitor these procedures. The 2003 revision adds another requirement for the sponsor to ensure that the supplier of a comparator agent has a system for advising the sponsor in the event that there is a need to recall any products.

Shipping, Returns, and Destruction

Annex 13 requires that a shipping order be produced in order to ship materials. The shipment can only be made when quality control releases the product and then is approved by the Regulatory department. Release from both groups should

be recorded and retained. The materials must be packaged to ensure that the product is protected during transport and storage, and that opening or tampering of the package is easily identified. An inventory of the shipment should be made and retained including the addressee information. A final requirement is the acknowledgement of a receipt in good condition. The 2003 revision adds a need for decoding arrangements to be available prior to the materials being shipped to the investigator site.

Shipments from one trial site to another should be avoided. If such transfers must be made, a detailed procedure of the process is required. Annex 13 specifically states that it is preferred that a product is returned to the sponsor for relabeling and possible retesting before being sent to the second site. Materials that are returned to the sponsor for whatever reason should be returned in a specified manner, be clearly identified, stored in a dedicated area, and accounted for in inventory.

Annex 13 clearly states that the sponsor is responsible for the destruction of all materials. Destruction of the materials should be recorded and carried out only after completion of the trial and compilation of the final report. Where a party other than the sponsor carries out destruction, that party must provide documentation detailing the identity of the materials destroyed and the quantities. The 2003 revision requires that the records of destruction be held by the sponsor. This is not a typical GMP practice because the site carrying out the activity holds the original documents.

Conclusion

Annex 13 attempts to deal with clinical supply specific issues that the "commercial" GMPs either do not address or do so in an inappropriate manner. Obviously, there are statements in Annex 13 that many will disagree with, but it should be remembered that these are guidelines, not rules, and that as experience of auditing clinical supply facilities is gained, they will undoubtedly change.

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This article identifies and discusses some of the regulatory and control system concerns for the utilization of electronic systems between sponsor and contractor companies for the preparation, control, and distribution of clinical trial materials, and provides some ideas for the proactive development of the relationship between sponsor and vendor that can minimize any adverse impact and maximize the strengths and value of the relationship.

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External Sourcing of Clinical Trial Materials

Part 2: Impact of Electronic Automation on the Sourcing Model for Clinical Supplies Preparation

by Charles F. Carney

Introduction

The business practices models for sourcing of clinical trial supplies preparation have traditionally relied on personal interactions to link the manual information and control systems of the sponsor and vendor. Even when electronic systems existed in both sites, these have traditionally been utilized only within that site, relying on manual interactions between sponsor and vendor for the transfer and review of information, data, and records, all in paper medium. In the future, we will see a change in paradigm toward a reliance on electronic interface, preparation, storage, retrieval, and review of information, data, and records. This change is required by the call for increasing efficiency and decreasing timelines for drug development. Some points that will be considered in this article are:

- the quality system points in the cGMP of the US and EU that need to be taken into account, including specific points in 21 CFR Part 11 and Annex 11 respectively
- achieving harmonization of concept and practice, between the sponsor and vendor, for interpretation of the regulatory requirements for qualification, validation, control, and interchange of information between separated electronic systems
- comparison of concerns when the electronic automation system is the same in the sponsor and vendor sites and when the electronic automation systems are different
- optimizing the interactions between the sponsor and vendor for the development, approval, execution, archiving, and retrieval of electronic automation records and data to ensure accountability, responsibility, and consistency

The Use of Electronic Systems

When the computer age arrived for pharmaceutical products, many thought that electronic automation could surely improve efficiency, effectiveness, and throughput within an organization, but could not be utilized between organizations. This resulted from the fear that differences in the computer concepts within each organization could potentially hinder or invalidate the interactions. Most felt that validation of the interface would only be possible if both organizations were utilizing the same computer system, configured in the very same way. Anticipating a very low probability for the existence of the exact same computer system and configuration in both organizations, most thought that the costs for validation of the linked computer systems would far outweigh the cost advantages of sourcing the work. Therefore, most have utilized manual systems for tracking and exchanging information and data when sourcing investigational materials from a contract manufacturer. However, in order to best leverage a sourcing relationship, one must take advantage of each efficiency and effectiveness factor in both organizations. Therefore, one must look for the ways to connect and utilize the electronic systems in the two organizations, to perform the evaluation of compliance, and to define the points of interaction between the two systems in such a way that all of these features can be accepted and utilized for the benefit of both the sponsor and the vendor.

Information for the preparation of clinical

materials includes: data in any of the manufacturing records, information for the receipt, holding, and distribution of products and associated reserve samples, information for the testing for release and stability evaluations of products, materials specifications, label specifications and text, information for any comparator products or ancillary medicaments or diagnostic goods for the trial, and all evaluations and reports for Out of Specification (OOS) results, deviations, and other quality investigations. One also could consider the Good Clinical Practices (GCP) information necessary for the execution of the trial at each of the sites, for example: case report forms, inventory and dispensing records, informed consent forms, protocol deviation reports, field complaints, etc. However, this article will consider the Good Manufacturing Practices (GMPs) issues and leave the consideration of the GCP issues as an exercise for the reader.

The optimal characteristics for such a combination and utilization of the two electronic systems for the manufacturing, packaging, labeling, and distribution of clinical supplies must contain elements of quality control, quality assurance, and validation that are understood for each of the systems working alone. Thus, the two companies can focus on ensuring that the interface between the two systems does not interfere with the existing capabilities and compliance of each system acting independently.

Quality and Management Systems

Most people recognize the important elements of cGMP compliance. Therefore, this discussion will only emphasize some of the points to consider for the utilization of electronic automation systems by sponsors and vendors in a working relationship. The requirements for computer systems continue to evolve, and therefore, this presentation is intended to be more conceptual than definitive. The recent withdrawal by the FDA of guidance documents for application of 21 CFR Part 11 is evidence that this regulatory agency is refining the meaning of compliance for electronic systems.

All regulatory systems recognize the increased consistency when properly qualified and validated electronic automation is utilized. However, these systems also recognize the value of human observation and recognition followed by intervention for something that is "not quite right." Therefore all compliance systems which will utilize electronic automation also should ensure that no loss in product quality, through loss of human oversight, may occur by the utilization of such systems.

An important aspect of all business and compliance systems which should never be overlooked or ignored is the role and responsibility of management personnel.[1-3] Just as the manufacturing management personnel within an organization must understand and rely on their counterparts in the computer support, analytical, and purchasing departments, so should these personnel know and understand the working of their manufacturing counterparts and those in the supporting departments in the vendor company as well. This requirement is implied in the US regulations and stated more explicitly in the EC regulations.[4] This combined management comprehension and joint execution of oversight brings added strength to the sourcing relationship.

The key aspects of electronic automation can be stated here with elaboration only as needed to support the ideas of this presentation. These electronic systems include, but are not limited to, computer aided systems for inventory management, manufacturing processes, analytical release and stability data management and reporting, label generation including randomizations and text, and excursion reporting and archiving. These systems support the quality management decisions made for each product produced. Because the electronic aspects are so important, and because there should be no confusion about these aspects, they are given special treatment within the regulations in the US[5] and in the EU.[6] The former is more detailed and has had associated with it, until recently, several separate guidance documents for interpretation. However, both need to be considered to have a complete compliance program suitable for allowing actions in the world.

The following special points need to be considered in order to assure that the link between the companies has taken them all into account for full compliance:

- detailed written description of systems and the links between them for the two companies, security, how they interact, who has authorization to perform what tasks in each system, quality system(s) oversight, and interactions for any changes
- assurance that data entry has been checked and that the data are consistent between the two companies (in their databases and in the archives)
- When first initiating use of electronic automation a check should be made, by running in parallel, that the electronic automation system and the manual system provide the same degrees of control and reliability of the information.
- Agreement should be reached concerning who can input, amend, or alter data and agreement on the process and communication of changes in authorization level with respect to data.
- The change control system needs to take into account the approval by the two quality assurance systems and the re-education of all concerning the changes. This includes any exercises for re-qualification, re-validation, and any changes in organizational structure.
- Security of stored data should be agreed and accessibility, durability, and accuracy of the stored or archived data should be evaluated periodically. The files backup plan should be agreed between the two entities. Additional points specified in the European regulations include:[7]
  - Detailed procedures should be in place and available for review.
  - Only authorized personnel should manipulate the electronic records and associated data and all transactions need to be clearly tracked by an electronic audit trail.
  - Back-up copies of records, on durable medium (magnetic tape, microfilm, paper or other) should be produced and archived.

- All data and controlled information should be readily available throughout the retention period.

A disaster recovery for failures and break-downs and alternate systems usage in times when the primary system becomes not usable must be agreed prior to initiation of the interaction.

A written agreement (contract) must always be in force during the relationship to avoid misunderstandings which could result in products of less than acceptable quality and all details need to be included specifically. Some of the critical points listed in the European regulations are:[8]

- The contract must state clearly the responsibilities and duties of each party.
- The contract must identify the pathway followed by the Qualified Person (QP) for releasing a batch.
- Any special technical arrangements should be specified.
- Information exchange should be complete and sufficient to ensure that the vendor is able to perform the requested work successfully and compliantly.
- All materials must comply with their specifications and be released for use by the QP.
- Use of subcontractors for work must be pre-approved by the sponsor.
- Materials purchase, product testing including sampling and in-process control testing, and release responsibilities must be specified clearly and accepted by both parties.
- Audits by sponsor and/or competent authorities must be clearly understood and accepted by the vendor.
- Annex 13 of the EC Guide also specifies that the contract must clearly state when product will be utilized in clinical trials both for manufacturing and for testing operations.[9]

Agreement for the QP must be in place and assignments of authority and responsibilities must be clearly written according to the requirements of the European regulations.[10] Some of the critical points are:

- How the QP of the sponsor takes over the decisions of the vendor and which decisions the QP of the sponsor makes based on work performed by the sponsor must be clearly defined and written.
- The QP, whether in the sponsor or the vendor firm, must be sufficiently knowledgeable of the specific nature of the investigational drug and its control to be able to perform the full functions required of the QP.
- An obligatory notification procedure must be specified for reporting of any aberrant data by the vendor to the sponsor.
- Any computer system used must meet the requirements of Annex 11.
- The identification and withdrawal of any product lot found, after release, to be hazardous because of a quality defect, must be assured and must occur without delay.

The quality system points in the US cGMPs, whether codified[11] or exemplified by inference[12] as a "customary practice," and codified in the GMP of the European Union,[13] and exemplified by inference in the rest of that document and its annexes need to be taken into account. These include specific assignments of personnel to the control duties specified for the quality control unit in the US and the production and analytical control personnel assignments of the EU. The additional points for clinical supplies stated in Annex 13 for quality assurance and quality control must be considered in any quality system for the preparation of clinical trial materials. This is particularly true for blinding, labeling, validation, distribution, returns, and destruction procedures and controls.

Harmonization of Concepts - Sponsor/Vendor

Very deliberate efforts and negotiations are required to achieve harmonization of concept and practice between the sponsor and vendor for interpretation of the regulatory requirements. This applies to manual systems as well as to electronic automation systems. Qualification, validation, control, and interchange of information occur between personnel as well as between separated electronic systems.

First and foremost both the sponsor and the vendor need to have a concept for gaining the understanding of the systems in the other site. This is relatively easier for the sponsor because the sponsor will usually visit a vendor site for technical and quality evaluations as part of the due diligence activities prior to proposing a contract relationship. The vendor seldom has the opportunity to visit the sponsor site and evaluate existing systems to the same degree. However, without having a proactive approach to gaining the information about the other participant in such an interaction, there will be no basis in the future to discuss any development or change in the relationship or change in the interactions of the two electronic systems, and no basis on which to find the appropriate resolutions for issues in either arena.

With a formal process available, both sponsor and vendor will be able to ask the appropriate questions and to state the situation within their organization and the expectations they have for any work done within the relationship.

Four concept areas, qualification, validation, control, and interchange, are critical for manual and electronic automation systems and these will be addressed:

Qualification

In a manual system, the personnel are qualified according to their education, training, experience, and their resultant ability to work within a standard operating system. The work must be correct with respect to scientific and technological as well as regulatory requirements. The qualification of manual systems can be performed by the review of training records, review for consistency and completeness of the SOP system, and review for completeness in documentation of changes or of investigation and resolution of deviations or failures.

Electronic systems can be used for technical (facilities and

equipment) control and for record and associated data generation and control. Qualification of these systems includes review of the technical capabilities and connectivity of the hardware, suitability of the software to perform the entry, manipulations, and storage of information (whether numeric or text), and review of the audit trail functionality. In addition, one must take the human interactions with the system into account. These interactions will be additional to the ones utilized in any manual system and must be specifically qualified for the electronic system. This evaluation can follow the same approach as stated for a manual system, but must be designed specifically for the electronic system being reviewed.

Validation

In a manual system, validation occurs in a two step process. First, the assessment for competence of the personnel who will act within the system and the completeness of their training is performed and then the conceptual evaluation for logical consistency and completeness of the linking procedural system is performed. These are some of the accountable tasks within the purview of the management for the quality system. Careful review and judgment of these personnel in the beginning, and continual review and assessment must be done in order to satisfy this validation requirement. For a manual system, this is documented by the signature of the responsible individual on specific documents (e.g., SOP approval, training records, etc.).

Validation of the electronic system must be performed according to written protocols for the performance of the hardware, performance of the software, and review that the data and associated audit trails are complete. Such protocols must be pre-approved for completeness prior to execution and then the executed results and conclusions also must be reviewed and approved. These exercises add to the evaluation and validation of the operations of the personnel and their capabilities to perform tasks associated with the electronic system.

Control

In a manual system, control is usually dependent on the clarity of the written Standard Operating Procedures (SOPs), the completeness of this procedural system, and on the integrity of the qualified personnel who are performing the tasks. This is documented by a signature. For critical steps, the control is further verified by a second signature, which verifies that the task was performed correctly and approved by the second signature.

In electronic systems, this control is managed by the electronic algorithm which requires steps to occur in a certain sequence, and prevents further progress of the process without the appropriate input of the required signatures. This limitation on access to the system by personnel is one of the most important control features from a management perspective. This control is documented in the audit trail within the system. This is the reason that great emphasis must be placed on establishing and maintaining the appropriate audit trail in every electronic system.

Interchange

In a manual system, exchange of information can be verbal or written, and can occur through telephone, fax, or computer e-mail. However, the only relevant information is that which is contained in the accepted format in the formal paper documentation system of the company with final approval signatures.

Electronic exchange must occur over very secure electronic systems only, and in systems which have the internal capability to monitor all exchanges, capability to allow input only by approved individuals according to allowed access procedures and identification algorithms, and to record all transactions in the audit trail. As mentioned above, these exchange-of-information interactions must occur according to certain rules, whereby the personnel who may enter or approve data are known and documented by their system name and access codes within the system. All entries, archives, and changes are challenged for correctness and assured for completeness by the system.

Automation Systems - Similarities and Differences

There are advantages when the sponsor and vendor both are using the same electronic automation system. In this case, each party already has an understanding of the structure, working algorithms, capabilities, and limitations of the system. And therefore the evaluation of qualification, validation, control, and interchange can occur much more readily. On the other hand, an electronic system can be configured and customized for utilization within any organization, and therefore, each party will need to understand the specific configuration and any customizations that have been done by the other party when performing the full evaluation.

When the sponsor and vendor each have a different computer system, additional time and effort will be needed to comprehend the system structure, working algorithms, capabilities, and limitations. In this case, the documentation associated with the installation and validation of any system will be very helpful. One of the best plans for dealing with audits by regulatory authorities is to have a descriptive book of information on each electronic system, similar to the Site Validation Master Plan for facilities and operations, that has a clear presentation of what the system is, how it works, who oversees its use, how the organization functions interact through it and links to all of the pertinent qualification, validation, and change information. This same book of information can be a very strong basis for the other party in a sponsor/vendor relationship to have an understanding of its electronic system.

Optimal Interactions - Sponsor/Vendor

Optimizing the interactions between the sponsor and vendor depends on the personnel and the systems that have been developed in each site to support an interaction. These systems should include the development, approval, execu-

tion, archiving, and retrieval of electronic information and data to ensure accountability, responsibility, and consistency. These systems will be linked to, but separate from, the existing GMP systems for manual records. Careful consideration must be given to establishing the connections for linking the in-house systems with the external systems. Some best practices include:

- clear understanding by each party of the capabilities of its system, desired information that needs to be exchanged, and the connection points for each category of information and data
- well written quality agreement, mutually accepted secrecy agreement to protect intellectual property, and contract
- clearly defined data and information structure in order to avoid ambiguity and to ensure easy incorporation into data bases and final reports
- strong interactions between the two quality units to ensure constant monitoring of systems and processes for data integrity and security in each site
- constant checking to ensure that the process of electronic information exchange is still the most efficient and effective possible
- periodic evaluation for update in hardware and software including periodic revalidations
- Agreement stating who will analyze the data, with which algorithms, who will review and approve, who will incorporate into reports, and how, and for how long the data will be archived
- establish well trained, knowledgeable, and experienced point persons in each organization

Summary

All companies will rely on outsourced support of clinical trial supplies preparation at some time. And the most effective interactions will occur when the best electronic systems practices are employed by each party. Such interactions will rely on clear identification of all interaction points and clearly defined procedures and control for all tasks. Some points to consider and current best practices have been presented here for each of these aspects.

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About the Author

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This article describes an objective process and points to consider in formulating the plan and decision to outsource any of the clinical trial supplies production, distribution, and reconciliation steps.

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External Sourcing of Clinical Trial Materials

Part 1: Process and Points to Consider

by Charles F. Carney

Introduction

The pharmaceutical industry continues to look for ways to optimize performance. Many companies in this industry have begun to re-evaluate what tasks they will consider core competence for performance internally and what tasks are not core competence and should be performed externally. Some have even proposed that pharmaceutical companies would perform best if they only performed research tasks and marketing tasks, and outsourced all of the developmental tasks.

One of the developmental tasks that is often considered for external sourcing is the preparation of clinical trial supplies. Today, many companies source some or all of the manufacturing, packaging, labeling, holding, distribution, and ultimate reconciliation and destruction of some clinical trial supplies through the utilization of contract firms. When queried about this, many reasons are given for the utilization of contracted capacities, including lack of labor or machine capacity, lack of the appropriate technology, or lack of expertise in the particular requirements for completing the task. For many, the decision to outsource seems to be made subjectively, using past practice and experiences as the guides with each case being independently considered. Others may be looking for an objective process. Therefore, it seems appropriate at this time to attempt to codify the logical bases for external sourcing of clinical supplies preparations. This will provide an objective process and decision map for those who may not yet have developed a systematic decision making process for these outsourcing decisions.

Organization and Decision Making

Every organization needs to develop the strategic statements relative to outsourcing the preparation of clinical trial materials. This is necessary to ensure that the best leverage is gained from any external interactions. It also ensures that all internal functions are agreed with respect to dealing with the relationship with another company. If outsourcing does not fit into the corporate strategic plan, the clinical trials supplies group should not even consider this possibility when planning for the execution of their work assignments. On the other hand, if outsourcing does fit into the corporate strategic plan, everyone in the organization should know this and be ready and willing to support the decision. This support will include the development of the interaction relationship and modification of any systems necessary to get the appropriate quality and quantity of work performed using external capacity. These functions will include all of the relevant functions in R&D (for example, pharmaceutics, analytical, quality assurance, project management) as well as the support functions in the corporation (for example, legal, purchasing, shipping and receiving).

The procedural system will need to be expanded to include those procedures necessary for the qualification and controlling of contract vendors. And this will necessitate additional training modules as well. The organization will need to determine who will make the decision, ultimately, for the outsourcing of work. Will the clinical trial group manager make this decision or will it be made by a team, by a team leader, an assigned outsourcing point-person, purchasing, or someone in the medical research group? The decision should usually be taken as a consensus view of the stakeholders, which is predicated to making the delivery to the clinical trial at the time needed by the customer.

The stakeholders in this case include all of the R&D functions (pharmaceutics, analytical, quality assurance) and the personnel in the medical department who will manage the execution and performance of the trial.

Outsourcing of work always puts an extra layer of burden on the sponsor. This burden affects each function at different times and in different ways. Providing the formulation and process for manufacturing of product at a contract site will have different demands and constraints than providing analytical test methods to the vendor or performing testing on samples coming from the vendor. Similarly, the burden on the quality assurance group will increase in their need to review systems and personnel performance both at the home site and at the vendor site. The shipping and receiving personnel also will have some constraints and demands on them for interacting with another group in another company. All of the interactions pathways, point persons for the interactions, and ways of interacting need to be developed and implemented prior to engaging in the first outsource project.

Traditionally, cost has not been an issue for clinical supplies operations, and therefore, the outsourcing of work was driven by the need to meet the time-line rather than the cost of the work. This may be changing today as pharmaceutical companies become more and more cost conscious in all areas of the business, including R&D operations. In addition, the trend today toward increased work load without increasing head count needs to be considered. Internal capacity is required to establish, oversee, and evaluate a relationship for using external capacity. This fact must not be overlooked in the development, implementation, and execution of an outsourcing program.

Multinational corporations will need to consider the impact on their outsourcing strategy when they have more than one clinical supplies group, each one in a different country, and even when the corporation is big enough to have more than one clinical supplies group in the same country. Such companies may want to have harmonized systems for outsourcing by all of the units in order to take best advantage of a relationship with vendors and to be able to negotiate the best prices with the vendors. The majority of clinical trials today are executed in multiple regulatory regions and multiple countries within each region. Also, each of the clinical supplies preparation vendors is able to work in all of these regions. Therefore, it may be beneficial to develop the working relationship on a corporate, rather than working unit, basis with each vendor. Harmonization of the work practices within the corporation for the various clinical supplies groups will pay dividends when the time comes to outsource a major clinical trial being performed in each of the regulatory regions in the world. The best utilization of internal capacity and the most appropriate utilization of external capacity can be assured using this approach.

This approach will work best when the interaction of the various personnel in the medical research disciplines in the corporation, in the various countries, also are harmonized. Consistency in the ways that requests are made, information is exchanged, and in the management of all changes between the medical and clinical supplies personnel will allow optimal performance of the execution work by the clinical supplies personnel.

The medical customer will always want supplies "on-demand." In addition, changes will always be needed in the preparation of supplies for each trial today. Protocols are complicated and guarantees for completion of all necessary regulatory hurdles, prior to the initiation date, are not possible. These changes-in-thinking of medical groups places great demands on the logistic flexibility and "magic-working" of CTM groups, including the work of their contract partners.

Currently, the costs for contracting of CTM preparations are reported to be greater in the EU than in the US. These costs include both the relative higher costs charged by the contract firms as well as the interaction costs for moving the materials between sponsor and vendor, because often the vendors are not in the same country as the sponsor. The UK and Ireland have the largest population of full support vendors which means that the mainland countries must export drugs to them for work. The interactions costs include importation and exportation fees, and less tangible costs for interactions in a "foreign language."

Special Points for Sponsor to Consider for any Project

With the strategy established, the personnel responsible for outsourcing need to consider how best to leverage the utilization of external capacity. This planning should include a long term view of the needs for outsourcing for specific trials or for whole programs.

For each trial, planning must account for a one time supply for the whole trial or whether initial supplies and follow-up supplies are needed for the successful execution of the trial. If the trial is a long term trial, then the capacity needs can be best supplied by an external partner, unless the sponsor is equipped with the necessary space and labor capacity to handle both new programs and ongoing programs. It seems, from casual conversations, that few sponsors are adequately staffed today or have adequate space to handle all of the short and long term programs in their portfolio. This is particularly true with respect to the increasing need for fast and flexible execution of the early phase program required today for proof of principle or final choice of compound to take to full development toward commercialization.

For the case that the sponsor is planning for multiple trials in a project, or perhaps for all of the trials in that project, the sponsor needs to consider whether there are any special handling needs, for example, refrigeration for proteins, extra space for individually packaged inhalation products, or ship on demand scenarios in the protocol to name a few. It is usually best to execute all of the packaging and labeling efforts in one site because of the efforts needed to establish and maintain the special conditions. In these cases, when outsourcing is necessary, a good decision is to plan for the outsourcing of all trials for that program. This may allow the best price negotiation and the most cost effective system development to accommodate the special needs for the mate-

rials for the trials.

New or special designs for trial protocols provide an opportunity to learn, but also may prove to be taxing to the clinical supplies group that is already working at full capacity. For example, when a new randomization model is needed, it is necessary to ensure that adequate validation of that new algorithm has been performed if this algorithm will be developed and implemented by the vendor. The development and execution of this validation should be a special consideration in the request for proposal sent by the sponsor to the vendor. This also will require that the sponsor perform a special re-evaluation of the vendor to ensure that it can be done adequately, both from the technology perspective and from the personnel expertise perspective. Therefore, part of the strategic thinking within the sponsor group should be an evaluation whether all randomizations will be supplied by the sponsor or whether the sponsor will rely on the vendor to perform these, and to manufacture, package, and label accordingly.

In some cases, special packaging configurations are needed to ensure subject compliance with the drug administration requirements of the protocol. Subject and investigator compliance with a protocol can oftentimes be enhanced by the manner in which the goods are packaged and labeled. Such special considerations as colored labels, patient box size, configuration of goods within a patient box, sizes of primary containers, and numbers of dosage units per container can oftentimes make a significant difference for ensuring compliance and for assisting in the reconciliations and accountabilities of drugs at the sites. On the other hand, it's very easy to overestimate the gain for compliance or accountability by such customizations. The personnel who are responsible for making the clinical supplies configuration decisions in the sponsor site need to have an objective view to support and defend such requests from the customer especially when outsourcing the work. The vendor also should be ready to assist in finding creative compliance-enhancing packaging and labeling which is also efficient and effective in the utilization of labor and materials.

Planning for the use of outsourced capacity should anticipate the need for changes at a later date. Both the sponsor and the vendor should anticipate that something may change during execution of the preparation or during execution of the trial. A mechanism for communication and for addressing the request for change and the change control should be established and maintained between the sponsor and vendor.

Similarly, planning for special distribution considerations such as stratified distribution according to some algorithm for differences in sex, race, or geographical location of the center should occur. The need for the special distribution needs to be understood by the clinical supplies group and communicated to the vendor. If any special computer programming is necessary, all of the qualification and validation requirements for computers need to be considered and implemented.

In some cases, an Interactive Voice Response System (IVRS) will be needed in order to manage a complicated distribution or the control and distribution of limited drug supplies. These systems are expensive to define and to establish, to train the personnel at the sites, to provide the correct linkage between the supply labels and the controlling system, and to ensure that the correct information is collected and managed according to the requirements specified in the protocol. Such systems are not to be used with every trial because of the costs involved, but can improve the collection and collation of information from complex trials. The second use of these systems can be for the conservation of drug products which are in short supply or to limit the amounts of materials distributed for controlled drugs.

If the use is for controlled drugs, the sponsor needs to ensure that the vendor has the appropriate physical plant and licenses. State and federal DEA licenses are required for the specific scheduled compounds and products that will be handled. In addition, specific physical access and monitoring controls need to be in place, as well as very detailed SOPs and personnel training, specifying the manner and methods for managing, recording, and destroying the drugs. The specific regulatory requirements of each country in which the controlled drugs will be studied must be considered for importation, distribution, accountability, and reconciliation. Chain of custody documentation and training of personnel in both the sponsor and vendor sites are important aspects for the successful management of scheduled drug products

The importation and exportation requirements for the trial and the abilities of the vendor to supply support of a bonded broker and good understanding of requirements and limitations need to be ensured continually because the rules and requirements change routinely.

Establishing and Maintaining Relationships with Vendors

The sponsor/vendor relationship is the cornerstone of each outsourcing success. A fully elaborated concept for the relationship and the efforts to develop this relationship proactively are necessary to ensure successful outsourcing of work. Both sponsor and vendor must have a similar quality position and a similar vision of success in order for the interactions to deliver results. The key points for establishing and maintaining the relationship include formal qualification of the vendor by the sponsor, development and implementation of the interaction procedures and responsibility assignments, utilization of a formal, detailed requesting and proposal development/acceptance routine, and a communication system that is objective and covers all interactions.

The comfort level and continuing allocation of work to a vendor depends on the initial impressions about capabilities of the vendor and the ongoing experience with the vendor. These are best evaluated by a formal process for identifying possible vendors and qualifying each for technical, quality, and business performance attributes. The initial impression of technical competence by the clinical supplies group and of quality compliance by the QA group will be lasting impressions that will influence all future interactions. A formal approach should be utilized for these evaluations. This ap-

proach will start with the development of an inspection check-list to ensure that all points are evaluated. This is important whether the evaluation is for technical, quality, or business competence.

Important aspects for the preparation of clinical supplies will include the depth and breadth of technical competence in the vendor organization which can ensure a rapid understanding of the job to be done and recommendations for the best contemporary scientifically and technologically sound ways to do it. Similarly, the quality organization must be up-to-date on all national and international regulatory requirements and expectations. It also must have the depth and breadth of contemporary quality assurance concepts to be thoroughly in-control while always looking for the flexibility to handle the ever changing landscape of clinical supplies preparations.

These evaluations should explore the most recent experiences, including both positive and negative experiences. Some negative aspects that require scrutiny include any increase in error frequency, complaints from the field for goods produced by the vendor, poor understanding of the science or technology that they have available in their shop, lack of ability to interpret protocol correctly, lack of ability to provide innovative and cost effective manufacturing, packaging, and/or labeling concepts for the protocol, and inability to express their corporate philosophy or expectations for the interactions.

The sponsor/vendor relationship needs to be maintained at the highest level of satisfaction by constant communication, honesty, openness, and teamwork. The importance of strength in technical and regulatory understanding on an international basis cannot be overemphasized for the success of this relationship.

For clinical supplies, quality and time to delivery usually take precedence over cost. However, cost has become a far greater factor for most sponsors today and every sponsor should look for some preferred pricing schedule from a vendor and also for any reasons for giving work preferentially to that vendor even when the price is higher than that offered by others. In some cases, there exist intangible points which make one relationship work better than another. These intangibles include personality compatibility, demonstration of dedication to the desires of that sponsor, responsiveness, and inventiveness. In most cases, these attributes cannot be measured in cash terms, but become the decisive factors in the successes achieved through the interactions.

The Quality structure of the vendor, particularly if that vendor has been associated with any kind of regulatory action or denial by the FDA or any other agency, is extremely critical. The sponsor should look for those vendors who constantly reinforce the understanding that they perform only value added work according to the most contemporary interpretation and application of the cGMP on a worldwide basis.

A procedural basis for the interactions should be established between the sponsor and vendor. This will mean that the SOP system of the sponsor will need to be expanded to include those activities with the external organizations. How the sponsor and vendor interact is critical, especially when protocols change or negative issues arise. The best approach is for the sponsor and vendor to develop and agree on the interaction model that will be employed. Otherwise, miscommunication and misunderstanding may impact the delivery of very important trial supplies.

Technical/Regulatory understanding by the vendor is crucial, and the sponsor should seek out the vendor with the best understanding and who turns this understanding into practice. The technical understanding must include formulation design, manufacturing techniques and process flow, packaging materials science, closure integrity factors, equipment function and its impact on the manufacturing, packaging or labeling, of product, and computer design, qualification, and validation to name a few. Regulatory understanding must include the cGMP requirements of the regulatory regions in which the clinical trials will be performed. At a minimum, the vendor must have full competence in the requirements of the US and EU for drug products and biological drug products, and devices, safety standards and requirements particularly for potent or potent/hazardous products, regulations for transportation, importation/exportation requirements and restrictions, and intellectual property regulations including patent and trade dress issues.

The connection between the quality systems of sponsor and vendor must be clear and include a thorough understanding of roles and responsibilities. This should take into account the requirements for decision making according to role of the Quality Control Unit of 21 CFR[1] and also of the quality management system, the Qualified Person, and the special application of the GMP for clinical supplies in the European Union.[2]

The quality management of all materials, whether for quality control testing or for quality assurance evaluation, review and approval, must be clearly specified for the sponsor/vendor relationship. Responsibilities for the quality control sampling and testing for starting materials, whether actives or excipients, in-process materials, packaged and labeled supplies, packaging materials, environmental validation samples, and purified water, to name a few, must be clearly defined. It should be clear which testing will be done by the sponsor and which will be done by the vendor. Understandings and agreements concerning the standards and acceptance criteria for this testing must be established between the sponsor and vendor. Subcontracting of analytical work, or any other work, by the vendor must be understood and agreed by the sponsor. And the review, approval, and disposition process and assigned responsibilities also must be clearly specified. All of this should be summarized in a written form and approved by both organizations.

A formal process should be developed for requesting work by the sponsor and the estimates of performing the work by the vendor. The sponsor's Request For Proposal (RFP) should include a detailed summary of all that will be needed, who will supply materials, the requested timing for completion, a copy of the trial protocol for reference, and any other specific

information necessary for the completion of the work. It should include all the necessary information in an objective and clear layout. Similarly, the vendor's proposal should address all points and should provide the confirmation of acceptance of responsibilities and agreement for providing the desired deliverables and for meeting the desired time lines. Costs for the work should be clearly and explicitly detailed in order for the sponsor to have a thorough understanding of the work that the vendor will provide and to ensure that the sponsor will receive the work that is needed.

Finally, and perhaps most importantly, a communication system must be established. This will work best if point personnel are assigned in the sponsor and vendor organization to ensure the most efficient and effective transmission of knowledge, desires, expectations, data, and decisions within each organization. This system also must include a process for resolution of conflict between the two organizations. While the desire in both companies will be for "no conflict" processes, nevertheless, on occasion, errors, delays, changes, and mishaps may interfere with any smooth process which has been envisioned. Objective and speedy resolution of these interruptions in the process must occur in order to maintain the cost effectiveness of the interactions.

An assumption that underlies all of these statements is that a contract between the sponsor and vendor will be negotiated and executed prior to any work being performed. Discussion of the development and establishment of terms of a contract would require a separate article altogether, and therefore, will not be further elaborated here. For the purpose of this discussion, realize that a contract is required and the elements of such a contract are clearly delineated in the European regulations[3] and understood through the concept of current best practices in the US regulations.

Decision Pathway

Once the sponsor/vendor relationship has been established, the sponsor which utilizes both in-house capacity and external capacity will need a logical, decision making pathway. Such a decision tree will ensure that objective decision making occurs for each case of outsourced work. One such decision tree could be imagined and is laid out below. Others could be imagined or this one could be modified to meet the exact requirements and organization of any vendor. It is presented here as a framework within which specific details can be added by any sponsor.

A. Primary considerations for a decision: available labor, technology, space for staging/storage, special distribution requirements, IVR requirements, uniqueness of the protocol, special temperature or relative humidity handling, other?
   1. If labor, technology, or space are not available at the time required for delivery of supplies, outsource.
      a. If temporary contracted labor is available and technology and space are not concerns, perform in-house.
   2. If experience with preparation for the special distribution requirements exists, perform in-house, otherwise seek external help.
   3. If IVR is required, exists in-house and available, utilize, otherwise outsource.
      a. For outsource, ensure that the IVR and clinical supplies preparation vendors are compatible and work together well.
      b. For in-house or outsource operations, education may be needed for the Medical customer and all interactions with internal groups (Medical, Formulation, Purchasing, Analytical, Traffic, Regulatory Affairs) must be established and tested.
      c. Develop validation plan for the IVR system and complete execution prior to the start of the trial.
   4. If special randomization, stratification, or other out of the ordinary packaging or labeling are needed by the protocol, and these can be accommodated in-house, then do so, otherwise seek external help.
      a. Ensure all US[4] and EU[5] computer qualification and validation requirements are taken into account.
   5. If temperature or relative humidity, or special configuration shipping is needed (for example, cold shipments, or containers must be in upright position), ensure that shipping conditions and materials required have been confirmed by the shipping test.
   6. Evaluate for any special import requirements (for example, USDA import permit for animal derived or biological materials, IND in place for API or drug products, patent or trade dress issues for comparator drugs); and for export constraints (for example, performance of the clinical protocol only in Listed countries or also in non-Listed countries, SGA prequalification for shipments to Philippines, import license availabilities in the countries to which the products will be sent including special "third country audit" requirements for Germany, special documentation and permits for scheduled drugs, and CTA in those countries which require it).[6]
   7. The Traffic group must maintain an awareness of special handling needs and the organization should ensure that bonded import brokers exist in all countries with sufficient capital to pay duties and expertise to manage the importation efficiently.

B. After the decision to outsource has been made: ensure that the final quality of the deliverables has been specified, determine the time needed to prepare supplies, determine the desired time of delivery, estimate the costs if the work were to be performed in-house, estimate the degree of flexibility for changes that may exist in the project, and choose to submit the request for proposal to the vendor with the greatest likelihood to meet the expectations for the project. If a competitive bidding process is required in the organization, the request will need to be submitted to the minimum number of appropriate vendors, as required by the organization.
   1. Include the requirements and clear definition for what work is requested of the vendor in the Request For

Proposal (RFP), including all of the relevant information gathered in A.

2. Determine whether the vendor will be chosen by competitive bid (cost) or by previous experience with a particular vendor in whom confidence exists because of proven record (quality) or by the evaluation for shortest period for delivery of goods (time).
   a. Traditionally, the decision has been determined by which vendor will provide the best Quality and shortest Time to Delivery over lowest Cost in making the sourcing decision. Recently, there has been a much stronger push toward competitive bidding between vendors to get the best price. While cost is critical, it is important that purchasing groups understand that the cost of preparing clinical trial supplies is a very small part of the overall costs of that trial, or the program for which that trial is being performed. It may prove beneficial to spend some time educating the purchasing agents that clinical trial materials are not commodities, and that many other intangible aspects need to be considered in the decision. These include, but are not limited to:
      i. technical understanding by the vendor for the protocol needs and their own ability to provide the supplies to meet the protocol, in the time frame
      ii. flexibility and willingness of the vendor to accommodate changes necessary during execution of the preparation because of new information received from the medical customer
      iii. ability of the vendor to overcome problems, errors, delays in receipt of materials, suddenly recognized deficiencies in materials supplied by sponsor, and to work with the sponsor to provide necessary investigations, solutions, and documentation required for adequate record keeping, control, and final decisions or approvals
      iv. honesty and openness of the vendor in recognizing own deficiencies, lack of understanding, or mistakes, and the honesty of open communications to resolve all issues objectively
      v. willingness of the vendor to ask questions for clarification and understanding
   b. If bidding is used, it must be objectively based. All of the vendors to whom the RFP is issued must have equal capabilities and have been equally evaluated according to their technical competence and regulatory compliance position. Not all vendors have the same strengths and capabilities, as outlined above.
      i. Prior decision should be made as to the acceptance criteria for a bid (for example, take the lowest, or take the middle, or…).
      ii. Turn around time for the proposal and bid and the completeness of the proposal to address the specific points in the RFP should be considered.
      iii. Preferred partner or guaranteed work pricing is preferred for the preparation of clinical trial materials over simple straight bid process because these supplies are not commodities, but rather are prepared uniquely for each protocol.

Some additional considerations for the size of the work being outsourced, whether to outsource only the specific trial or all of the trials for the program, and how many different vendors to manage at one time should occur in order to evaluate, plan, and execute the outsourcing decisions. The most cost effective approach is combining work at the vendor according to the project or according to the pattern of complexity of a series of protocols for related programs, perhaps by dosage form type or special packaging/labeling needs. This should take the strengths and special capabilities of the vendor into account. It's best to ask the vendor, during the evaluation, to state strengths and niche capabilities. Some scale advantages and conservation of concept development time can occur when like jobs are bundled at a vendor site.

The sponsor needs to have a concept for what it will do in-house and what is best done externally. For example, the sponsor with limited staging and warehousing space needs to consider doing only small preparation jobs (Phase I and II trials) in-house and contracting the larger (Phase III and IV) jobs.

And the sponsor also should think carefully about long term protocols, for example three to five year duration protocols requiring significant re-supply and continuation supply efforts. This decision making will depend on whether the sponsor decides to spend time ensuring that the new projects get the best in-house attention, when there is the greatest need for attention to ensure the project will go forward, or whether to attend to the near market projects for which there is greater certainty of success, and therefore, more surety of income. Many clinical supply groups focus on the smaller, early phase, projects, in-house and contract out the larger, later phase, less risky, but more capacity and time consuming, jobs. However, each sponsor needs to make this assessment according to its strategic and tactical thinking.

Distribution Considerations

Distribution of clinical supplies is complex and can be best treated in a separate, devoted, article. Only some brief comments will be made here with respect to the outsourcing of distribution activities for distribution from the US.

Distribution from the US is limited by the complicated export laws. These have relaxed in the last few years since the renovation of the law in 1996. However, with the new concerns about terrorism some congressional members are talking about tightening both the importation and exportation controls. The current law can be used to best advantage by performing all trials according to the requirements of the US IND,[7] by performing foreign site trials in Tier One (listed) countries,[8] and by applying early for authorization to ship to the non-Tier One (non-listed) countries.[9] There seems to be some relaxation for transshipment of CTM through a Tier-One country to a non-Tier-One country if the Principle Investigator in the Tier-One country takes accountability to ensure

that the trial will be conducted according to the principles and practices in place in the Tier-One country. This development needs to be watched carefully and this first impression needs to be validated before transshipments of this nature become routine. If distribution will be managed by the vendor, a very close collaboration between sponsor and vendor will be needed to ensure that both organizations understand and comply with all of the requirements.

Summary

Utilization of contracted resources for the preparation of clinical trial supplies has increased significantly over the last decade. An objective process, which fits into the tactical requirements of the sponsor company required to meet its strategic goals for success, will be the best approach. Such an objective process has been outlined here with some emphasis on the points to consider for working in the international arena.

References

1. 21 Code of Federal Regulations 211.22.
2. EC Guide to Good Manufacturing Practice for Medicinal Products and Active Pharmaceutical Ingredients, 4th. Ed., Chapter 1, Annex 13, and Annex 16.
3. EC Guide to Good Manufacturing Practice for Medicinal Products and Active Pharmaceutical Ingredients, 4th. Ed., Chapter 7.
4. 21 Code of Federal Regulations 211.68 and 11.1.
5. EC Guide to Good Manufacturing Practice for Medicinal Products and Active Pharmaceutical Ingredients, 4th. Ed., Annex 11.
6. The importation and exportation requirements in each country are complicated and subject to change. Complete elaboration of these therefore cannot be provided in this short article. An appropriate tactical approach for maintaining the knowledge base may be to research specific questions through Web-based sites, such as www.fda.gov and www.usda.gov. A database for governmental regulatory contact information has been established at www.ispe.org which can prove useful for questions relating to clinical supplies. Another organization maintains a useful file of direct links to the various, pharmaceutically relevant, governmental Web sites at www.pharmedassociates.com/links.asp.
7. 21 Code of Federal Regulations 312.110(b)(1).
8. 21 Code of Federal Regulations 312.110(b)(4).
9. 21 Code of Federal Regulations 312.110(b)(2).

See External Sourcing - Part 2 for About the Author.