

This is Part 2 of an article that discusses the problems associated with the handling of potent solids in development stage of manufacturing Active Pharmaceutical Ingredients (APIs).

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Process Containment Design for Development Facility - Part 2

Case Study for a Large Scale Laboratory

by Lewis Walker

Introduction

This article discusses a case study for a Large Scale Laboratory (LSL), intended as a multi-purpose laboratory for the manufacturing of kilo scale quantities of primary pharmaceutical products for use in clinical trials. This case study should be considered as generic and not representative of any facility in operation or design anywhere in the world. In order to meet the requirements for new processes, which result from the new product portfolio from research and development, a new LSL is required to enhance the capabilities of kilo scale manufacturing. The LSL needs to meet the requirements of the new products, along with current and future regulatory requirements. New products (especially those in the field of oncology) may be potent materials and the requirements for the handling of these products is a specific requirement for enhancement of the existing kilo scale manufacturing facilities.

This case study aims to discuss the key containment features for the design of the LSL that are required for compliance with GMP requirements for the manufacturer of intermediates and APIs that will be used in clinical trials, and for compliance with Control of Substances Hazardous to Health (COSHH) legislation. A quick reference table is provided - *Table A*.

Process Description

The plant is to be designed as a flexible, multi-product facility with the equipment being split into two general laboratory units, plus one purification/high containment laboratory. A number of product stages are to be manufactured simultaneously; some of these products are expected to be highly potent or late stage API (purification stage) products.

Scrubbers and vent systems should be fully flexible, and shared systems should be allowed between all units. Cross contamination via vent and vacuum streams must be eliminated.

Laboratory units will comprise:

- two (2) 100 liter reactors
- two (2) 20 liter reactors
- two (2) tray vacuum ovens

These will be delivered in a phased and modular approach. Each will be housed in a containment enclosure, traditionally a walk-in fume cupboard.

Each will require service space for two "special process" units, which will facilitate the swift introduction of novel technology when required.

The new LSL will be a stand-alone facility with full capability for analysis, services, dispensation, and storage of raw materials and equipment, office space, and hygiene amenities.

Containment and Isolation Requirements

Product Protection

A concept of Levels of Protection will be used based on:

- the possible exposure of the drug substance to the environment
- the stage of synthesis
- the risk of contamination
- the impact of trace levels of contamination at that particular stage

Each step of the process should be categorized as open or closed, and the appropriate level of protection applied. Wherever possible, designers should provide a design for closed processing.

Product protection requirements, including the segregation of processing areas, should be consistent with those provided in the ISPE Baseline® Guide for Bulk Pharmaceutical Chemicals. During the conceptual design, the points where the process and product are exposed will be identified and minimized to provide product protection.

Raw materials will be sampled in a dedicated sampling area in the warehouse, and both the

Handling Technique	Appropriate Quantities	Containment Levels Achievable	Comments
Bulk Bin: Dump	100 kg and above	200 $\mu\text{g}/\text{m}^3$ -10 $\mu\text{g}/\text{m}^3$	Problems associated with docking/ undocking, filling, and cleaning
Bulk Bin: Controlled	20 kg and above	Potential high containment when bin is in place	As above. Simply moves the containment problem to other areas.
Glove Box: Manual	Less than 25 kg	1 $\mu\text{g}/\text{m}^3$ or less	Not suitable for bulk handling
Glove Box: Keg Tipper	25 kg and above	1 $\mu\text{g}/\text{m}^3$ or less	Handling large quantities may prove to be complex
Down Flow Booth	1 - 25 kg 25 - 250 kg	20-30 $\mu\text{g}/\text{m}^3$	Protection only exists in the downflow laminar region
LEV - Complex System	Suitable for unusual equipment	10 $\mu\text{g}/\text{m}^3$	Containment achievable depends on the proprietary system design
Airsuit	Not good for large amounts of manual work or difficult work	500 : 1	Must be used in conjunction with other techniques
General Flow Booths	Suitable for unusual equipment	200 $\mu\text{g}/\text{m}^3$	The level of protection is generally compromised by the position of the operator or equipment
Fume Cupboards	Small Scale only	50 - 100 $\mu\text{g}/\text{m}^3$	More traditionally geared to Gaseous system containment
Note: All figures quoted are merely intended to be indicative. Specific designs should be looked at by an expert. The results in practice during operation, however, should be carefully monitored. The author's view is that stringent testing is of the highest importance.			

Table A. Quick reference table.

product and operators will be protected. API and actives will be sampled in the Laboratory Units.

Operator Protection - Health, Safety, and Environmental Considerations

Information on the Operation Exposure Limit (OEL) values for design will be obtained prior to making a decision on the worst case. It is likely that intermediates and products will have OEL values in the range of 0.1 mg/m³ to 0.0001 mg/m³. It has to be determined if all the enclosures will be designed to operate with the lowest concentrations or for the range of products identified for that group of enclosures.

The filtration of exhausted air will be through HEPA filters. Fixed or mobile scrubbers will be used to remove toxic vapors. The proximity of the exhaust from the LSL and the air inlets of adjacent buildings will be arranged to prevent cross-contamination.

General and Purification Laboratory Units

Containment and prevention of cross contamination is required in the following areas:

Open Processing Areas - Solids:

- Raw Material Sampling
- Raw Material Dispensing
- Active Material Charging
- Reactor Sampling
- Active Material Transport
- Active Material Discharge

Open Processing Areas - Liquids:

- Raw Material Sampling
- Raw Material Dispensing, inside and outside
- Local Raw Material Charging

Piped Supplies of Gases and Liquids:

- Material supplied by pipeline, e.g., nitrogen, solvent, etc.
- Shared Vacuum Connections

- Shared Vent Connections
- Cleaning Media

Maintenance of equipment and inspection following cleaning is required.

Product Requirements

For Purification Stage Processing, the following controls are required:

- HVAC Air Quality: Filtered to EU10, Temperature and Humidity Controlled (for personnel comfort only)
- Gas Filter: 1 μm
- Liquids Filter: 1 μm
- Pressure Regime: Airlock at Positive Pressure
- Personnel Gowning Requirements: Clean Personal Protection Equipment (PPE) required for open Operations.
- Access Control: Airlock
- Cleaning: CIP by Procedure

For Intermediate/General Stage Processing, the following controls are required:

- HVAC Air Quality: Filtered to EU7, Temperature and Humidity Controlled (for personnel comfort only)
- Gas Filter: 10 μm
- Liquids Filter: 10 μm
- Pressure Regime: Airlock at Positive Pressure
- Cleaning: CIP by Procedure
- Personnel Gowning Requirements: Clean PPE for open Processing Operation
- Access Control: Airlock

Hazardous Material Containment Requirements

Solids - Materials of the following bands will be handled:

- Potent Materials of OEL down to 0.1 $\mu\text{g}/\text{m}^3$ these products may be cytotoxic
- General active material in the range 50 to 200 $\mu\text{g}/\text{m}^3$

Approach	Maximum Containment Achievable	GMP Containment	HVAC Requirements	Ergonomics	Cost	Remarks
Fume Cupboard (or flow booth)	50 $\mu\text{g}\cdot\text{m}^{-3}$ max	Low risk of cross contamination from air in multi-product environment. Poor external cleaning.	Large	Good	Low Equipment High Facility	Current accepted practice. Not optimum containment approach.
All in Glove Box	1 $\mu\text{g}\cdot\text{m}^{-3}$	Poor external equipment cleaning, risk of cross contamination in open handling.	Zero	Poor	High Equipment Low Facility	Retains some problems of existing system.
Glove Box for open areas	1 $\mu\text{g}\cdot\text{m}^{-3}$	High	Small	Medium	Medium Equipment Medium Facility	Number of boxes depend on the contained equipment used.
Alpha/Beta Ports	1 $\mu\text{g}\cdot\text{m}^{-3}$	High	Small	Good	High Equipment Low Facility	Requires special dispensary systems.

Table B. Comparison of generic containment options.

- Non-hazardous Raw Materials
- Pyrophoric Catalyst Materials (not only in hydrogenation)

Liquids:

- Toxic Liquids to OEL of approximately 3 ppm for reagents
- General solvents

Gases:

- Toxic Gases including halogens of OEL 0.03 ppm
- Asphyxiants
- Flammable gases, including hydrogen

Hydrogen and pyrophoric catalyst should be handled in a suitable segregated area or facility.

Process Operations

The plant will be under the supervision of chemists during the course of batch productions.

The reactors will be made of glass/steel with glass lids and condensers. There are also Hastelloy vessels in the scope of the project. There are no constraints on the LSL by a requirement for materials of construction that are identical to manufacturing, as the material from the LSL will not be used for pivotal stability studies. Plant set-up for a particular manufacturing run will be manual.

Pipe and hose set-ups and equipment assignment will be performed with minimal automated valves and control schemes. It is expected that the chemists involved in managing the process will continuously monitor all plant operations and processes. The use of batch records for recording the plant set-up for making API for use in clinical trials is required.

The plant instrumentation will provide batch processing data and plant performance data. Repetitive sequencing tasks, such as vessel jacket services control and inerting will be automated.

The gathering of plant process data for future interrogation is a cGMP requirement. This information will need to be gathered from the process and be accessible on a batch-by-batch basis. The data must be accessible to allow retrospective interrogation of the database and reporting of the batch data. The interface to the data will be of critical importance and must focus on ease of use and easy retrieval of data. It is recommended that instruments are purchased that will permit their future connection to a data collection system. If a system is

installed as part of this project, it must comply with FDA and EU requirements. Any electronic data produced must comply with 21 CFR Part 11.

Before preparing intermediates and APIs, the chemists will define the levels of control, protection, and validation that are appropriate to each process, based on an understanding of the process chemistry. The specification of the APIs will be determined, as well as the impurity profile. Any critical steps and parameters, which affect that specification, will be identified. This will include the assessment of chemical, physical, and biological factors.

Critical parameters may be different for each unit operation of the process. Typically, critical parameters are reactor temperature and oven temperature.

Alternative Containment Philosophies

Fume Cupboard

Traditionally, such facilities use walk-in fume cupboards to provide containment for all processing areas. In general, all open processing for solids or liquids is carried out in a fume cupboard.

If the operator is carrying out any operations within the cupboard, appropriate Respiratory Protective Equipment (RPE) is required.

The air supply to the fume cupboard is from the general laboratory area. This air is supplied to a quality as required by the area standard. Multiple fume cupboards are served by the same supply. Products and raw materials are transported through this shared area.

Containment within the fume cupboard is achieved by air entering the cupboard with a face velocity of 0.5 $\text{m}\cdot\text{s}^{-1}$

Within the cupboard materials are handled in an open fashion. Fittings and external surfaces within the fume cupboard are as smooth and crevice free as is reasonably practicable.

Internal cleaning of the plant is performed with manual cleaning procedures followed by visual inspection.

External cleaning of the plant within the fume cupboards is performed by assumed destruction of materials following general (water) wash down.

Glove Box

As an alternative to placing all the equipment within a large fume cupboard, a glove box may be used to enclose all, or some, of the equipment.

Total Glove Box Enclosure

Placing all the equipment within the glove box gives an identical philosophy to that for the fume cupboard, but increases the containment capability of the system. The following should be considered:

- a glove box to carry out the task is likely to be very large and expensive
- large airflow systems would not be required
- external contamination of the process equipment would continue as per the fume cupboard approach
- significant ergonomic issues are likely with this approach

Glove Box Control of Open Processing Areas

Using a glove box to handle all the areas of open processing of solids and liquids relies on the enclosed equipment to give primary protection in certain areas.

Requirements:

- Reactor head glove box for solids charging, sampling and lid removal
- Liquid charge box
- Filter glove box

Alpha/Beta Ports

Using alpha/beta ports to handle all the areas of open processing of solids and liquids relies on the enclosed equipment to give primary protection in certain areas.

Requirements:

- Solids Charging
- Contained Sampling System
- Contained Liquid Charge System
- Filter Discharge System: This is only possible with fixed pressure filter dryer type systems or similar

Contained Equipment

A significant contributor to the risk for loss of containment is the use of non-contained process equipment. The most significant items are solids charging, the filter and dryer where potent materials are isolated and transported outside the current containment equipment boundaries.

In order to address the filtration and drying issue, contained equipment for these areas could be considered. Equipment for consideration includes:

- Laboratory scale contained pressure filter
- Laboratory scale contained pressure filter dryer
- Fixed exotic filter types
- Flash or Spray Dryers
- Placing the dryer in the same containment suite as the filtration equipment to avoid the need to transfer across a corridor

Dispensary Requirements

Solids Dispensary: Raw materials and active intermediates enter the building from the site stores or other production plant.

All material movements must be controlled. A laydown area with canopy is required for weather protection for material that cannot immediately enter the material laydown area within the building. A cold store area is required (for outgoing materials only).

A raw material dispensary and sampling area is required. This must cater for general material and potent materials. If an alpha/beta port system is to be used then the dispensary must accommodate this system.

Minimum requirements, therefore, would be:

- Fume cupboard/flow booth dispensary for materials down to OEL of $50\mu\text{g}\text{m}^{-3}$, including weigh scales and alpha/beta change station if necessary
- Glove box dispensary for materials down to OEL of $0.1\mu\text{g}\text{m}^{-3}$ including CIP system, weigh scales, and alpha/beta port change station if necessary

Discussion

Table B presents benefits and concerns associated with each of the philosophies outlined. The optimum solution may be considered to be a hybrid of the options depending on scale of equipment, cost of containment technology, the relative benefits of a single finish approach, and the operational requirements of the system. This idea is developed in the following discussion sections and Table B.

Options for Containment Technology - Summary of Discussions

Fume Cupboard

The general fume cupboard has been shown to provide containment in the OEL of 50 to $100\mu\text{g}\text{m}^{-3}$ range. (reference: data received from previous site based monitoring). However, this uses a time-weighted average to achieve the low levels and shows that a fume cupboard is inappropriate for potent and sensitizing solid materials.

The fume cupboard has inherent problems with the sash window (that regardless of the number of panes used) may obstruct ergonomic operation.

Other issues are the external contamination of the cupboard contents and internals during solids charging, and the risk of cross contamination from adjacent or opposite fume cupboard operation.

Downflow Booth Fume Cupboard

A downflow booth can be shown to protect to levels of 20 to $50\mu\text{g}\text{m}^{-3}$. The air curtain allows complete open access to the process equipment by the plant operator. The air curtain also can be shown to be of a controlled quality by local filtration. The air curtain may not protect equipment in the layout, e.g., the filter located below other equipment that breaks the downflow pattern.

Other issues include the external contamination of the cupboard contents and internals during solids charging, and the risk of cross contamination from adjacent or opposite fume cupboard operation. Once through, air usage may require significant air through put.

Alpha/Beta Technology

The split butterfly technology can be applied to all reactors in any type of booth on an 'as required' basis. The device itself contains approximately $10\mu\text{g}\text{m}^{-3}$, thus operating within a cupboard primary containment of the order of $0.1\mu\text{g}\text{m}^{-3}$ is achieved. It should be noted that the container and connection will be contaminated to a small amount after charging and careful wipe down is required when operated in this fashion. A

significant benefit is the reduction of contamination of the booth internals.

Contained Pressure Equipment

Laboratory scale pressure filter dryers are available which could be used with fixed or removable containment technology to meet the maximum containment requirements. Such a device could be installed in the "spare" fume cupboard. However, such a device has both positive and negative impact for process data collection.

Glove Box Containment

Glove boxes are available which can meet the maximum containment level, and which can be demounted from fixed equipment, e.g., tray dryers, with appropriate design.

Glove ports that are added to general fume cupboards are unlikely to provide ergonomic design or the requisite levels of containment.

Approach

In selecting the approach, the following principles should be followed:

- Ergonomic operation must be provided. If this is poor, then containment may be compromised by inappropriate operation of equipment, e.g., opening fume cupboards too wide, or pushing gloves out of glove boxes, etc.
- Combinations of equipment may be used to upgrade the facility where appropriate.
- Potent product materials should not be hand carried around the open areas of the laboratory.
- The facility boundary where potent materials are to be handled must be of design appropriate for high levels of control, e.g., airlocks, floor bunds, controlled access etc.

Options for Containment

The split butterfly valve in a cupboard (on an 'as need' basis) is to be the primary containment route for solids charging. A dispensary glove box will be required to change the split butterfly valve container.

For filtration and drying, three options are to be developed. One option requires a third laboratory area, and the other options have two general laboratories with high containment features in local areas:

Option 1: The Use of a Separate Purification/High Containment Laboratory

In this area, typical equipment could be used in order to allow pures processing at normal levels using current technology. Where high containment is required, the operator would be required to suit up (full air suit), as appropriate. Downflow booths will be used to allow ergonomic operation in this specific area for suited-up staff.

Using this approach, the potential for contamination of other products would be high, so single product manufacture only would be the most probable use of the laboratory. Two such laboratories may be required to manufacture highly potent material, or two purification stages, simultaneously.

The following options do not require a separate laboratory. However, they may require the entire general area to be of a

higher standard.

Option 2: Tray Dryers in Glove Boxes

The glove boxes could be permanent or fitted when required with the fume cupboard sash raised to the roof.

Handling of the slurry paste would be critical; the filter could be handled inside the tray dryer glove box, or be passed from cupboard to box via a pass port operated by glove port from the fume cupboard.

Discharge of material would be via alpha/beta port or other flexible containment system.

Option 3: Mobile Pressure Filters with Flexible Containment Systems

These could be installed in the current "spare bays" for high containment operation. This would have little impact on the facility design, but may hinder process flexibility if this were the only high containment drying option.

Other flexible equipment options may be used to support the containment provided by downflow or similar technology. The benefit of using combinations of containment technology is the flexibility in operation allowed by this approach.

Discussion

Option 1 offers a potentially high cost, but well understood and secure operating route.

Options 2 offers a reduced overall footprint and HVAC system requirement, but at higher process equipment cost. This option also may allow alternative layout configurations by reducing the system to two laboratories.

Option 3 only impacts if the technology combination is considered acceptable to delete the high containment laboratory requirement.

Full benefit analysis will follow vendor information and schematic layout of "adaptable tray dryer."

Fundamental questions include:

- Could primary containment technology be used to delete the purification laboratory and reduce footprint?
- Could a purification stage product be manufactured with another (highly potent) material in the same facility?

A primary aim of the design approach will be to provide as much flexibility as possible for the installation of developing containment technology. The downflow enclosures, which allow full-face opening capability, facilitate future flexibility.

Discussion of Potency of Materials Handled

The selection of the containment equipment for the facility depends on the OEL of the materials to be processed. In general, APIs are increasing in potency by design and the OELs assigned to the products are often low, as these are based on the pharmacological activity of the material.

At the development stage, materials have not undergone toxicology trials, therefore, very low OEL levels (e.g., $1\mu\text{g}\text{m}^{-3}$ or less) are often assigned on a conservative basis.

Historical data shows that of recent APIs processed, final OEL figures are circa: $5\% < 1\mu\text{g}\text{m}^{-3}$ $20\% < 501\mu\text{g}\text{m}^{-3}$ and $75\% > 50\mu\text{g}\text{m}^{-3}$.

The equipment selected, therefore, was intended to reflect the mix of containment requirements above.

However, ever tightening COSHH regulations have driven the number of products to be assigned low OELs to perhaps 80-90% of all new products.

In order to meet such a requirement, therefore, all equipment should be designed for high containment.

A compromise was reached, where all "High Risk" operations, e.g., tray dryers, were, fitted out with high containment capability. However, only 20% of reactor solids addition point were so designed.

Discussion of Materials Potency

The selection of the containment equipment for the facility depends on the OEL of the materials to be processed.

- The use of alpha/beta ports or small glove boxes for local-handling requirements has sufficient potential benefit to merit further investigation.
- The use of a glove box or fume cupboard which contains both filter and dryer may have potential benefit.
- The use of a contained filter dryer may have a potential benefit.

Selected Basis of Containment

Purification Laboratory

A segregated purification and high containment laboratory will be provided. This will be designed to handle a single laboratory unit in a stand-alone fashion.

Equipment will include:

- Four reactors in fume cupboards with downflow capability
- Two tray dryers in downflow booths (with space for the addition of a demountable glove box)

The reactor fume cupboards will be linked to the tray dryer booths by a pass port system to ensure process material is never handled outside the booth area.

A high quality cleanroom type airlock access system is required to this laboratory.

General Laboratories

The general laboratories are required to hold three general laboratory units:

- Twelve Reactors in general fume cupboards
- Four Tray Dryers (with potential for demountable glove boxes) downflow booths
- Two spare units in standard fume cupboards capable of handling novel technology and demountable glove boxes
- Access and spill control for the laboratory is required. The laboratory must be maintained at negative pressure to the externals with double door access
- If contained equipment is to be used, e.g., filter dyers in the spare bays, then high containment glove bag systems or similar devices will be used for high containment pack off.

Dispensary

Raw Materials in/out:

Duties have been identified:

- Batching Out:

- Bench
- Low Level
- Walk in
- Sample:
 - Walk in
 - Low Level

Potent material:

- Glove Box:
 - For charging split battery/valve containers
 - For handling potent samples

In order to meet this duty, the requirement would be:

Two large recirculatory downflow booths with work bench area to allow five simultaneous operating spaces

- One dispensary glove box
- A segregated storage area for materials and samples is required.

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This article provides an insight into the regulator's view on the topic of innovation. A model approach to achieving sector innovation is discussed, based on the author's industrial and regulatory experience. Relevant MCA regulatory background is given and the means to influence interested parties and the regulators are discussed.

This article is based on a presentation at the ISPE UK Annual Seminar, "Improving Value Through Engineering Innovation," November 15, 2001, Nottingham, England. The views expressed in this article are personal and do not necessarily represent those of the referenced committees and working parties.

An MCA Inspection Perspective on Innovation

by Anthony Trill

For innovative engineering to stand any chance of success, those ideas and creations need to be promoted and shared openly. A relevant definition of 'innovation' for our regulated industry sector is "innovation is a novel development for the better."

Some may feel that regulators are more associated with inertia rather than innovation! The author hopes, however, that this article will counter that stereotypical image by demonstrating the proactive inter-relationships that help to foster innovation and progress.

In the author's experience, 'paradigm shifts' take-off when benefits and attributes can be fully recognized by the majority so that they willingly 'buy into' and share the initiatives. The industry really has to want that change and organize itself appropriately! Otherwise, the exercise may be seen as so much 'kite flying' for narrow interests. Once a certain momentum has built up and ideas have been fully crystallized, then the initiating focus group needs to seek a reputable sponsor to give the project professional 'ownership.' It certainly worked for automated systems and computer systems guidance with the Pharmaceutical Industry Computer Systems Validation Forum (PICSVF) evolving into the Good Automated Manufacturing Practice (GAMP) Forum supported by ISPE and more recently Supplier Forum's absorption into the latter.

This article will give examples to show how the pharmaceutical sector has enabled new technologies and solutions with the support and understanding of the regulatory community. Examples will be given to demonstrate how receptive regulators such as the UK Medicines Control Agency (MCA) are to change and innovation. Some recent initiatives also will be explored.

EU directives require changes to be implemented in line with the advance of science and technologies. Refer to EC Directive: 65/65 (as amended): January 26, 1965 "on the approximation of provisions laid down by law, regulation, or administrative action relating to medicinal products."

Article 9a of European Commission (EC) Directive 65/65/EEC, as amended states:

"After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the methods of preparation and control provided for in points 4 and 7 of Article 4, take account of technical and scientific progress and introduce any changes that may be required to enable that medicinal product to be manufactured and checked by generally accepted scientific methods. These changes shall be subject to the approval of the competent authority of the Member State concerned."

(Point 4 of the indicated Article 4 refers to a brief description of the method of preparation and point 7 of Article 4 refers to a description of the control testing methods employed by the manufacturer etc.)

The regulatory framework, therefore, discourages inertia and positively encourages organizations to introduce innovative manufacturing and control changes. Enlightened regulatory affairs departments in industry will assist in the change management and implementation processes to ensure approval on assessment and inspection. Good Manufacturing Practice (GMP) guidelines permit a flexible interpretation of the means to achieve compliance within the principles of Quality Assurance (QA).

The 'Introduction' to the GMP Guide states:

"It is recognized that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Assurance. The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Assurance at least equivalent to those set out in this guide."

Therefore, equivalent means to achieve the same outcome are permitted under GMP. Personal experience (and Chapter 1 (1.2) of the EC GMP) reveals that 'Quality Assurance' is a wide-ranging concept not only incorporating GMP, but also other factors outside the scope of the GMP guidance.

GMP requirements are not always totally prescriptive and are the reason why guidelines may have to evolve to meet the recognized needs of both the industry and inspectors, e.g., for validation and qualification in general and for computerized systems. (The term 'Inspector' in the EC is equivalent to 'Investigator' in the US.) New guidance documents may eventually emerge as new Annexes to the GMP Guide, or in Pharmaceutical Inspection Cooperation Scheme (PIC/S), International Committee on Harmonization (ICH) publications, or as best practice publications from professional institutions or standards bodies, such as:

- GAMP Forum
- ISPE
- PDA
- Parenteral Society
- Pharmaceutical Quality Group (PQG) (a sub-committee of the UK Inst. of QA)
- National Physical Laboratory, UK (NPL)
- National Computing Centre, UK (NCC)
- British Standards Institute for Information Systems (BSI-DISC)
- ISO
- European Committee for Standardization (CEN)

Sometimes innovative guidance can be drawn from other industry, government, and service sectors and adapted for our sector.

The requirements for methods of manufacture and testing are detailed in European Union Rules and Guidance Vol. II (A&B) in the Notice to Applicants for Marketing Authorizations and Variations. There also are related CPMP/ICH and CPMP/QWP guidelines, (e.g., for a common technical document, analytical method validation and process validation), together with annexes to the GMP Guide, e.g., Annex 15 'Qualification and Validation' and Annex 18 'GMP for Active Pharmaceutical Ingredients.'

For innovative medicinal products (and also biotechnology-based products), it is appropriate to consider using the Centralized Procedures for New Applications since these are intended to cover newer technologies. Further information on these may be obtained from the MCA's Information Centre.

There is flexibility within Manufacturing and Marketing Authorizations, which is linked to the logical constraints of validation and measures to satisfy regulators on grounds of product quality, safety, and efficacy. If the result were a better quality-assured product, process, or method, with reduced risks to the end user, then it would be considered beneficial to expedite the innovative change. Where the proposed change may actually reduce the margin of safety, quality, or efficacy of the product; however, it would be difficult to justify the change.

The following sections explore the means to implement innovative changes firstly for company specific cases and secondly for industry-wide movements.

Company Specific Innovative Changes

Data in support of novel dosage forms and devices will be presented to regulatory assessors as part of the dossier submitted for new marketing authorization applications. The application should have been structured in line with the 'Notice to Applicants.' During the development stages, the organization should have discussed any difficult issues relating to regulatory requirements with pharmaceutical and medical assessors, as well as drawing on internal experts. It may be helpful to include the local Medicines Inspector in some of the discussions (with the organization and jointly with MCA Assessors), especially where site knowledge, GMP issues and shared topics, such as validation and process technologies, are being considered. This process should facilitate the understanding and resolution of any issues.

When innovative dosage form projects are approaching key project milestones for implementation planning, then it is sensible to consult the local Medicines Inspector and request comments on the proposed plans and technologies. This is particularly important where the project concerns the introduction of new processes and dosage forms to the site, and should prevent any unpleasant revelations during a subsequent inspection.

Proposed company specific innovative changes may involve new or significant changes to:

- Product Ranges
- Premises
- Equipment
- Procedures
- Methods
- Processes
- Contracts
- Management

In such cases, it is recommended that organizations make local Medicines Inspectors aware of their plans at an early stage and provide a one-page summary of the proposed innovation.

Inspectors are busy people and it is prudent for companies to arrange 'snappy' presentations, highlighting any matters of concern arising from their own regulatory compliance and risk assessment exercises. It is important for organizations to identify weak points in proposals at the outset of discussions, rather than wait for Inspectors and Assessors who will tend to find them, as this will save time for both parties. Most regulators are suspicious of miraculous claims so it is essential to avoid hyperbole and marketing styles.

Inspectors will readily comment on plans and proposals, and indicate any GMP compliance concerns apparent in the proposals. Additional supporting data and controls may be requested. Inspectors also will advise on any licensing changes that may be necessary and whether further meetings may be useful with other MCA colleagues or third parties. Where variations to the registered process are indicated, close liaison with a relevant Pharmaceutical Assessor will be necessary. For difficult process variations, it may be necessary for the

Inspector to provide expert advice to the Pharmaceutical Assessor. Sources of further guidance also may be discussed. However, it is important to note that the inspector cannot be expected to approve detailed project plans for implementing such changes as this could frustrate future MCA audits/inspections of the site.

Once the significant change (innovative or otherwise) has been implemented, an MCA inspection should be arranged. This may be additional to the routine cyclical program, depending on timing and resourcing.

Global or Industrial Sector Changes

Global or industrial sector changes refer to innovative change projects driven by the pharmaceutical industry to achieve common goals and objectives for the entire pharmaceutical sector. Such projects usually relate to fundamental new technologies, where emerging standards, guidance, and requirements are far from mature.

Many innovative projects in the industry involve automated instruments, processes, and systems.

The author has personal experience with one such classical example relating to computerized or automated systems with the GAMP Forum project.

In the late 1980s, like-minded individuals in the pharmaceutical industry identified a need for a better understanding of this subject for business needs, but also in respect of FDA and other regulatory inspections. Serious inspection findings were being reported internationally and impacting businesses. Firms recognized that there was a common need for sector guidance on quality and validation requirements for computerized systems. This led to the establishment in the UK of the PICSVF in 1990.

As a specialist for MCA in the subject, the author was invited to join a working party with industry specialists and our initial fruit was known as the 'Validation Management Guide' (VMAN) led by Tony Margetts. In 1992/93, VMAN-II working drafts, together with several case studies, were discussed at several seminars and reviewed in Pharmaceutical Technology International.¹ These guidelines sought to formalize the project methodology and contractual terms for new systems between a customer and a supplier - specifying the management system, documentation, and records for subsequent acceptance by the customer.

Following consultation with industry, the VMAN prototype evolved into the first validation guideline for the topic. This was entitled: "Validation of Automated Systems in Pharmaceutical Manufacturing" and was formally launched in March 1994 in London at a conference entitled "Good Automated Manufacturing Practice in the Pharmaceutical Industry." With speakers from the international pharmaceutical industry, the MCA regulators, major automated systems suppliers, and the UK government, GAMP had arrived. The meeting was well attended and reported as a 'landmark event.' The guideline built on recognized published standards and best practices in the various disciplines, in a common-sense fashion, demonstrating life cycle quality assurance and validation. It was hoped that the guide would ultimately have wide acceptance by industry and certification bodies. It was recognized, however, that to achieve this, it might be necessary to obtain 'ownership' and an executive authority.²

PICSVF evolved into the GAMP Forum following a suggestion from the author for a GMP related acronym. A series of improved editions of the GAMP Guide for Suppliers and Users

were issued during the 1990s initially with support from industry sponsors, such as Logica, but ultimately with ISPE. GAMP 3 was published in 1998 and GAMP 4 was launched in December 2002. GAMP America was launched to meet demand and to encourage participation and ownership of the initiative in North and South America. The GAMP Forum continues as a successful sub-committee of ISPE, with international participation and a wide range of special interest groups working on specific topics.

Key Steps for the Success of the GAMP Forum Project

Some of the key steps along the way for the success of the GAMP Forum project are described below. With complex topics such as 'computerized systems' and 'validation,' significant progress could not be made until the terminology was defined for basic system elements, such as:

- Computer
- Hardware
- Software
- Computer System
- Computerized System
- System Development Life Cycle

It was then necessary to define the problems and issues that had to be addressed particularly for the quality assurance, validation, qualification, and inspection aspects. This in turn allowed the scope of the guidance to be defined.

The next step was to search for and identify relevant existing guidance and standards from which to draw. Early MCA input was to recommend:

- NCC publications on Software Tools and Real Time Systems (STARTS) and structured project methodologies
- National Accreditation of Measurement and Sampling (NAMAS) publications
- Recent government sponsored reviews of software quality
- Supplier certification initiatives, including 'Tick-IT' (a Scheme for Software Sector Quality Certification (BSI-DISC), which is analogous to 'Check-IT' in a US context)
- Existing quality standards and guidelines

Throughout the process industry, members collaborated to share experiences with systems and to facilitate the drafting of best practice guidance. This, in turn, was referred to the MCA Inspectorate for comment and feedback.

It was soon recognized that there was a need to ensure that quality was built into software and systems as they could not be quality assured by testing afterwards. Therefore, suppliers were encouraged and pressured into understanding the compliance issues affecting the pharmaceutical sector and required to follow the new standards and guidelines to ensure that quality was demonstrably built into their products.



Figure 1. MAIL, the bimonthly updating service published by MCA.

The Logica³ and Price Waterhouse⁴ reports for DTI in the late 1980s on software quality standards rapidly followed by the 1989/90 Tick-IT scheme for software sector quality certification from BSI (and sponsored by the CBI) provided the impetus. More recently, MCA, DTI, the GAMP Forum, and industry supported the formation of a Supplier Forum under the UK Government's Sector Challenge scheme to further encourage the process of supplier understanding of sector quality issues and product improvements. The Supplier Forum has organized regular meetings and produced open guidance material. Continuity with the GAMP Forum was assured via a common industry steering committee member and MCA regulatory input to both steering committees in a co-sponsorship role. The industry board of the GAMP Forum maintained independence and direction above the steering committees. The Supplier Forum became a sub-group of GAMP Forum within ISPE during 2001.

Suppliers, developers, and vendors were now positively enthused about building quality into their software and systems products, accommodating audits, and providing added value performance and validation evidence and assistance to customers. The time was right to expand the guidance into more challenging topical areas, such as the large and small common computerized applications to be found installed in the pharmaceutical sector. Recently, this has led to an expanded management strategy in the GAMP guidance for different classes of systems, followed by a major contribution from the special interest group on electronic records and electronic signatures.

During steering committee meetings, the author advised the group to consider BS 7799 (2000) on Information Security Management, Part 1 of which has been fast-tracked for ISO status and recently adopted as ISO 17799 as a Code of Practice for Information Security Management. Following participation in the DTI User Group for BS7799, the author rapidly became convinced that it was essential for firms to be able to demonstrate the implementation of an Information Security Management System equivalent to BS7799 if they were going to have any chance of running compliant paperless systems with electronic records and electronic signatures. This point was proposed by the author at a number of conferences and discussed with Paul Motise of the FDA during video-panel discussions. The Information Security Management standard in the UK also is supported by a number of detailed codes of practice related to risk assessment, risk reduction measures, auditing, evidential value of electronic documents, archiving, etc., and the appropriate ones have been recommended at industry meetings and to the GAMP Forum. Details of the codes are available from BSI-DISC.

In parallel with the drafting processes, the GAMP Forum has maintained contact with its grassroots membership in the various international companies in the UK, Europe, and the Americas with regular meetings and a series of training courses. It also has ensured constructive collaboration with other industry groups working on common objectives - such as PDA, JETT, APV, and GMA NAMUR. For particular topics, the GAMP Forum Industry Board also has held discussions with the FDA in collaboration with other groups. These meetings have been held in relation to specific US regulations, such as 21 CFR Part 11, and possible ways to demonstrate compliance. The results of these deliberations are fed back to the special interest groups drafting the guidance and so the process continues in an iterative fashion.

The GAMP Forum and ISPE also have established very informative Web sites for members, enquirers, and committee members with different levels of access.

Model Approach for Successful Sector Wide Innovative Initiatives

From personal experience and by drawing upon the success of the GAMP Forum project (and its precursor) over the past 10 to 12 years, it is possible to propose a model sequence for more general application to sector-wide innovative projects as follows:

1. Build a critical mass of interest in the underlying theme through industry wide focus groups.
2. Establish a steering committee or project management structure across the industry sector.
3. Cooperate to define the route of the problem or opportunity so that objectives may be clearly stated and understood.
4. Clarify all terminology so that everyone can understand clearly.
5. Outline the scope of the position paper and interpretative guidance that will be needed so that all parties will have a better understanding of the innovative topic.

6. Carry out research and identify best practices and guidance that already may be established in the subject area, perhaps from other sectors.
 7. Develop and draft additional sector specific case material and guidance in special interest or focus groups.
 8. Liaise as appropriate with regulatory inspectors and assessors for feedback, comment, and direction.
 9. List the 'products' or 'outputs' from the exercise, e.g., processes, dosage form types, or technologies, and rank the proposed implementation sequence.
 10. Consider seminars to consider prototype versions of position papers and guidance.
 11. Publish the documents and the results of the discussions and seminars in journals and on a Web site and draw conclusions.
 12. Seek affiliation with professional, engineering, or standards type associations for sponsorship and assistance in completing the project and publishing the resulting documents and lobbying for wider acceptance.
 13. Encourage all relevant parties to share and 'buy into' the initiative, including the regulators.
 14. Consider the launch and distribution arrangements for the 'products' and associated documents.
 15. Launch the final 'products' and documents and control future changes with version control if necessary. Maintain the infrastructure to review and to introduce additional material, or if objectives are met and revision/addition will not be necessary, consider winding down the voluntary groups managing the initiative.
- Amendments to 75/319/EEC
 - Directive on GCP; GMP aspects and Qualified Person role
 - Importation of unlicensed medicines
 - Mutual Recognition Agreements
 - Freedom of Information and MCA Inspection Reports
 - ICH GMP for Active Pharmaceutical Ingredients
 - NHS extemporaneous preparations
 - QP certification and batch release
 - Moves toward continuous licensing
 - The control of storage temperatures of medicinal products and mean kinetic temperature
 - PQG draft guidelines for excipients
 - Borderline products review panel
 - NHS concerns over potential contamination risks from cytotoxic packaging
 - PIC/S document on parametric release
 - Compliance with CPMP guidelines on TSE
 - Biotechnology national measurements system

Good Laboratory Practice (GLP) Consultative Committee

The GLP Consultative Committee, chaired by Dr. Roger Alexander of MCA, meets annually with delegates from the various regulatory agencies (MCA and other UK government departments) and industry trade associations. The objectives of the committee are to advise and provide information to industry and to act as a forum for consultation, discussion, and feedback on GLP matters. Minutes are circulated to attendees and cascaded to industry via their trade associations and a report on the meeting is published in 'Quasar' by the British Association of Research Quality Assurance (BARQA).

New Technologies Forum

This was set up in 1999 between MCA and the pharmaceutical industry, coordinated by the Royal Pharmaceutical Society. The primary purpose of the forum is to promote a mutual understanding of new technologies and their applications and impact across both the pharmaceutical industry and the regulatory arenas. Topics discussed in the first two years have included:

- Raman Spectroscopy
- Process Measurement and Control
- Acoustic Emission and Ultrasound Spectroscopy

MCA Contact Points and Information Sources

'MAIL,' the bimonthly updating service published by MCA, provides up to date organizational structures and contact points by subject in appendices. This information also is available via the Medicines Control Agency's Web site at <http://www.mca.gov.uk>.

'MAIL' publishes information on topical issues such as developments and performance statistics affecting the pharmaceutical industry and MCA in addition to reporting on the activities of committees and forums, such as the New Technologies Forum in which the MCA are involved - *Figure 1*.

Consultative Committee for GMP and Good Distribution Practice (GDP) (Wholesale Dealing)

This committee was established in 1999 to provide a forum for professional bodies and trade associations to discuss with the MCA any matters concerning the manufacture and distribution of medicines. Dr. Gordon Munro, Head of Inspection and Enforcement Division, chairs the committee. Since inception, this group has discussed a wide variety of topics (reported in 'MAIL'), including:

- GMP for Starting Materials

The MCA was receptive to the application of these new technologies that had the potential to provide a better understanding of the processes used in production. The MCA already recognizes the principle of parametric release and the concept of the move from final product testing to good process control. This approach was seen as consistent with the PIC/S guidance document on parametric release and the development of guidelines by the Quality Working Party of the Committee on Proprietary and Medicinal Products (CPMP).

Following the first meeting of the New Technologies Forum 'MAIL 113' reported that:

"The onus is on the industrial user to explain and educate the assessor in any new or novel application of technology. We would actively encourage companies adopting such approaches to seek meetings with relevant MCA personnel prior to making any submissions. The adoption of such a proactive approach would provide the basis for mutual understanding of the technology and more importantly the underlying application philosophy which is essential to enable regulators to make informed judgments regarding validity of the approach in the assessment of any subsequent submission."

Quality Working Party

The Quality Working Party (QWP) comprises assessors from the different member states of the European Union in support of the work of the CPMP. A number of notes for guidance have been produced by CPMP, including:

- CPMP/QWP/848/96 'Process Validation' - effective September 2001
- CPMP/QWP/2845/00 Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurized Metered Dose Inhalation Products (CPMP adopted March '02)
- CPMP/QWP/3015/99 'Parametric Release' - effective September 2001
- CPMP/QWP/160/01 'Concept paper on the use of Near Infrared Spectroscopy'
- CPMP/ICH/381/95 'Validation of Analytical Methods - the Terminology'
- CPMP/ICH/281/95 'Validation of Analytical Methodology'
- CPMP/ICH/367/96 'Specifications'
- CPMP/BWP/2490/00 Note for Guidance on Cell Culture Inactivated Influenza Vaccines (Adopted by CPMP January 2002)
- (CPMP/QWP/158/01) *Revision* Note for Guidance on the Quality of Water for Pharmaceutical Use
- CPMP/QWP/1719/00 Note for Guidance on Medicinal Gases: Pharmaceutical Documentation

Inspectors

All inspectors have industry backgrounds and can readily relate to proposals for changes put forward by industry. In addition, they make their views known in a variety of ways, such as:

- speaking at professional and technical meetings
- engaging with special interest groups
- publishing papers and guidelines
- committee work

Industry has the knowledge of technologies and puts it into practice. It knows its strengths and weaknesses. Inspectors will be interested in the organization's risk assessments and where appropriate the Failure Mode Effects Analysis (FMEA) report. Beyond the technology and validation issues, inspectors may be interested in other relevant matters concerning, for example, the impact of the change on the current product and process mix, resource balancing, and congestion/building constraints.

National inspectorates advise on GMP compliance issues. The Ad-Hoc Inspector's Working Party provides advice on GMP matters that may have a European dimension.

Conclusion

The benefits of innovation must be fully recognized by those who will be affected before any significant progress can occur. The industry must want the change and then organize itself appropriately to enable success of an innovative project. Once such a project has gained sufficient momentum and concepts are established, then those driving the innovation need to seek a reputable sponsor to give the project professional 'ownership.'

The UK MCA is receptive to change and innovation and regulations positively encourage organizations to innovate. The GMP Guide has stood the test of time for fundamental principles and it is gradually evolving while maintaining its flexibility.

The GAMP Forum project is an example of a successful global sector-wide innovation and following its success suggests a model for other global initiatives.

Example innovations (some taken for granted) from the recent past that impact on regulated activities include:

- Digital technology and computerized systems
- Automated: instruments, machines, lines, warehouses, and entire factories
- Building and energy management systems
- Bar code reading, data encoding, security, and identification
- Automated random stock location, movements, and materials control
- Electronic records, documents, and information systems
- Integrated IT systems and databases; intranets; Internet; email
- Automated sterilize-in-place (SIP) systems
- Metered dose inhalers/dry powder inhalers
- LAL endotoxin testing

- Automated aseptic Blow-fill-seal technology
- TOC water testing
- Isolator technology
- Robots in manufacturing and laboratories (automated sampling etc.)
- High shear/speed mixing
- NIR identity testing and in-process controls
- Non-intrusive blending/content measurements
- Parametric release of terminally sterilized products
- The biotechnology revolution and genome project
- Automated electronic leak detection and inspection systems
- Novel dosage forms and devices
- Clean welding technologies
- RO water
- CAD and superior finishes/materials
- Modular construction/versatile plants
- Rapid identification techniques for microbes and impurities
- DNA fingerprinting
- The 'validation industry'
- Systems integrators
- Supplier certification/sub-contracting
- Virtual companies

The notes for guidance produced by CPMP may be obtained from the Euro Direct at the MCA Information Center Tel: + 44 (0) 207 273 0353. For further information concerning discussion topics, see 'MAIL' and the MCA Web site at <http://www.mca.gov.uk>. For current, up to date listings of MCA committees and publications, readers should refer to the MCA Web site at <http://www.mca.gov.uk> or E-mail: info@mca.gov.uk. Note that EuroDirect publications may be obtained from the same source.

Inspectors also may be contacted at the regional office numbers, (Chester, Hitchin, York and East Grinstead) which are also listed in 'MAIL.'


Since the original presentation on which this article is based, the European Codification Directives (2001/82/EC and 2001/83/EC) have been adopted. These have repealed and replaced the pre-existing major directives and amendments dating from 1965 for human and veterinary medicines. The new codified, consolidated, Directives became effective on December 18, 2001. References to particular directives in this article may be updated by reference to the new Codification directives.

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About the Author



Anthony Trill is a Senior Inspector with the MCA and is based at the Chester Regional Office. He holds an honors degree in pharmacy and a Masters in pharmaceutical technology, is an IRCA Lead Assessor, and eligible as an EC Qualified Person. Prior to joining the Medicines Inspectorate in 1984, Trill had worked for more than 18 years for three multinational pharmaceutical companies. In addition to routine inspection activities in the UK and overseas, he holds several committee memberships, including the GAMP Forum's Steering Committee and the UK Interdepartmental Committee for Software Engineering (ICSE). He is currently the working group leader for PIC/S⁷ Guidance document on "Best Practices for Computerised Systems in Regulated GxP Environments" (Latest 50-page draft: January 2002). Trill is a regular speaker/lecturer at national and international meetings and is widely published.^{5,6} 

This article discusses how systems thinking can help companies understand risk decision-making to help establish more effective risk management practices in the clinical supplies process.

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Systems Thinking and the Risky Business of Clinical Supplies

by Jean Singer

Drug developers make decisions at risk every day. To focus resources, they may pursue some drug candidates and abandon others; to create leading edge science, they may invest millions in new technologies with no guaranteed outcome; to accelerate development, they may launch critical path activities before a study is fully defined; and to speed market introduction, they may pursue unconventional strategies with regulatory agencies.

Risk decisions gone wrong can have grave consequences. For example, an inadequate study design or the misinterpretation of regulatory requirements can cause the FDA to reject data costing hundreds of millions of dollars and years of effort to generate. On the other hand, risk taking can offer extraordinary gains, such as the chance to more quickly place a new medicine in the hands of someone desperately ill, or the opportunity to generate a million dollars a day in revenue from a new blockbuster product. In this setting, a company's ability to manage risk - that is, to understand risk in a way that enables them to judge which risks to take and which to decline - can determine its success. Much is at stake.

This article proposes that systems thinking can help companies to better understand the phenomenon of risk decision-making and to see the dynamics that surround it in a way that will help them establish more effective risk management practices. We will use as our context, risk decision-making in the clinical supplies process.

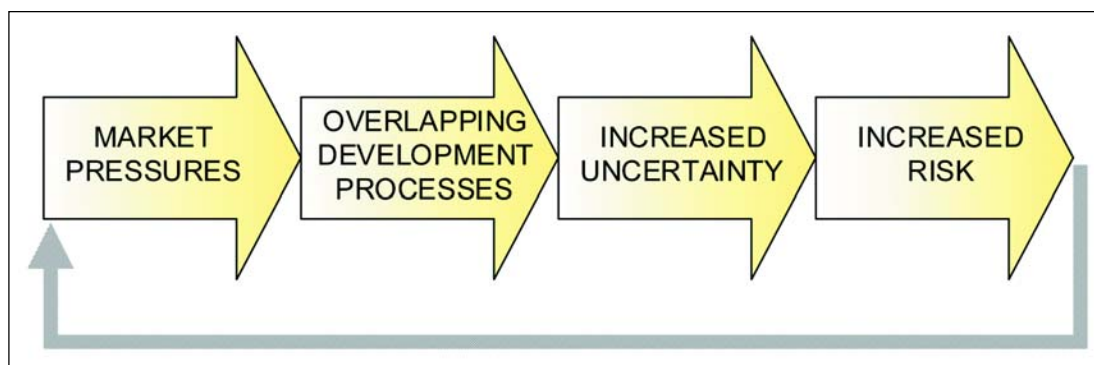
Introducing Systems Thinking

Systems thinking is a way of examining the world, of shaping and focusing how we perceive and analyze phenomena. A systems approach looks outward for wholes rather than inward for constituents. "Wholes" are of interest because they reveal properties, called emergent properties, which are not apparent when one examines only component parts. For example, wetness is a property of water as a whole, and one which we would overlook if we only examined the hydrogen and oxygen atoms of which water is comprised.^{1,2}

Systems thinking also concentrates on dynamic relationships rather than static properties. It seeks explanations in the associations among elements, how they connect to and affect each other, rather than how they are constituted individually. There is a temporal aspect to systems thinking, which seeks patterns recurring over time. It is a "framework for seeing interrelationships rather than things, for seeing patterns of change rather than static snapshots."³

The systems approach is distinguished from the Cartesian, or reductionist paradigm, in which a complex phenomenon is understood by analysis of its parts at increasingly smaller levels. The Cartesian approach is often illustrated by Descartes's clockworks. To predict the movement of the clock hands we look internal to the clock, at the motion of its gears and levers. Inside we see one gear driving the next, teeth slotting and releasing in steady motion, the same orderly

Figure 1. Market dynamics and risk.



sequence driving a predictable march of hands around the face. Descartes believed any problem could likewise be understood by isolating its elements and explaining the complex by finding simple, rule-driven origins.^{4,5}

Descartes saw in the machine-like functioning of the clock-works a representation of biological systems as well. This metaphor found a modern-day home in early artificial intelligence efforts. Scientists attempted to endow computers with the human capacity for decision-making by breaking expert knowledge into its component parts, feeding a set of logical rules into machines, and running them through their paces at high speed. However, the information processing model for intelligence could not replicate the decision-making capability of human experts. Studies of experts such as chess masters or senior Air Force pilots showed that they act not by high speed processing of rules, but by absorbing and responding to patterns and situations holistically and intuitively, without decomposition.⁵

This discussion of the various merits of systems thinking should not be interpreted as an abandonment of Cartesian logic. Gears go a long way toward explaining the workings of a clock. Decomposition of knowledge into rules may not explain the behavior of expert pilots, but it does provide a basis for training novices; it may not allow you to defeat a chess master, but it will allow you to compete with players of advanced skill.⁵ The intent of this article is not to discredit Cartesian logic, but rather to introduce systems thinking as a new and relatively unexplored means of gaining new understanding.

What does it mean, then, to examine risk decision-making from a systems point of view? It means that our unit of analysis is not the single risk decision decomposed into the details of how it is made, but aggregates of decisions over time or across programs, to see patterns or trends. Our attention is focused not on individual decision-makers, but on the relationships among decision-makers, or between individuals and the teams, departments, and companies of which they are a part. Our emphasis is not on isolated decision-making influences, e.g., loss aversion or risk aversion, but on the interplay among them or the effect of the organizational environment upon them.

Defining Risk Systemically

In the literature, risk is defined in a variety of ways. Among these are “the potential for adverse impact of areas of uncertainty on a decision or action path,”⁶ “the possibility that something will go wrong to prevent - directly or indirectly - the achievement of specific business objectives,”⁷ “the possibility of loss, injury, disadvantage, or destruction,”⁸ or simply “performance variance.” Most risk definitions share two common themes. One is that risk occurs under conditions of uncertainty, when we make decisions or are placed in situations whose outcomes are unpredictable. The second is that risk is often perceived as negative, the possibility that something will go wrong. Most definitions contain a reference to an undesirable outcome: “adverse impact,” “loss, injury, disadvantage, or destruction,” “negative variation.”

Managers generally associate risk with negative outcomes.⁹ This assertion is supported, but only partially, by a series of discussions with members of clinical supplies departments. Asked how they would define risk if they had to devise a definition of their own, five out of six respondents included in their definitions negative terms such as “danger,” “hazard,” “failure,” and “things going wrong.” Three saw benefits to risk taking as well, and expressed this as “no risk, no gain,” “in

doing this, we may find a better way to do things,” and “risk is knowledgeably trying to leverage something for a gain.” One definition was neutral. No one described risk entirely in terms which were positive. In this small, informal sample, the most common response to risk was negative, but half the participants recognized a positive dimension as well.

A systems view of risk encourages us to consider the “whole” of risk dynamics, both the threat of failure or loss and the opportunity for gain. Otherwise, we’re seeing just one side of a two-sided coin. The second side offers an opportunity for distinction, and according to Jarrett, “exceptional rewards for exceptional wisdom in understanding and characterizing uncertainty, and exceptional creativity in accommodating, overcoming, or mitigating potential adversity.”⁶

Linguistically, the term “risk” is in fact negative. We talk about the risk of a plane crash or a project exceeding budget. We don’t speak of the risk that the plane will take off on time or that the project will be completed according to plan. Strictly speaking, risk *is* the potential for an adverse outcome in a situation under uncertainty. However, the result of risk-taking can be either an adverse outcome or a benefit. The duality of risk is an emergent property which arises from taking a more holistic view.

Examples within the clinical supplies process illustrate how both opportunity and threat play into decisions at risk. A clinical supplies group may decide to manufacture a large quantity of drug for a series of studies, betting that all the studies will use the same drug. They take this risk because it presents the opportunity to take drug manufacturing off the project’s critical path, and to realize economies of scale. However, should the study requirements change, they will have wasted time and money to manufacture drug product that is subsequently destroyed. Similarly, a clinical supplies group may decide to print labels prior to obtaining formal approval of foreign language translations. They may want to do this because the translation review process is lengthy and they are fairly confident that their translation is correct. However, if the translation turns out to be inaccurate and changes must be made, the group will have to reprint all the labels, losing time in the long run.

Systems thinking also directs us to consider the context in which risk decision-making occurs. It encourages us to look outside the individual risk decisions to the surrounding company and industry environments in order to understand the larger dynamics that affect risk decisions. In the clinical supplies process, we can better understand risk by looking outward to pharmaceutical market forces.

The pharmaceutical marketplace is competitive, and one of the ways in which drug companies gain advantage is to be first on the market, or early to market with an innovative drug. The company that can pare R&D cycle time down from the dozen or so years it currently takes carves for itself a competitive edge. In recent years, most companies have examined and realigned their development processes for greater efficiency. In many cases, they have found that parallel or overlapping processes will achieve new product introduction faster than activities conducted in serial.

However, a consequence of overlapping processes is to increase uncertainty. Study B may be initiated before the results of its predecessor, Study A, are finalized, and without the helpful information that Study A would provide. Or, as described above, Activity B (printing labels) may be initiated before Activity A (foreign language approval) is complete. With these types of increasing uncertainty comes increased risk.

Figure 1 illustrates the relationships between market dynamics and risk. This is, of course, just one of many systems perspectives that can be taken. However, it highlights for pharmaceutical managers that given the context of the marketplace, risk is inevitable. A systems point of view argues that rather than attempting to avoid risk, managers should concentrate their energies on understanding it and leveraging it to their advantage.

Decision-Making Myopia and Risk Burden

Risk decision-makers often exhibit a characteristic called "myopia."^{10,11} Myopia is typified by a narrow framing of risk decisions and a narrow framing of risk outcomes. The myopic decision-maker considers decisions one at a time, neglecting the statistics of past experience, and overlooking the opportunity to consider a current decision as one of a pool of similar decisions to be made now and in the future. Since statistical aggregation works to mitigate relative risk,¹⁰ a myopic decision-maker will exhibit overly cautious attitudes toward risk. The myopic decision-maker also will evaluate her gains and losses frequently. This concentration on short-term rather than total payoff increases the probability that she will observe a loss and also creates a tendency toward risk-averse decisions. The result of myopia tends to be short-term decision-making rather than long-term policy formation.¹¹

Myopia in general does not produce good decision-making, yet it may well be a general feature of human cognition.¹¹ Myopia also works counter to systems thinking. A systems perspective would examine aggregates rather than individual decisions, and would evaluate success or failure broadly over time, rather than on a one-by-one basis.

Features of the environment can either reinforce myopia or discourage it.¹¹ We would expect that a clinical supplies organization which tracks risk decision-making over time to provide its employees with an aggregate view, and which develops databases and tools for broad-based risk analysis, is more likely to mitigate the effects of myopia than one which leaves employees to their individual means of making decisions. Managers who bring groups of employees together for discussions of past and prospective risks, who develop a shared understanding of risk tolerance and jointly agree upon risk policies also may be able to help employees to take the broader view.

An organization which neglects to provide employees with adequate policies, procedures, and tools for managing risk may not only allow decision-making myopia to dominate, but also may place a disproportionate share of the risk burden on the shoulders of the individual employees. Clearly stated risk policies and procedures, and well-established tools for risk analysis provide the employee with a basis for making decisions which transcend her individual assessments and her personal risk tolerance. With guidance, decisions can reflect the composite values, tolerances, and needs of the organization, and a losing bet is a shared loss. On the other hand, an organization which places no policies, procedures, or tools at the disposal of the employee leaves her with none but her own means to make risk decisions, and isolates her should her decision result in a loss.

As an illustration, if I ask an employee to make a bet on a coin toss on behalf of his organization and provide him with no guiding organizational policy, he will make this bet on the basis of his own risk assessments and tolerance. Should he lose the bet, it is fully his loss. If I ask an employee to make a bet

on a coin toss on behalf of his organization, and that organization has a policy of accepting all risks with a 70% or greater probability of winning, the employee has at his disposal the larger scope of considerations that the organization has presumably factored into its policy. Should he lose the bet, he not only has an organizational partner with whom to share the loss, but may still "win" in terms of his contribution to aggregate or long-term results.

In a clinical supplies context, the individual clinical supplies project manager who is faced with a decision, for example, whether or not to pre-package a large quantity of drug supplies, and is left to her own risk tendencies without organizational guidance, may make a myopic or overly risk-averse decision. On the other hand, if she has the benefit of tools which have tracked the success of "brite stocking" over time, she will be more likely to factor statistical probabilities into her decision; if R&D has an established practice whereby decisions of this type are made in a team setting, with shared team accountability, she may be better able to consider a scope of risks and benefits beyond her own; if the company has a policy which rewards contributions to aggregate risk performance rather than single outcomes, she is more likely to perceive this decision as one in a pool of many; and if the clinical supplies department has a forum and language for open discussion of risk, she is more likely to understand and rely on not just her own, but her department's tolerance for this type of risk-taking. A systems viewpoint encourages companies to provide broad organizational supports which may mitigate the tendency toward decision-making myopia, and better share the burden of risk decision-making between the individual and the organization.

A Cybernetic View

Cybernetics is defined by Weiner¹² as "the entire field of control and communication theory, whether in the machine or in the animal." The cybernetic view is concerned with interrelationships rather than the properties of the individual actors, consistent with the systems viewpoint. Central to cybernetics is the concept of feedback. Feedback is a "circularity of action"¹³ which exists between parts of a dynamic system - *Figure 2a*. Simply put, A affects B. B then reciprocally affects A and changes A, which in turn continues the cycle by again affecting B, but in a modified way.

Circularity of action underlies clinical supplies risk decision-making in a number of ways. Two examples will be discussed. The first applies to the dynamics of group decision-making. In the clinical supplies process, risk decisions can be made unilaterally by an individual such as the clinical supplies project leader, or they can be made jointly with other parties such as the medical representative or the project team. The advantage of unilateral decision-making is that it is fast. However, joint decision-making has the advantages of bringing diverse opinions to bear, exposing the issue to debate, drawing on a larger base of knowledge, and gaining joint commitment to a course of action and its potential consequences. Further, when parties participate in joint decision-making, they have the opportunity to affect and change each other in a reciprocal way. Debate (if it is effective) will likely involve an exchange of information on each other's processes, resulting in co-education. If the medical representative learns more about the clinical supplies process, he will likely approach the next interaction differently, more knowledgeably - *Figure 2b*. We can envision the exchange between the parties

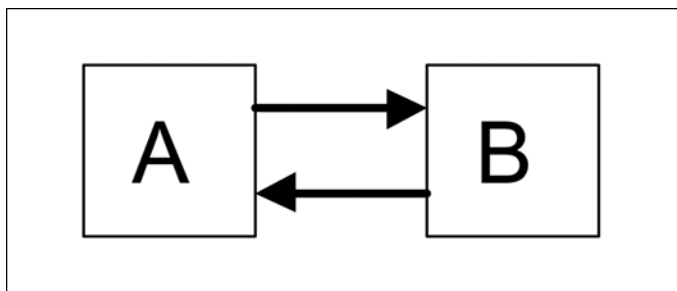


Figure 2a. Circularity of action.

creating a positive cycle of increasing familiarity, and one hopes, openness, and trust. However, the cycle could work destructively as well, where withholding information or uncooperative behaviors creates a cold war type build-up of mistrust and defensiveness.

A cybernetic view can be combined with the concept of “appreciative settings” to help us understand the reciprocal relationships between organizational policies and individual risk behavior. “Appreciative settings” consist of what we notice, our norms, and the comparison we make between the two. Based on our past experiences, we have standards or norms which define for us that which is acceptable or good, and distinguish it from what is unacceptable or bad. These standards or norms affect what we notice; our attention is more readily drawn to those features of a situation which are relevant to evaluation against the norm. Once we act, the outcomes of our behavior may modify the norms, changing the way that future situations are evaluated.^{2,14}

We can theorize how risk decision-making would operate on the basis of appreciative settings. Individuals have past experiences and a host of factors which influence the risks they are willing to take and those they are not, i.e., their risk tolerance. A given situation will be evaluated on the basis of noticed and relevant facts. These are then compared to the acceptable standard (risk tolerance) to arrive at a decision.

Risk evaluation occurs, consciously or unconsciously, whether management chooses to frame it and control it or not. The question is whether the noticed facts are those which produce the optimal risk decision for the company and whether the norms and standards against which the individual makes her judgment are the shared or most effective ones for the company as a whole. If management wishes to control decision-making behaviors so that the best outcomes for the company are produced, it must provide instructions or constraints some-

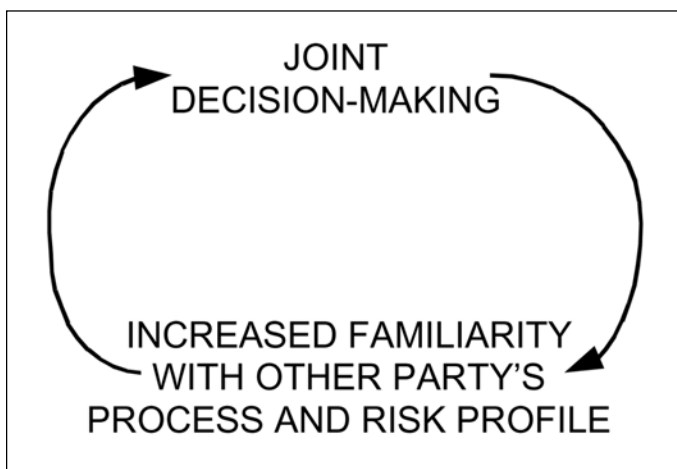


Figure 2b. Circularity of action in risk decision making.

where in the decision-making environment.

One way in which instructions and constraints can be provided in the clinical supplies process is shown in Figure 3. When posed with a risk decision, the decision-maker considers the risk policies, procedures, and tools which are available. These affect the noticed facts. For example, a policy may require that an individual investigate certain government regulations or consider effects on human health. Cultural norms also would play a role by affecting noticed facts and inferring the standard for acceptable risk tolerance. A decision is made and it has an outcome. The decision and its outcome provide situational experience. In the clinical supplies process, few decisions are made under the exact same set of circumstances. Variation arises from differences in the experimental compound, the study design, the regulatory climate, the therapeutic area under study, the personalities of the project team members, and almost a limitless number of sources. Therefore, each risk decision provides experience for the collective knowledge base, but this information must be understood in terms of its surrounding circumstances.

The next step, evaluation, is key to establishing a cycle within which management can provide instructions or constraints, and continually adapt to new knowledge or changing environmental conditions. An evaluation provides the opportunity to bring certain facts to the forefront and make them part of the noticed constellation. For example, an evaluation can ask whether a decision was reasonable in light of past statistical performance. This communicates or reinforces the instruction that past statistical performance is an organizational standard and should be used to qualify future decisions. The evaluation also can take situational experience and use it to further interpret and clarify existing policies and practices. Changing environmental conditions or situations not previously encountered can provide the basis to modify existing policies and practices, or to challenge existing cultural norms.

Managers can use the evaluation to establish or reinforce standards of risk tolerance, particularly those which are difficult to quantify and for which a tacit understanding is the only - or perhaps the best - type that can be obtained. Because clinical supplies risk decisions are characterized by many variables and tradeoffs which are difficult to quantify, it is often fruitless to try to prescribe exact boundaries on risk tolerance. Should a decision-maker tolerate a 25% chance that pre-printed labels will be inaccurate to gain a three-day savings in cycle time? What if it were a five-day savings? What if the probability of inaccurate labels were 20%? What if it were a 30% probability that the labels would be inaccurate, but not in a way that affected study outcome or patient health? A well-established cultural understanding of acceptable risk is often preferable to an attempt to circumscribe every possible combination with a risk policy or practice.

As shown in Figure 3, the results of the evaluation affect the existing risk policies, practices, tools, and culture, which then feed into subsequent risk decision-making, and the cycle continues.

This theory is just one of many different cybernetic relationships which may help managers understand the dynamics of risk decision-making. Other instructive relationships may be found in the context of mutual feedback between industry and individual companies, reciprocal relationships among peer employees, between individuals and teams, and between departments who act as partners in the clinical supplies process.

Seeing Patterns in Chaos

Until relatively recently, science relied on mathematical tools which were for the most part linear, “exact, deterministic equations of motion for simple systems; and the equations of thermodynamics, based on statistical analysis of average quantities for complex systems.”¹⁴ However, nature does not conform to linearity; it is richly complex in ways that classical tools are sometimes at a loss to describe. Over the last several decades, new concepts and techniques have been developed for dealing with highly complex systems. These go by many names, but can be said to fall under the umbrella of “dynamical systems theory.” Chaos theory is one branch of dynamical systems theory.

Dynamical systems theory is a mathematically-based set of concepts and tools which are finding ever-broadening application in fields ranging from biology to economics. But can dynamical systems theory help us better understand social systems, such as those which surround risk decision-making in the clinical supplies process? The expectation is not that we will start predicting human behavior by means of mathematical equations, but perhaps there is something in the concepts or visual images of dynamical systems theory that will strike a chord as well for social dynamics.

According to Daneke, chaos is defined as a “dynamical system exhibiting aperiodic behavior. While appearing to be random, its behavior is deterministic.”¹⁵ A chaotic system appears to have no rhyme or reason to the eye that is seeking dependably recurrent behavior. The agitation of boiling water, the shifting of weather patterns, the march of waves on the ocean - they have no strict regularity and yet they have pattern. Similarly, the clinical supplies process may feel unstable, like it is constantly being blown by the winds of changing circumstances. Study designs are recast, new shipping rules appear, and recruitment rates accelerate or peter off in ways that seem to defy any rational planning. However, if we are attuned to chaos, we may be able to see patterns where we would otherwise have written off behavior as random and not worthy of our attention.

Aperiodic behavior yet stability, non-equilibrium yet order. These are conditions which may at first seem contradictory yet in complex systems they are regular companions. Clinical supplies risk is a phenomenon which may seem to be governed by forces which are random or factors which are so complex that we cannot envision a way to comprehend them. However, based on the experience of dynamical systems theory, perhaps we should not assume that risk situations which each seem unique have no pattern, or because conditions continue to shift that there is no order. The challenge for clinical supplies managers may be to abandon the quest for predictability and instead develop systems which sense and respond to the patterns of chaos.

First Steps

At a recent ISPE conference, representatives from clinical supplies organizations gathered to talk about their experiences managing risk. The group’s consensus was that clinical supplies departments were at the beginning stages of understanding risk and establishing formal risk management programs. A systems perspective argues that as companies approach the question of how to manage risk, they take a holistic view. In doing so, they should see risk as not just a threat, but an opportunity as well, and a lever to use to their advantage. They should head off myopic decision-making and appropriately distribute risk burden by providing policies, practices, and tools that reflect broad risk objectives and serve the

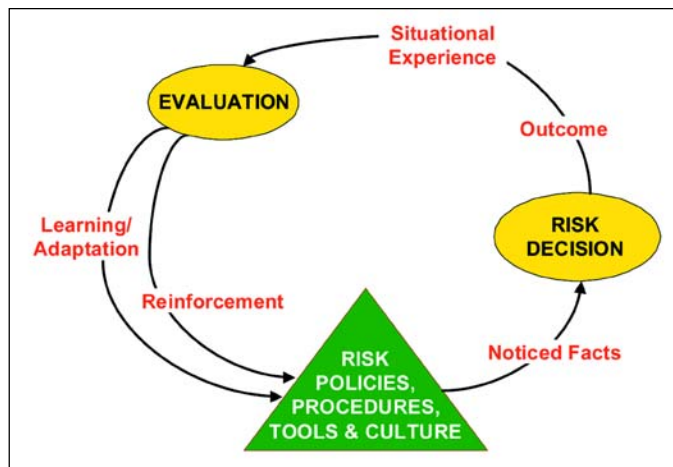


Figure 3. Theorized risk management cycle.

interest of the organization as a whole. They should enable individuals to make both informed and intuitive risk decisions by underpinning formal practices with a shared language and forums for discussion of risk, and a cultural understanding of the risk tolerance in various quarters of the organization. With these foundations, organizations can take decisive steps toward managing the risky business of clinical supplies.

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About the Author



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This article presents a program for planning and executing commissioning.

Commissioning - Key to Project Success

by Don Owings

Introduction

Your plant is built and IQs are finished. What do you do next? OQs? Unfortunately, if that is the plan, you have most likely lost schedule and budget. Why? Well, when the validation team pushes the buttons for the OQ, the system probably won't work. What happens now is that maintenance is called, the validation OQ starts looking like a first grade coloring book, schedule slips, the validation costs are taking an upward trend and the screaming starts. There has been no plan to turn your company's capital investment into what it really needs - product coming out the door and available for sale.

So, what should have been done? Basically, there is a step between the IQ (or the turnover package, or a "mechanically complete" facility) and the completion of the OQ. It is commissioning - *Figure 1*.

Here we will discuss a program for commissioning. This includes both planning and execution. Finally, we will give two examples of commissioning effort - which provide a real world background to commissioning.

Definitions are also important. In this article, OQ refers to demonstrating that the system in question functions in a simulated (usually water and air) process environment. By some definitions, including those of the ISPE Commissioning and Qualification Baseline® Guide,¹ system performance elements are cov-

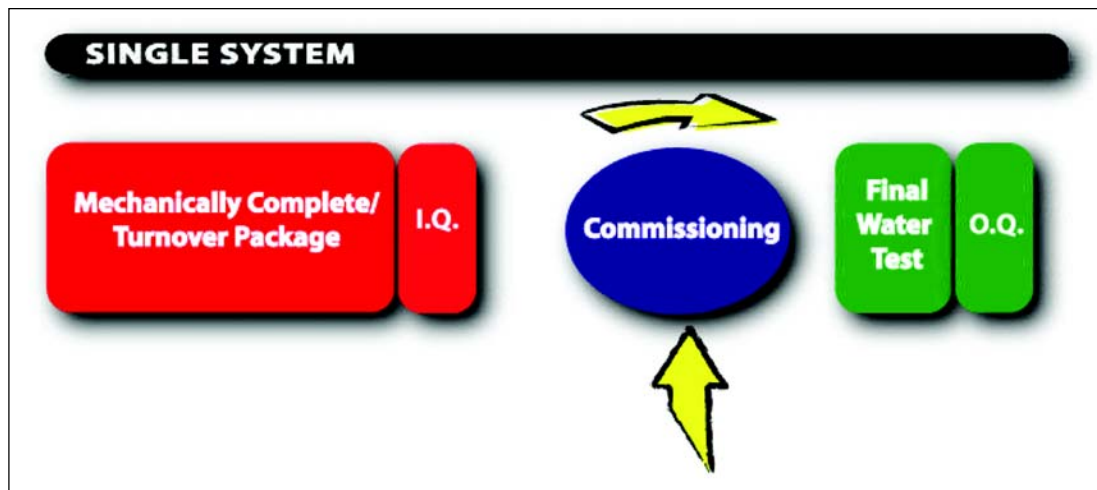
ered in Performance Qualification (PQ). In both example projects, OQ represented the bulk of the work. PQ was only used in the performance of the WFI and the clean steam systems for the biological commissioning project. This article also recognizes Product Validation (PV) to indicate the introduction of product - an activity only indicated here.

What is Commissioning?

Commissioning also has been called start-up or water running. It consists of using water and air to demonstrate that the facility can be run and meet its technical objectives. If this sounds like an OQ, basically it is. The problem is that most facilities do not run like they should when simulated process fluids are introduced. It is easy to ask why, but difficult to explain - except by reference to Murphy's Law (also known as Sod's Law or the Law of Perversity of Nature). As most of us know, it states, "If something is likely to go wrong, it will."

If every element of design were perfect, if everyone understood the processes in infinite detail, if every piece manufactured were what was specified, and if every installer knew the full intent of the drawings he was following, then there is a chance, just a chance, that everything would go well. But, we live in the real world. The design is not perfect; the automation concepts are not fully thought out; and not every piece of equipment is perfectly built. The pro-

Figure 1. Drive commissioning into start-up.



cess descriptions, i.e., the design basis, may not be complete. The installation may look right to someone doing an IQ, but it is possible that the wrong valve has been installed, that the C_v on a control valve is wrong, or that the sanitary steam trap is installed upside down. Indeed, if everything were done perfectly, the costs of the facility would be significantly higher. The point is that things will go wrong.

When they go wrong, neither the construction contractor nor the validation team is ideally trained to take corrective action - that is, to trouble shoot. The construction contractor will pick up the drawings and demonstrate that the system is installed correctly. The validation personnel are there to ensure that the facility is performing as outlined in the OQ protocol. It is not working and their protocols are being filled with evidence that it does not work. In situations like this, most operators will stand around with their hands in their pockets - they too are not trained to trouble shoot problems like this. Nor are your maintenance personnel.

This is where the commissioning team fits. Clearly, people who make up commissioning must understand the unit operations - and the nature of the equipment, which has been designed to perform those unit operations. Typically, these are chemical engineers and occasionally mechanical engineers. Most critically, they are hands-on individuals, with good intuitive skills.

To effectively commission, two elements are required: organization and execution. And, as will continually be stressed in

this article, the commissioning team must understand and use change control to ensure that validation is addressed in their efforts.

How does Commissioning Relate to Validation?

Another way to look at the role of the commissioning team is that its goal is to “whip” the facility into shape once the IQ is finished so that the OQ can go smoothly. So, when the IQ is finished, the commissioning team for that system moves in. They begin testing to ensure that the OQ expectations will be met.

Obviously, for maximum efficiency, the commissioning team should have access to validation OQ protocols. With these, they can fully test the equipment to be sure it performs as expected. They will, as required, take corrective action.

The commissioning team also must be trained in change management. If “corrective action” means changes in any aspect of the design (size of pump, installation of instruments, re-piping, etc.) the appropriate documentation must reflect these changes. Documentation of the reasons will be required. If there are physical changes, the IQ will have to be updated. If, as often happens, the software needs to be tuned or modified, the User Requirement Specification (URS) must be updated.

Finally, communications are important. As an IQ is being finished, the designated team needs to know. And, as a unit or system shows that it is nearing “ready for OQ,” the validation team needs to be informed. In this way, the facility moves efficiently to its real goal: production.

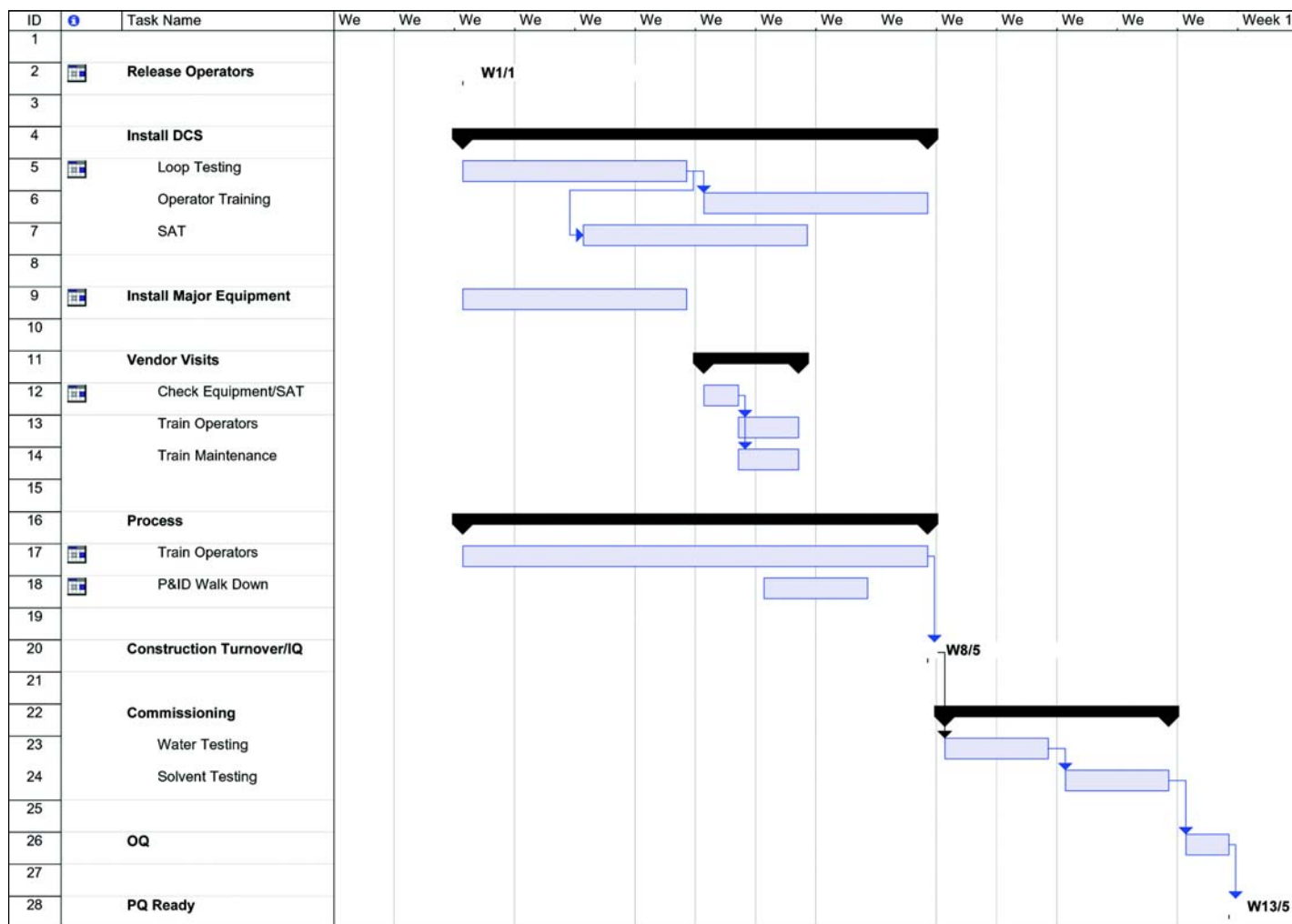


Figure 2. Pre-commissioning/commissioning single system.

Organizing for Commissioning (or Pre-Commissioning)

Commissioning needs to be part of managing the overall project. It should appear in project schedules from the outset. The bones of the plan should be developed as preliminary engineering is being completed. As design is being finished and before construction begins, the commissioning plan should be complete. Otherwise the construction completion program will be flawed and it is possible that the commissioning system delivery needs will not have been adequately addressed. Moreover, this planning effort has two phases: anticipating start-up and execution.

The pre-commissioning plan is easily overlooked. Some of the elements to be considered are:

- Training - operators, maintenance, and the Commissioning Team itself.
- Automation - How are the three groups going to learn how it works? The best approach is a simulation. Will automation be finished in time? Or, are you going to have to do an off line screen familiarization?
- Equipment - How are the three groups going to become familiar with the equipment types and their operation? The best approach is to schedule vendors of critical equipment to give presentations to each group. If possible, this should be scheduled after the unit has arrived on site and been set in place. Part of the presentation can be on site looking at the unit. (The vendor also can inspect the unit and verify that the installation is satisfactory.) Consider having the vendor on site when their piece of equipment is being water tested - and again when product is introduced. (This activity is often written into the purchase order.)
- Installation - How are the groups going to become familiar with locations of all the elements? Walking down the P&IDs in small groups is the best technique. However, this has to be scheduled so that the groups are not stumbling over each other - or worse yet, interfering with construction.
- Spare Parts - What is likely to be consumed during start-up? Will you need spare pumps, filter housings, resin, etc? If they are not there - or readily available - your start-up could be delayed.
- Start-up Materials - What other materials will you need prior to the introduction of product? Will you be using unique materials to simulate a process step? Will you need solvents? Be sure they are there. Over estimate the quantities needed (often, unused materials can be returned if not needed for the process).

As an example, single system, precommissioning/commissioning schedule has been developed from these components - *Figure 2*.

The Commissioning Schedule

Now, having laid the base for the start-up, the next step is to organize it. Use the systems as defined by the validation master plan. The schedule is developed by working from the end point backwards.

The most difficult task is determining how much time to allocate to commissioning each system. Our approach has been

to consider each system and then estimate how long it will take to start it up. We have done this by looking at the complexity of the system, the familiarity of the start-up team with that system. We then polled the team members and developed a best guess.

You can now assemble a start-up plan from the delivery time for the OQ and from the time for start-up. With resource loading, you will be able to fine-tune the information. What this accomplishes is a preliminary plan for IQ completion. An example of the planning from the completion backwards for a three system commissioning is shown in *Figure 3*. In this example, System 2 is seen as being the most complex. Therefore the IQ for this system must be completed before System 1, even though System 1 will see product first.

The next step is to review the construction/IQ completion plan. They probably do not align. If you begin the start-up planning effort early enough, you can work with the construction team to adjust the finishing schedule

Still the task is not finished. Once you know when the commissioning program will begin, you can then develop the schedule for the pre-commissioning activities. Look once again at the required timeframes and then determine when they need to begin. Work backwards from the projected IQ finishing dates. You now have a complete schedule - your path to a smoother OQ- and to an earlier introduction of product.

Organizing the Commissioning Team

The commissioning team needs to be composed of people, who understand the process, understand the equipment, and can think logically - people who can isolate problems and who can take corrective action. The production management will be key. However, start-up is typically a chaotic effort with many activities occurring simultaneously. As a result, there usually are too few people available from the plant management pool. And, sometimes their experience does not cover all types of problems encountered during start-up. Therefore, to ensure the smoothest start-up possible, it will be necessary to augment the local staff.

Two possible internal sources for a start-up staff are: process design personnel and maintenance management. Additionally, some companies, who have significant capital programs, may have a pool of experienced commissioning people they can draw from. Smaller companies may be forced to look outside. Consultants and engineering companies may be able to provide additional support resources.

The operators also will be part of the team, but often as observers. Remember, their role is to operate the plant, not to make it work. Plan on mobilizing selected construction and maintenance personnel to take the corrective action as required. In your planning, also recognize that some members of the commissioning team may be responsible for assisting the introduction of product to the process (PQ). Depending upon the overall plan, their role in product introduction at the front end of a process, may take them away from commissioning the end of the process.

Getting Started

With the preplanning and the formation of the commissioning team, you are ready to begin.

There are four elements to the start of a commissioning program - *Figure 4*:

1. utilities must be available
2. turnover package complete (IQ finished)

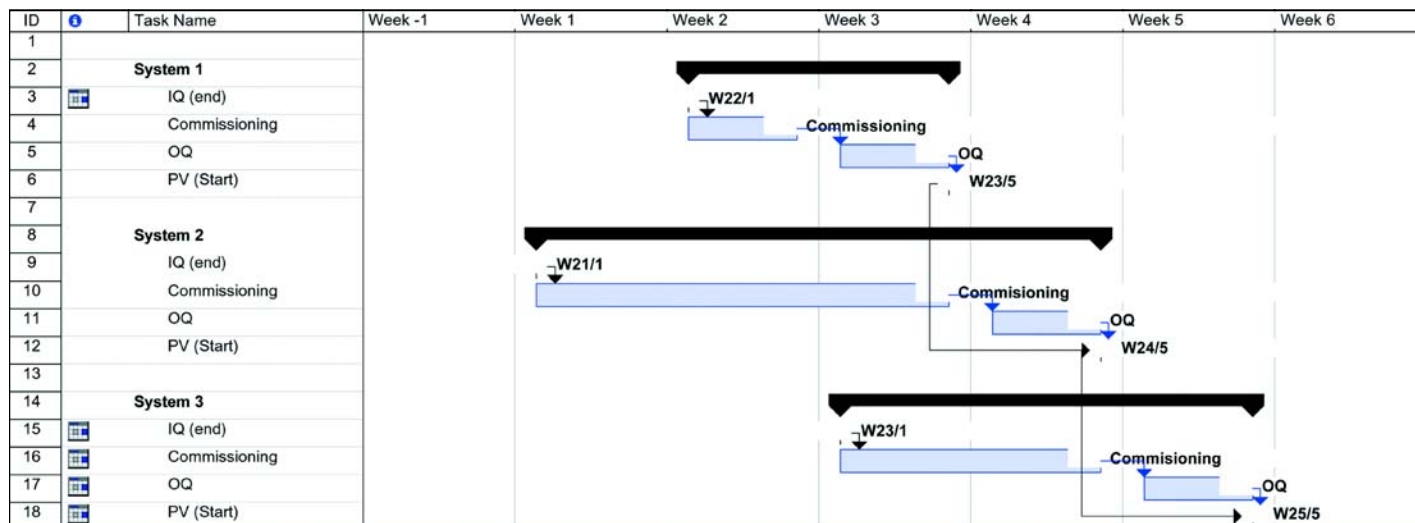


Figure 3. Using PQ and estimated commissioning time to establish construction (IQ).

3. protocols for testing ready (and conforming to the OQ)
4. trained commissioning staff ready

Examples

Centeon - Marburg, Germany

Centeon (now Aventis Behring) decided to update one of their plasma processing facilities. Because of the worldwide shortage, the shutdown, rebuild, and restart of production was critical. Design began in March of 1997. The facility was shut down in late November and the interior was gutted in less than four weeks. Installation of new equipment began as soon as space was cleared.

Centeon's project and senior management both recognized the value of planning the commissioning effort and authorized an outside contractor to work alongside the facilities staff to bring it on stream. The outside contractor was also the design firm. The full process engineering team was offered to work with Centeon. The proposal was accepted.

The facility had four production lines, a clean utility complex, and a CIP system. Installation and start-up of the clean utility complex was the first priority. The RO unit, the WFI unit and the clean steam generator were installed and available for testing in early February. (Construction completion deadlines by production line were established.)

Four teams were created: one for utilities, two, each responsible for two production lines, and one for support equipment (autoclaves, depyrogenation ovens and washers). Each team divided their units into systems, which were in turn divided into subsystems as defined by the automation. A sequence schedule for each was created. Since the utilities had to be up and running before any production line could be started, they received the initial thrust. Next, specific support equipment had to be available before start-up of a process line could begin.

As the team went to work, the problems began to appear - some small, but time consuming, some major. For example, there were problems balancing temperature tempering systems to tight specification. Some errors were discovered in piping. However, the greatest challenge was keeping the construction completion plan coordinated between the different units.

Each subsystem was brought on line in sequence. Although, if a problem requiring reconfiguration of the subsystem developed, the team did advance to the next one. As a subsystem was completed, it was turned over to validation for OQ completion.

In most cases, OQ validation proceeded smoothly although there were some problems with reproducible temperature mapping and further adjustments were required.

Each of the four teams held a daily meeting in their section of the plant. These meetings were held at different times so that the Commissioning Manager and key construction personnel could attend all of them. In addition, separate daily meetings were held with validation and with the Centeon facilities team. There were the inevitable concerns about schedules and budgets. But everyone was aware of the status and of the progress.

The first production line was on stream early in May of 1998 and was approved by European regulatory authorities by the end of the month. All production lines were operational by the end of July. The FDA visit in September of 1998 was satisfactory. The facility was licensed to sell product in the USA.

Confidential Client - European Location

This site produces fine chemicals and provides products to the global market. The specific project related to an expansion of an existing product capability and involved a mix of both new and previously demonstrated technologies. The new installation is highly automated.

While the product does not require validation for either US or European regulatory authorities, the client decided to do so. By following the teachings of validation, it was believed that the new facility would come on stream more cleanly and efficiently.

The commissioning was seen as the link between the IQ and the OQ. It was divided into the two elements: preparation and execution. The primary focus of preparation was the operators. Experienced operators were to be seconded to the new process. Younger operators had to be recruited and trained to replace them. So new operators had to be hired and trained for the existing production train before the experienced individuals were released for training on the new process.

The experienced operators needed to be trained in:

1. the new installation
2. the new equipment
3. the new automation

Organizing the training was a challenge. There were a total of 39 operators. It was felt that the smaller the group, the more effective the training would be - particularly on automation. The following scheme was devised. The operators were divided into three groups of 13 each. Then, each day was divided into three 2 ½ hour sessions. Three classrooms were established - each dedicated to one of the three training issues. In any room, the topic of the day was repeated three times. The operators rotated between rooms so that each group of 13 spent one session in each room.

To train in the installation, the operators went over the P&IDs in the training room. Then, in groups of three, they walked down the P&IDs as the installation was being completed. In addition, key technical staff provided training on the unit operations and the chemistry.

The new equipment sessions often used vendors of key equipment to train the operators. This effort was supplemented by a presentation by the plant technical personnel of the purpose of the equipment and the technology being implemented.

The project was particularly fortunate when it came to automation training. The development of the software was significantly ahead of the installation of the physical plant. It was possible to complete the control room and install the software before construction was completed. This allowed training of the operators in the actual control room. Simulation software was identified to add a level of reality to the exercise.

Additional technical personnel to assist with the start-up had to be identified, released, and made familiar with the processes as well. The maintenance personnel had to learn about the new equipment. The training needs for both of these groups were identified and scheduled.

The next step was to organize start-up itself. The new installation was organized by the automation. There were a number of "systems". Each system was composed of "function blocks" or steps. The sequence of starting up systems was identified. To start-up a system, each step was tested and then the sequence of the function blocks was run, completing the start-up of the system.

At this point, all tests were with water and air. Some were started before the end of construction. However, there were also steps where solvents were used and it was necessary to test them with the solvents and before product was introduced. Scheduling of the overall start-up had to recognize the water testing phase and the solvent testing phases - and to ensure that the solvent testing phase did not begin before the end of construction.

During water testing, lock-out procedures on completed equipment were instituted. Once solvent testing began, additional explosion avoidance procedures were implemented. Solvent testing did not start until all IQs were completed.

The result of this planning, in the client project manager's words, is that "the initial commissioning with water and solvents went very well and generally according to plan."

Conclusion: Organization Pays

Mechanical completion of a new facility is only a step on the path to the ultimate goal - putting product out the door. The two greatest failures that can be made are:

- to focus on incremental steps (engineering, construction, validation) rather than the project as a whole
- to believe that once the IQ was complete, it would be a

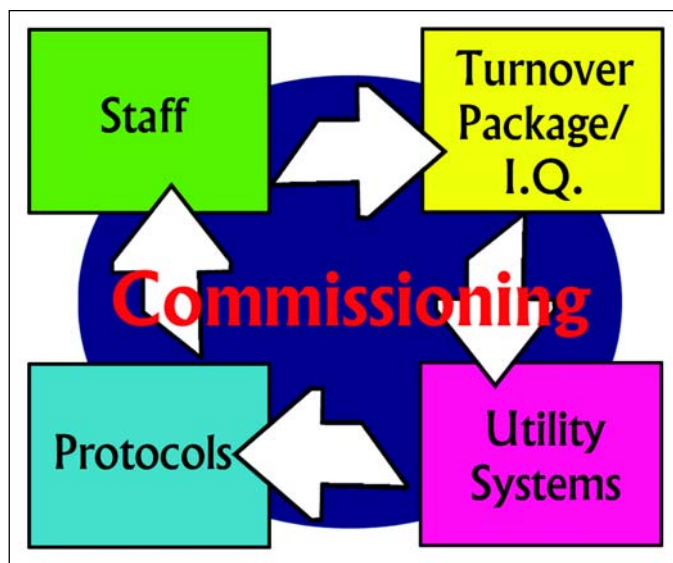


Figure 4. Impacting factors of commissioning.

simple issue for validation to quickly finish the OQ. Unfortunately, most validation people are not there to start-up a facility.

What this article shows is that with proper planning, trained personnel, backed with sufficient resources, speed a project to completion.

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This article presents a case study on the application of S88.01 in the design of a multi-product biotech manufacturing facility, where flexibility, modularity, and cGMP compliance were major objectives.

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Things Go Better with S88: A New Approach to the Engineering Process

by Vince Miller

Introduction

This article presents a case study on developing process control concepts using S88.01 and the Functional Specification as an integral part of the engineering design process. The methodology utilized for this project produces some important advantages over the traditional engineering process. The case study follows the development of a multi-product biotech plant through three phases of design. A brief review of the traditional engineering process and some of its pitfalls will set the stage for this discussion.

The Traditional Engineering Process
The Conceptual Design Phase usually begins with the development of a Process Description

which is a high level overview of the major process steps. Based on this description, Process Block Flow Diagrams are developed to illustrate major unit operations, product flows, and major ingredients. Notes are added to the drawings to describe operations, concepts, and anything else that is not easily illustrated graphically. The client reviews these process design documents and returns comments and corrections as part of a "review-revise-approve" cycle. After final approval, a rough "order of magnitude" estimate is compiled to check the project against budget and expected ROI criteria.

The Preliminary Design Phase begins after the conceptual process design is completed and the feasibility of the project justified. Process

Flow Diagrams (PFDs) are developed based on the Block Flow Diagrams to show major pieces of equipment and material flows. After the PFDs are approved, each unit operation is fleshed out on a Piping and Instrumentation Diagram (P&ID). P&IDs typically show all process connections to and from a vessel, including pipe sizes, instrumentation, and valves. The drawings usually depict a control strategy using ISA symbology, dashed lines, and narrative.

The client reviews the completed design package, and a more accurate cost estimate is prepared at the end of preliminary design based on budgetary equipment costs and material takeoffs. This estimate supports a request for capital project appropriation and verification of the project budgets and timeline. If the project is approved to move forward, the P&IDs and other documents are released for detailed design.

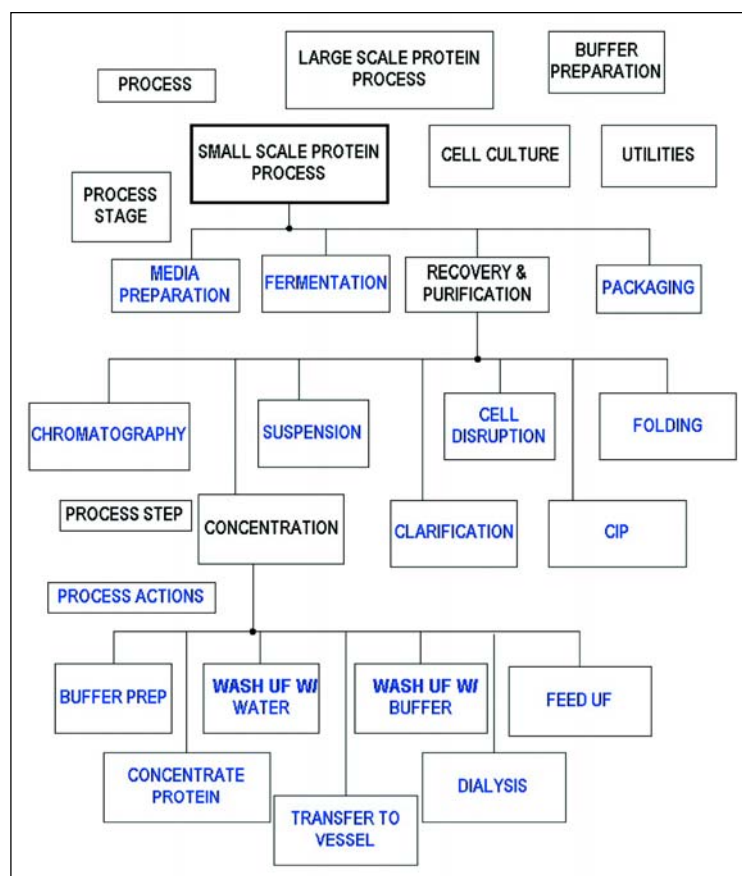


Figure 1. The process model.

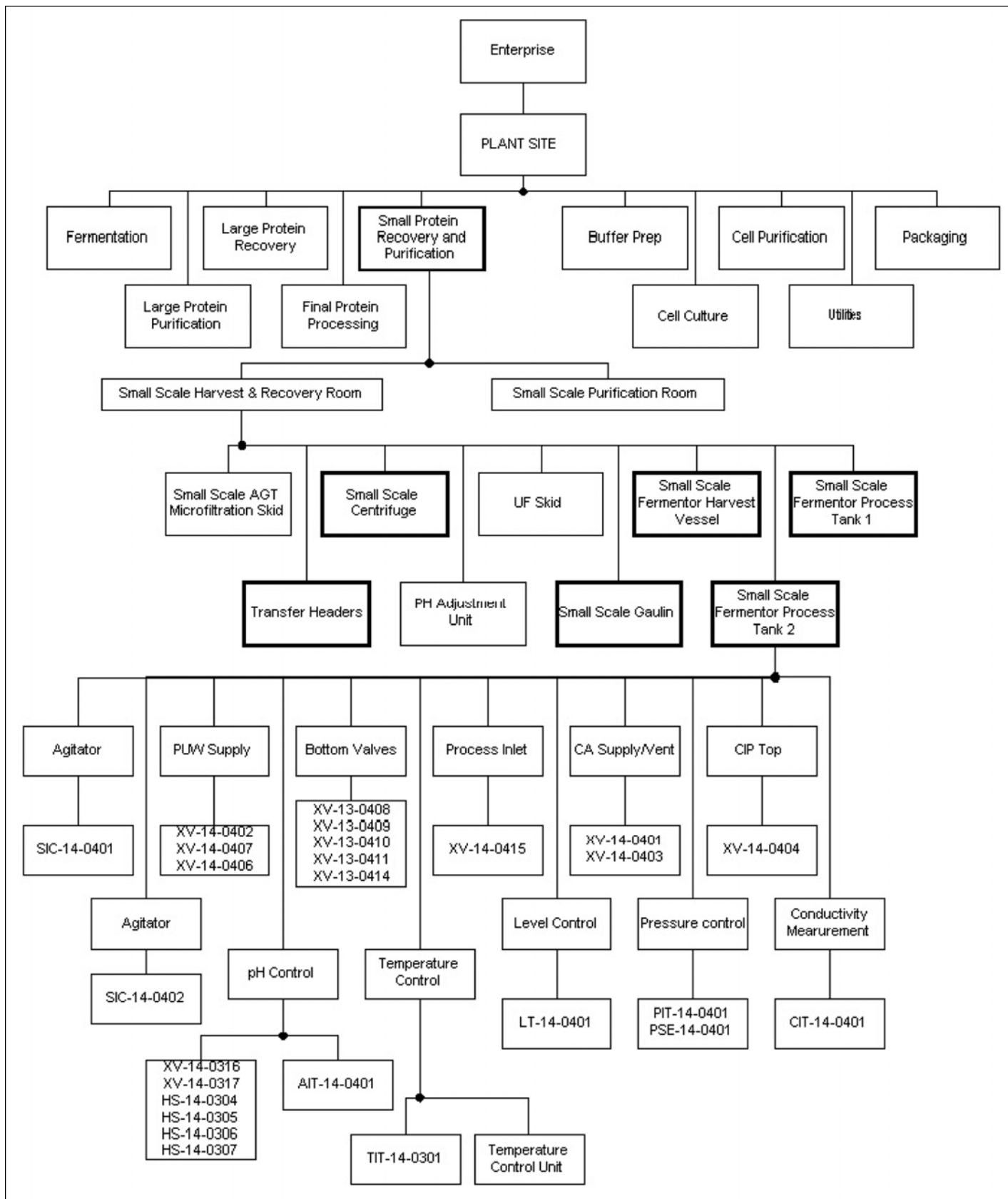


Figure 2. The physical model.

The Detailed Design Phase builds on the preliminary design package. Equipment and instrumentation specifications, instrument index, and loop sheets are started based on informa-

tion derived from the P&IDs. A control system must be selected and the architecture sufficiently understood in order to assign I/O points, develop cable schedules, and design control panels.

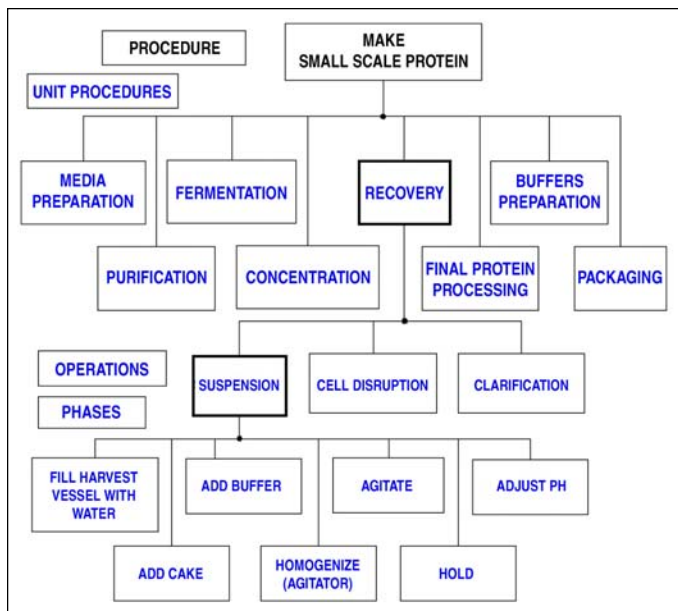


Figure 3. The procedural model.

A control strategy document may be written by the engineering firm, but often this defaults to the client or to a third party systems integrator.

Bid packages are developed and suitable contractors are selected for the construction phase. A construction cost estimate can be developed at the end of detailed design based on contractor bids to confirm that sufficient funds are available to complete the project. Control system hardware and software suppliers and systems integrators are usually selected at this point.

Pitfalls in the Traditional Engineering Process

The Overworked P&ID

Complex batch sequences and control algorithms are difficult to illustrate on P&ID drawings using lines and symbols, especially when there are multiple flow paths and more than one unit operation for each vessel. Tracing dotted lines to understand the control relationships between equipment entities is confusing and cumbersome. CIP and SIP operations

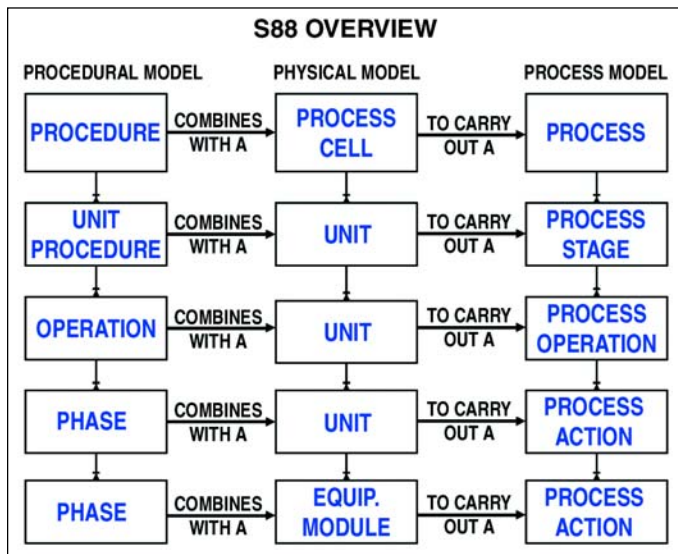


Figure 4. Integrating the models.

controlled as part of a larger system are especially difficult to illustrate effectively.

Imbedding control strategy information on the drawings in the form of valve matrix tables and control notes complicates the management of change strategy and consumes relatively expensive space on the P&ID. CAD machines are not efficient word processors so it is expensive to revise a drawing every time the control strategy is updated during the design development and subsequent review cycles. Maintaining this textual information on the drawings throughout the life cycle is also time consuming and expensive.

ISA symbols, notes, and matrices do not address timing, information management, and operator interaction, nor do they describe an organized approach to the software development task. Eventually, the symbology must be interpreted and documented in a written software specification. With half of the control strategy symbolized on drawings and half narrated in a document, it is almost impossible to avoid at least some duplication of data, which severely complicates the management of change.

Because the P&IDs do not tell the whole story, the design package is approved without a thorough review of the control strategy. Important elements that are missed in the early stages will be more difficult to add later on.

Automation Engineering as an Afterthought

Because of the inadequacies of the P&ID as mentioned above, the automation strategy is not sufficiently documented at the end of preliminary design to accurately understand its complexity and impact on cost and schedule. Yet, the project timeline usually requires the control system to be selected and the software development task to start immediately. In the best of scenarios, the client will insist on approving a written Functional Specification (FS) before allowing software code to be developed. It is sometimes assumed that internal client resources will have time to produce the document. When this doesn't happen, it falls to the systems integrators to develop a specification by interpreting the intent of the process design depicted on the drawings and to fill in the blanks where needed.

This effort requires intensive collaboration with both the client and process designers to rehash what has already been reviewed and approved, which is an expensive duplication of effort. Some of the original architects of the process design may not even be available at this stage. To complicate matters further, gaps may be discovered between the physical capabilities that are already being installed and the desired functionality that has just now become known because the strategy is thoroughly discussed for the first time after the design has been reviewed and released for construction. This results in changes to the physical entities very late with magnified impact to project cost and schedule and less than desirable results for the client.

The problem mushrooms as critical planning and project control steps are inclined to be omitted with no clear software design criteria in place and a shrinking timeline. Additional people may be pulled into the project in order to meet the schedule. Without clear design criteria, each developer uses their individual creativity to achieve the quickest means to an end. The result is usually less than ideal.

Commissioning and Validation Under Pressure

In turn, the lack of documentation and late start turns the commissioning and validation task into a nightmare. The

ripple effect spreads, as test protocols must now be written while the software design is still in flux. It is not wise to expend man-hours to develop protocols to test an undocumented under-developed software design, but on the other hand, the costs of a late start-up are unbearable. Thus, the validation effort starts late and is caught in the critical path all the way to the end.

There is a Better Way!

To avoid these problems, a change in philosophy is required. The FS can no longer be an *optional feature* to be developed as an afterthought. Rather, it must become a critical function of the engineering process; a deliverable no less important than drawings and equipment specifications. The FS must be born during the conceptual design phase to describe the unit operations and design concepts depicted on Block Flow Diagrams. It must continue to grow during the preliminary design phase to describe the equipment functions and control strategies depicted on P&IDs. It reaches maturity during the detailed design phase as every function of every device, from transmitter to algorithm is defined. The FS then lives on, functioning as an important design document to support control system configuration, commissioning, validation, and management of change for the life of the facility.

The following describes how this approach was utilized in the design of a multi-product biotech manufacturing plant where flexibility, modularity, time to market, and cGMP compliance were major objectives. The models and terminology described in ANSI/ISA S88.01 are a crucial element of this methodology; providing a framework on which to organize and develop batch control concepts on drawings and in the FS from birth to maturity, and beyond.

Using S88 and the FS in the Design Process Educating the Engineer and the Customer

It should come as no surprise that an understanding of S88 is not a major concern of most process engineers. After all, it is a batch control standard, and controls are specified by *someone else*. Even the I&C engineers in traditional engineering firms have had very little exposure to S88, because in the traditional approach, the control strategy is developed by *someone else*. Unless a new approach is taken, the clients of traditional engineering firms are going to take their business to *...someone else!* It is critical that lead engineers in these disciplines understand that good automation practices must be designed in, and the earlier the better. When given the opportunity, the process engineers and control systems engineers involved with this project were very receptive to learning more about S88 because it provided a way to simplify a very complex task into manageable, and understandable pieces. The process also resulted in a very satisfied customer.

However, the customer must be sold on this idea as well; not knowing that there is a better way and that the pitfalls of the traditional engineering process can be avoided. Project leaders on the client's side do not always feel the pain felt by those managing the automation and validation portions of the project, as they wait for information while the timeline shrinks. They may not understand that the process control strategy must be tightly coupled to the process facility design. They must be told that the responsibility to develop and document that strategy must be shifted from "*someone else*" to those who are developing the process design, and the start time must be shifted from later...to now!

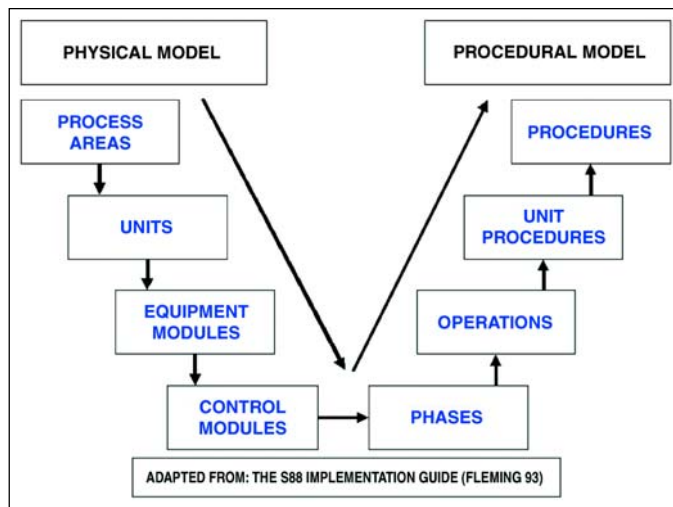


Figure 5. The modularization process.

S88 Models Applied

There are many useful models presented in ANSI/ISA S88.01 Batch Control Part 1: Models and Terminology. Those that are particularly applicable during the early phases of design are the Process, Physical, and Procedural Models.

It is assumed that the reader has some knowledge of S88 and has access to that document for reference. Several good resources that provide a more in depth discussion of S88.01 are listed in the References section. The following paragraphs provide a very brief overview of the Process, Physical, and Procedural Models as applied to this project and documented in the FS. Refer to the figures for illustration where noted, however, the collapsible features of the document which allow the reviewer to drill down within the models are better illustrated in an electronic format as part of an interactive presentation.

The Process Model

In the Process Model, the process is broken down into Process Stages, consisting of Process Operations, which contain Process Actions. Relating this model to our example, as illustrated in Figure 1, the major processes are Small Scale Protein, Large Scale Protein, Cell Culture, Buffer Preparation, and Utilities. Drilling down within the Small Scale Protein Process, the Process Stages are Media Preparation, Fermentation, Recovery and Purification, and Packaging. Within the Recovery and Purification Process Stage, the Process Steps are Suspension, Cell Disruption, Clarification, Folding, Chromatography, Concentration, and CIP. Within the Concentration Process Step, the Process Actions are Buffer Prep, Wash UF with Water, Wash UF with Buffer, Feed UF, Concentrate Protein, Dialysis, and Transfer to Vessel. Each of the other Processes can be similarly broken down into Process Stages, Process Steps, and Process Actions.

The Physical Model

To construct the Physical Model, physical entities within the enterprise are organized according to Sites, which contain Process Areas, Process Cells, and Units, which in turn consist of Equipment Modules and Control Modules. For this example, as illustrated in Figure 2, the Site contains nine Process Areas: Fermentation, Large Protein Recovery, Large Protein Purification, Small Protein Recovery and Purification, Final Protein

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During the early stages, similarities in design entities are identified and exploited to create standard entities, or objects, with a set of common attributes to provide capabilities to perform a given function.

”

Processing, Buffer Prep, Cell Culture, Cell Culture Purification, Packaging, and Utilities. Within each Process Area, there are Process Cells, Units, Equipment Modules, and Control Modules. For example, Process Cells within Small Protein Recovery and Purification are “Small Scale Harvest and Recovery” and “Small Scale Purification.” Drilling down further, Figure 2 illustrates the Equipment Modules within the Small Scale Fermentor Process Tank 2.

The Procedural Model

According to the **Procedural Model**, a **Procedure** consists of **Unit Procedures**, **Operations**, and **Phases**. Figure 3 illustrates the Procedure “Make Small Scale Protein” which consists of Unit Procedures: Media Preparation, Fermentation, Recovery, Buffer Preparation, Purification, Concentration, Final Processing, and Packaging. Operations within the Recovery procedure are Suspension, Cell Disruption, and Clarification. The Phases within the Suspension Operation are Fill Vessel with Water, Add Buffer, Agitate, Adjust PH, Add Cake, Homogenize, and Hold.

Integrating the Models

Figure 4 shows how the three models are interrelated to form a complete system. The engineering process develops a design, which implements the process technology at the desired scale

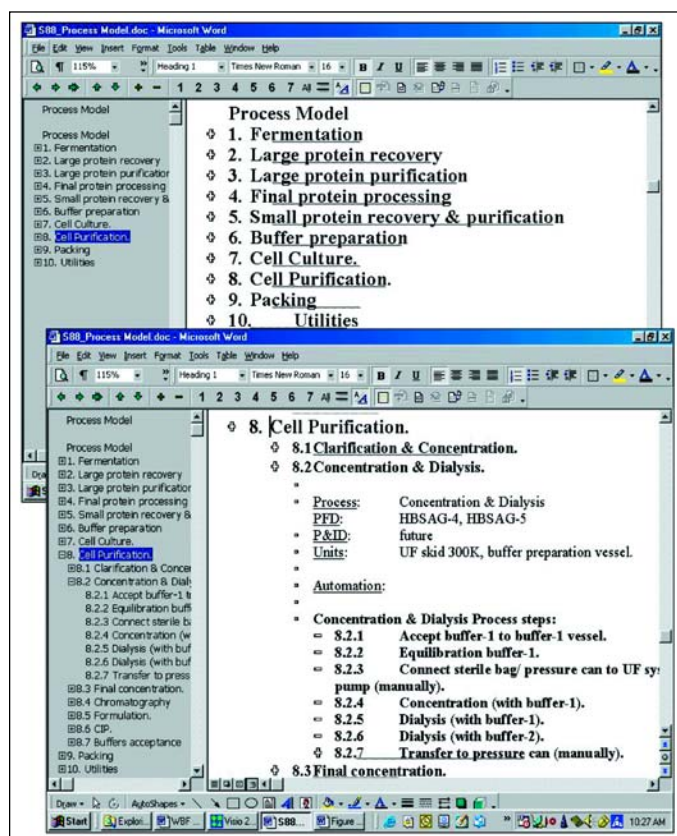


Figure 6. Block Flow Diagram description in the FS.

through the physical and procedural models. The Physical Model is constructed from the top down and it documents the fundamental physical capabilities of the equipment, piping, and controls. Then, using the basic functional capabilities of equipment modules and control modules as building blocks, the procedural model is built from the bottom up. Figure 5 illustrates the modularization process.

Modules, Standards, Objects, and Aliases

Using the S88 structure in the FS, leads the engineering process toward a modular, object-oriented design. During the early stages, similarities in design entities are identified and exploited to create standard entities, or objects, with a set of common attributes to provide capabilities to perform a given function. These concepts will be developed throughout the design process and exploited throughout the life cycle of the facility.

With an understanding of this new approach established, the engineering process can now be traced through the Conceptual, Preliminary, and Detailed Design phases of the project.

S88 and the FS in Conceptual Design

During conceptual design, the Process Model is typically developed down to the unit Process Actions level only, as depicted on the process Block Flow Diagrams. The FS is constructed using the Outline and Document Map view so that its structure can mimic the expandable features of the S88 Process Model. Figure 6 shows the high level outline of the FS at this stage with a section for each of the major Process Stages. Within each process section, the process stages and process operations depicted on the Block Flows are listed and described. Figure 6 illustrates how the outline is expanded to describe the Cell Purification section of the Block Flow Diagram.

The S88 Functional Specification: A New Conceptual Design Deliverable

The expandable/collapsible features of the FS make it a valuable illustration tool when the conceptual design package is presented to the client for review. This allows a very detailed review of the process design and process automation concepts, which serves as an early checkpoint to ensure that the design is on track to meet the needs of the customer. Once reviewed and approved, the models described in the FS can be fleshed out as the design process continues in the preliminary design phase.

S88 and the FS in Preliminary Design

During preliminary design, the approved Block Flow Diagrams give way to Process Flow Diagrams (PFDs), which show major process steps, material flows, and major pieces of equipment. In order to meet the goal for a flexible, multi-product facility, care is taken throughout the design process to ensure that the physical capabilities developed in the equipment are separated from the recipe requirements of any single product.

As the process design is developed in the PFDs, the Physical and Procedural Models are documented in the Functional

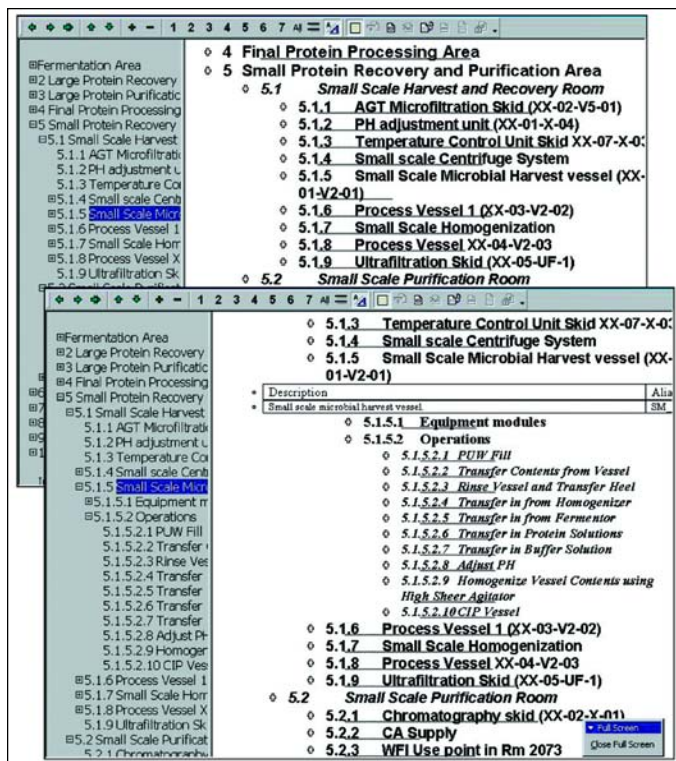


Figure 7. PFD description in the FS.

Specification (FS) down to the Units level. Figure 7 provides an illustration of this process using the Small Protein Purification and Recovery Area, which contains the Unit, Small Scale Microbial Harvest Vessel as shown on the PFD.

As the PFDs give way to P&IDs, valves, pumps, instrumentation, and other equipment associated with each unit are grouped logically into Equipment Modules and Control Modules assigned to the Units already defined. Figure 8 provides an illustration of how the physical entities depicted on the P&ID are documented in the Physical Model in the FS. The capabilities of Equipment and Control Modules are described in detail in the appropriate sections. These capabilities will become the basic building blocks for Operations and Unit Procedures in the Procedural Model.

S88 Structure in the Functional Specification Document

The FS is prepared using the “outline mode” and the “master document view” in order to mimic the collapsible and modular features of the S88 models. This structure allows the FS to be continually updated as a work-in-progress in order to provide documentation as the concepts are developed and illustrated on the PFDs and P&IDs. In this format, the FS is complementary to the drawings by providing an easily understandable description of the strategy for process control, as well as general performance specifications and system architecture.

Because the FS begins life in the early stages of the project, opportunities for modularization and standardization can be identified and developed. For example, if one basic vessel configuration can be developed, time and money will be saved in equipment specifications, control strategy design, software development, and validation. Documenting the standards in the FS provides a model for the entire project team to follow. Figure 9 is an excerpt from the Specifications and Definitions Section of the FS, which illustrates how standard module classes can be documented along with other design features of

the process control strategy.

S88 Leads to an Object Oriented Design

The S88 methodology helps to highlight opportunities for modularity and standardization and therefore leads naturally to an object oriented design. Standard valve, instrumentation, and equipment configurations, can be grouped into Equipment Module classes, each with a common set of attributes. As design proceeds, the number of unique classes (equipment or control module types) is minimized by using standard configurations where possible. Unique names are assigned to each class and listed in a concordance, as illustrated in Table A.

These standard classes are described in the Specifications and Definitions Section of the FS (Figure 9). Efficiency is gained when the specification for each class is written once and referenced throughout the Physical and Procedural Models. The “write once use often” philosophy also will pay dividends during the development of software applications and validation protocols later in the project. For example, in this project, 2000 field devices and 700 pieces of equipment were grouped into only 50 classes. The “fail-closed on/off valve” [XV01_FC] control module was re-used more than 400 times. The “purified water drop” [PUW_DROP] equipment module was re-used at least 30 times. Unique module classes are easily tracked to each instance in the Physical and Procedural Models by using the Concordance to create an Index of these text strings as they are used in the main body of the FS

Each instance of a module class is easily linked to unique field devices and equipment by using aliases. This feature is illustrated using the equipment module “PUW_DROP” listed in the Concordance of Module Classifications (Table A). Figure 10 illustrates drilling down in the Physical and Procedural Models section of the FS to find an instance of the PUW_DROP equipment module in the Small Scale Microbial Harvest Vessel. The corresponding design details of this module class are found by drilling down within Section I: System Specifications and Definitions. Notice that aliases are assigned to each control module and the text refers the reader to Section 1 for the phase definitions for this standard equipment module.

Aliases are used to associate standard modules to specific equipment numbers or tag numbers as shown on the P&IDs. Therefore, tag numbers and equipment numbers are listed in one place only. This establishes a single point of data transfer from drawing to document, allowing changes to P&IDs to be more quickly incorporated in the FS. Later, during detailed software design, the aliases, rather than tag numbers, are used in phase logic diagrams or sequential function charts so that each entity is completely portable.

The S88 Functional Specification: A New Preliminary Design Deliverable

At the conclusion of Preliminary Design, the level of detail in the FS is sufficient to fully explain the process automation strategy and to support further development of the control system design, as well as the commissioning and validation strategies. The FS supports an in-depth review cycle at this stage of the project. Individual sections can be broken out and reviewed, revised, and approved separately while continuing to be part of a cohesive document. In the electronic format, the FS can be collapsed for a high-level overview or expanded to provide the appropriate level of detail. Users can start at any Process Area level and drill down to greater levels of detail as needed. The S88 structure provides solid linkage between the

- ▣ Fermentation Area
- ▣ 2 Large Protein Recover
- ▣ 3 Large Protein Purifica
- ▣ 4 Final Protein Processir
- ▣ 5 Small Protein Recover
 - ▣ 5.1 **Small Scale Harve**
 - 5.1.1 AGT Microfiltra
 - 5.1.2 PH adjustmen
 - 5.1.3 Temperature C
 - ▣ 5.1.4 Small scale Ce
 - ▣ 5.1.5 Small Scale Mi
 - ▣ 5.1.5.1 Equipment
 - ▣ 5.1.5.1.1 Agitato
 - ▣ 5.1.5.1.2 Agitato
 - ▣ 5.1.5.1.3 Process
 - ▣ 5.1.5.1.4 PUW St
 - ▣ 5.1.5.1.5 CA Sup

- ▣ 5.1 **Small Scale Harvest and Recovery Room**
 - ▣ 5.1.1 AGT Microfiltration Skid (XX-02-V5-01)
 - ▣ 5.1.2 PH adjustment unit (XX-01-X-04)
 - ▣ 5.1.3 Temperature Control Unit Skid XX-07-X-03
 - ▣ 5.1.4 Small scale Centrifuge System
 - ▣ 5.1.5 Small Scale Microbial Harvest vessel (XX-01-V2-01)

Description	Alias	Class
Small scale microbial harvest vessel.	SM_Harvest	Vessel 1

 - ▣ 5.1.5.1 Equipment modules
 - ▣ 5.1.5.1.1 Agitator1 (XX-01-A-01)
 - ▣ 5.1.5.1.2 Agitator 2 (XX-01-A-02)
 - ▣ 5.1.5.1.3 Process Inlet 1
 - ▣ 5.1.5.1.4 PUW Supply
 - ▣ 5.1.5.1.5 CA Supply/Vent
 - ▣ 5.1.5.1.6 PH Control
 - ▣ 5.1.5.1.7 Temperature Control
 - ▣ 5.1.5.1.8 CIP Supply
 - ▣ 5.1.5.1.9 Outlet Valve
 - ▣ 5.1.5.1.10 Pressure Measurement

- ▣ Fermentation Area
- ▣ 2 Large Protein Recover
- ▣ 3 Large Protein Purifica
- ▣ 4 Final Protein Processir
- ▣ 5 Small Protein Recover
 - ▣ 5.1 Small Scale Harve:
 - 5.1.1 AGT Microfiltra
 - 5.1.2 PH adjustmen
 - 5.1.3 Temperature C
 - ▣ 5.1.4 Small scale Ce
 - ▣ 5.1.5 Small Scale Mi
 - ▣ 5.1.5.1 Equipment
 - ▣ 5.1.5.1.1 Agitato
 - ▣ 5.1.5.1.2 Agitato
 - ▣ 5.1.5.1.3 Process
 - ▣ 5.1.5.1.4 PUW St
 - ▣ 5.1.5.1.5 CA Sup
 - ▣ 5.1.5.1.6 PH Cor
 - ▣ 5.1.5.1.7 Tempel
 - 5.1.5.1.7.1 Cor
 - 5.1.5.1.7.2 Pha
 - 5.1.5.1.8 CIP Su
 - 5.1.5.1.9 Outlet
 - 5.1.5.1.10 **Pressu**
 - 5.1.5.1.11 Level
 - 5.1.5.1.12 Condu

- ▣ 5.1.5.1 Equipment modules
 - ▣ 5.1.5.1.1 Agitator1 (XX-01-A-01)
 - ▣ 5.1.5.1.2 Agitator 2 (XX-01-A-02)
 - ▣ 5.1.5.1.3 Process Inlet 1
 - ▣ 5.1.5.1.4 PUW Supply
 - ▣ 5.1.5.1.5 CA Supply/Vent
 - ▣ 5.1.5.1.6 PH Control
 - ▣ 5.1.5.1.7 Temperature Control

Description	Alias	Class
Controls temperature using Temperature control unit.	Temp_ctrl	TIC_Loop3

- ▣ 5.1.5.1.7.1 Control Modules

Tagname	Service	Alias	Class	Parameters
TIC-XX-0101	Temperature control algorithm	TIC1	PID1	Set point, tuning parameters.
TTT-XX-0101	Vessel Temperature Measurement	TEMPPV	TTT1	
- ▣ 5.1.5.1.7.2 Phases

Phases	Alias	Parameters	Description
Initialize	INIT		
Control Temperature	CTRL_to_SP	Formula: set point, tuning parameters. Interlock: TCU in V2-01 phase	
Full Heat	HEAT	Set point, max time	Position valves for full heat mode.
Full Cool	COOL	Set point, max time	Position valves for full cool mode.

Figure 8. Physical model description in the FS, documenting entities on P&ID.

process design depicted on drawings and the control strategy described in the FS. The P&IDs and associated control strategy can be thoroughly reviewed as one package. The collapsible features of the S88 models make it easy to trace the equipment entities depicted on the P&IDs to the corresponding details in FS. This approach produces many advantages, such as:

- The FS provides supporting narrative to P&IDs by describing physical attributes, interrelationships, and complex sequences in a well-organized, readable format.
- System performance specifications contained in the FS reflect the true complexity of the automation strategy to support a comprehensive vendor bid package. Quantities and attributes are tracked using the concordance and index features.

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Because the FS begins life in the early stages of the project, opportunities for modularization and standardization can be identified and developed.

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- The modular structure documented in the FS also can be reflected in the system architecture concept without committing to a particular brand of system before the requirements of the system are fully known. The architecture can be collapsed or expanded to achieve the appropriate level of hardware and software modularity - *Figure 11*.
- The FS serves as a valuable communication tool in presenting the proposed automation concepts to the customer for approval, and to third parties such as system integrators and validation service providers.
- Detailed software design and validation protocol development can begin earlier on the project time line.
- It supports a very effective HAZOPs review because the FS provides a concise explanation of all controls and interlocks.

Thus, the PFDs, P&IDs, and the FS form a cohesive preliminary design package that provides a solid foundation to support forthcoming detailed design activities. The FS supports

the selection of qualified software and hardware vendor(s) and their incorporation into the project team. Potential vendors can be challenged to build a sample Unit module to show how the strategy would be implemented using their system. This test case can be used to compare the features of different systems and to create a benchmark for time and cost estimates. Because the FS contains sufficient detail in the physical and procedural models, it becomes a key communication tool between the process designer and the control system suppliers, integrators, and programmers.

S88 and the FS in Detailed Design

Detailed design activities proceed in much the same manner as in the traditional engineering process, except that with an object oriented S88 design outlined and the control strategy documented in a detailed FS...**things go better**. In fact, things go much better. Many of the pitfalls of the traditional engineering process have been avoided. P&IDs are easier to read and maintain because they are not cluttered with confusing dotted lines, cryptic control notes, and inadequate valve matrices. Details contained in the FS leave no doubt of the designer's intentions.

The automation engineering effort can ramp up quickly with a qualified control system platform selected and a qualified systems integrator on the team. *Nobody* has to wait for *somebody* to write the FS, which makes the job easier for *everybody*! The modular structure of the FS helps to organize the detailed design effort when multiple people need access to the same information. I&C Engineers have solid documentation of instrument ranges and performance criteria to support detailed specifications and vendor bid packages. Control system hardware and software engineers can begin to develop the standard modules and objects with clear performance criteria clearly defined.

The FS Documents Software Design Details

The last piece that must be added to the FS is the detailed software design. A well-planned modular software design must start with well-planned documentation. The S88 structure of the FS provides for the addition of detailed software design information in an organized format, at any level, without impacting the rest of the document. The modular layout supports analysis and further development by multiple people if necessary. This important task can be performed by the engineering firm or the system integrator(s) or both.

Tight timelines and budgets often put a strain on the software design effort and there is ample pressure to cut corners to meet schedule. However, without the detailed software design specifications as a foundation, the validation strategy is on shaky ground because Good Manufacturing Practices mandate that we build what the design documents specify, not vice-versa. To avoid this trap, these tasks must be established on the project timeline at very early planning stages of the project. The S88 FS supports an accurate assessment of the magnitude and complexity of the software design/development task from its birth, during the conceptual design

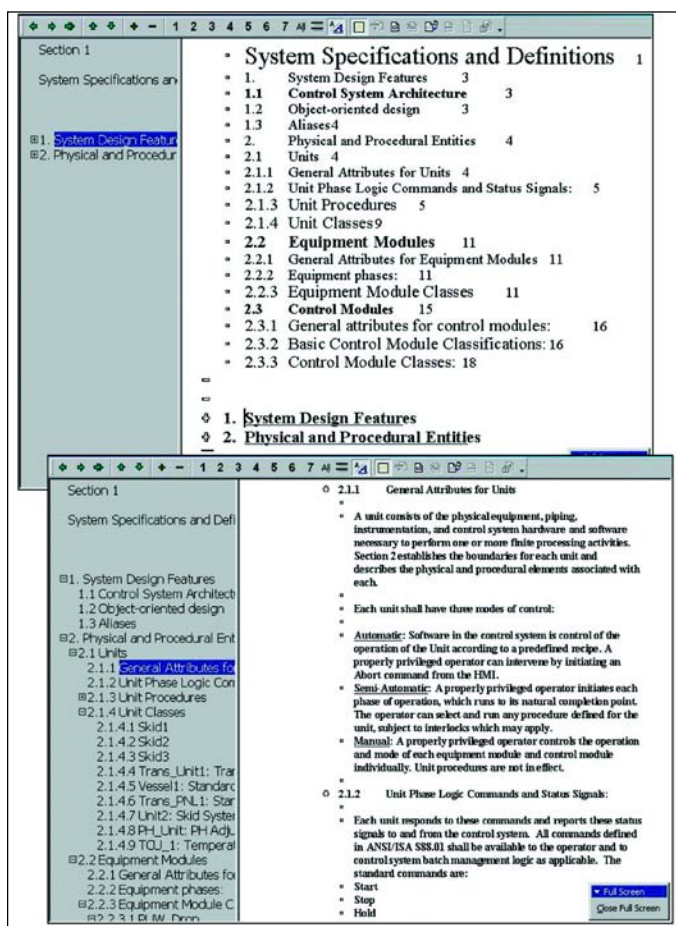


Figure 9. Documenting the standard module classes in the FS.

TERM (exact text string from FS)	TEXT (for INDEX listing)	Brief Narrative Description
Skid1	Unit Class: Skid1	Skid with complete control system with multiple modes and recipe control (As in fermentor 1.1.1.1)
Trans_Unit1	Unit Class: Trans_Unit1	Transfer unit as in 1.4.6
Vessel1	Unit Class: Vessel1	Standard fixed vessel
Trans_PNL1	Unit Class: Trans_PNL1	Transfer panel as in 1.4.3
PH_Unit	Unit Class: PH_Unit	Ph adjustment unit (5.1.2)
TCU_1	Unit Class: TCU_1	TCU for temp control
UNIT2	Unit Class: UNIT2	Unit operation made up of Skid mounted system with supporting EM and CM controlled by the PCS. (as in CIP systems)
PUW_Drop	EM Class: PUW_Drop	Standard PUW drop
WFI_Drop1	EM Class: WFI_Drop1	Standard WFI drop
WFI_Drop2	EM Class: WFI_Drop2	Standard WFI drop with SIP connections (as in 7.3.2.1)
WFI_USE1	EM Class: WFI_USE1	Single valve WFI drop to sink, with HS to call for hot or cold WFI. (5.2.3)
CA_Supply	EM Class: CA_Supply	Std CA supply/vent valves
FIC_Loop1	EM Class: FIC_Loop1	Std flow loop
FIC_Loop2	EM Class: FIC_Loop2	Ethanol flow loop
LIC_Loop1	EM Class: LIC_Loop1	On/Off level loop (WFI Storage (13.4.3.1)
XV01A_FC	CM Class: XV01A_FC	Std fail closed on/off valve with limits
XV01A_FO	CM Class: XV01A_FO	Std fail open on/off valve with limits

Table A. Concordance of module classifications (partial listing).

Continued on page 38.

phase, so appropriate labor resources and time can be allocated early.

The object-oriented design allows the systems integrator to get a head start on software development because standard modules can be developed independently of the larger integration tasks. The FS provides a tool to track quantities and attributes of each standard module. Alias names are assigned to provide the link between each instance of the standard module to the physical devices associated with the unique process application. This keeps the software design isolated from equipment tagging and numbering. Figure 10 illustrates this feature using the “PUW_Drop” equipment module class.

Modularity in the FS Supports Management of Change

As the design process proceeds from concept to detail and finally to implementation, change management becomes increasingly important because parallel efforts are underway in many areas. Changes in process design have a larger “ripple effect” in later stages. A well thought out modular design helps to minimize the frequency and impact of changes. Likewise, control system hardware is easily allocated in modules of sufficient size to handle the well-defined I/O and processing requirements for each logical grouping of equipment entities. The hardware and software architecture is not left to chance according to the whims of the system integrator. Instead, it is clearly defined in a FS, which is built using the same concepts.

S88 and the FS Support Construction Planning

In this project, it was critical to provide for a phased implementation of the new facility. Certain areas were to be constructed and commissioned first in order to meet production demands.

Using the FS and working backwards from target dates, the equipment, instrumentation, and control system components that will be needed to make a process area operational can be easily identified. The modular design allows the FS to be used as a tool to assist in assigning priorities and controlling project schedule, especially in cases requiring a phased implementation.

S88 and the FS Support Commissioning and Validation

The information in the FS helps to keep the validation team engaged and in the loop throughout the design process, which ensures that validation is a feature of the design and not an afterthought. Tasks associated with preparing validation plans and protocols must be identified early and itemized on the project schedule to ensure the overall success of the project.

The S88 format supports an organized, cost effective commissioning and validation strategy, because at the completion of preliminary design, it contains enough detail to understand the complexity of the tasks involved. Test methodologies can be developed for standard classes of equipment modules and control modules. Software modules can be tested as part of its associated equipment entity.

The modularity and portability of the FS supports the development of Factory Acceptance Tests (FAT) and software simulation tests. FAT and software test protocols can be created directly from the FS, because the structure is congruent with the hardware and software architecture of the control system. Individual sections can be spun off as needed to meet scheduling requirements.

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...PFDs, P&IDs, and the FS form a cohesive preliminary design package that provides a solid foundation to support forthcoming detailed design activities.

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Description	Alias	Class		
Small Scale Microbial Harvest vessel (XX-01-V2-01)	SM_Harvest	Vessel 1		
5.1.5.1.4 Equipment modules				
5.1.5.1.4.1 Agitator 1 (XX-01-A-01)				
5.1.5.1.4.2 Agitator 2 (XX-01-A-02)				
5.1.5.1.4.3 Process Inlet 1				
5.1.5.1.4.4 PUW Supply				
5.1.5.1.4.1 Control Modules				
Tagname	Service	Alias	Class	Parameters
XV-XX-0109	Supply	PUW_SUP	XV01A_FC	
XV-XX-0110	Inlet	PUW_INLET	XV01A_FC	Interlocks: CA_VENT open, PUW Supply's "good"
XV-XX-0111	Flush	PUW_FLUSH	XV01A_FC	
5.1.5.1.4.2 Phases				
Note: See Section 1 for typical phase definitions				
5.1.5.1.4.3 Control Modules				
2.2.3.1.1 PUW Drop				
Standardized three valve purified water drop. The functions described in the following tables apply to multiple instances of this module, which are defined in Section 2. Phases are defined in this section once, for all, to avoid unnecessary repetition in Section 2. The specific Tagnames assigned to each instance are listed in Section 2. See Appendix 1 for page references.				
2.2.3.1.1.1 PUW Supply				
Description	Alias	Class		
PUW Supply	PUW_SUP	PUW Drop		
2.2.3.1.1.1 Control Modules				
Tagname	Service	Alias	Class	Parameters
XV-xxxx	Supply	PUW_SUP	XV01B_FC	
XV-xxxx	Inlet	PUW_INLET	XV01B_FC	Interlocks: CA_VENT open, PUW Supply's "good"
XV-xxxx	Flush	PUW_FLUSH	XV01B_FC	
2.2.3.1.1.2 Phases				
Phases	Alias	Parameters	Description	
Initials	INIT		Clear all status values. Place all control modules in automatic mode.	
PUW Flush	PUW_FLUSH	Interlocks: Parameter: Flush time	Open PUW_FLUSH valve. Open PUW_SUP valve. Wait for (flush time). Close PUW_SUP valve. Wait for (flush time). Close PUW_FLUSH valve.	
PUW Sample	PUW_SAMPLE	Interlocks: Parameter: sample delay, sample time	Open PUW_FLUSH valve. Wait for (sample delay) to allow operator to get from HSE to sample location. Open PUW_SUP valve. Wait for (sample time). Close PUW_SUP valve. Wait for (flush time). Close PUW_FLUSH valve.	
PUW Drain	PUW_DRAIN	Parameter: drain time	Open PUW_FLUSH valve. Wait for (drain time). Close PUW_FLUSH.	
PUW Fill	PUW_FILL	Interlocks: PUW Supply "good", CA_VENT open, high press alarm off. Parameter: Level set point, fill time	Open PUW_FLUSH valve. Open PUW_SUP valve. Wait for (flush time). Open PUW_INLET. Wait for (level set point) or (fill time) => (fill time). Close PUW_SUP. Wait for (flush time).	

Figure 10. Drilling down within the FS to find "PUW_Drop" Equipment Module Instance, and finding correspondence specifications in Section 1.

Conclusion

In this project, the FS was handed off to a third party systems integrator as part of the Preliminary Design package. The Detailed Design phase was handled by an engineering and construction firm familiar with local codes and customs, and with offices convenient to the project site. The FS was used for a very detailed review of the automation strategy and for pre-qualification of the systems integrator. It served a key role in the selection of a process control system capable of performing as specified.

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Acknowledgements

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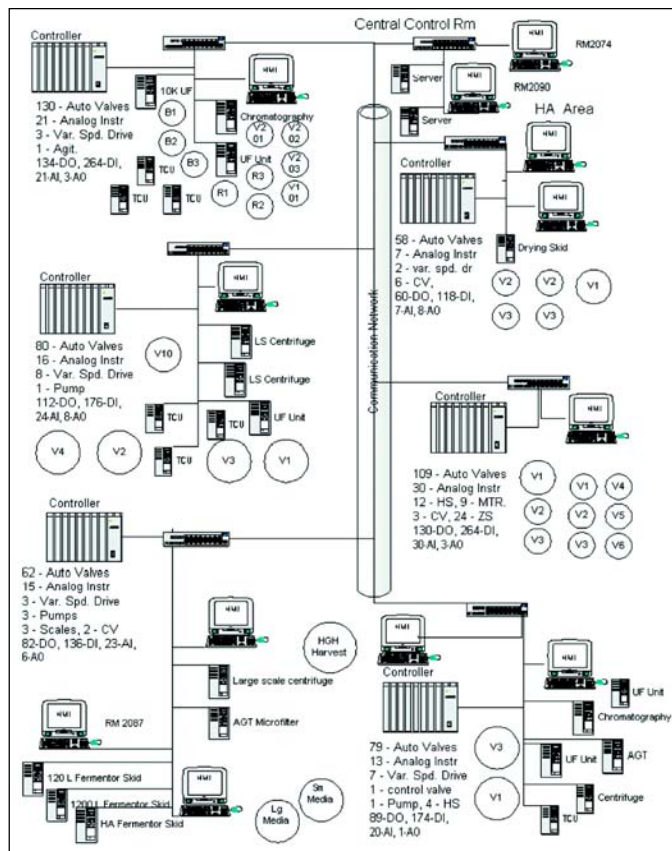


Figure 11. Modular control system architectural concept.

About the Author



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This article discusses specific challenges faced by pharmaceutical and biotechnology companies when evaluating and implementing a clinical supply chain system.

Next-Generation Clinical Supply Chain Management Systems

by Douglas Meyer, MBA RPh

Introduction

Pharmaceutical and biotechnology companies are facing ever-increasing demands to speed their drugs to market while maintaining or trimming their costs. The clinical supply chain is often in the critical path of the drug development process, and the effectiveness of any supply chain is greatly impacted by the systems that control the underlying processes - *Figure 1*.¹ This has caused many companies to invest time, effort, and financial resources in the evaluation and implementation of a world-class supply chain system. This article aims to delineate the specific challenges faced by these companies and to provide a comprehensive set of guidelines to be followed when evaluating such systems.

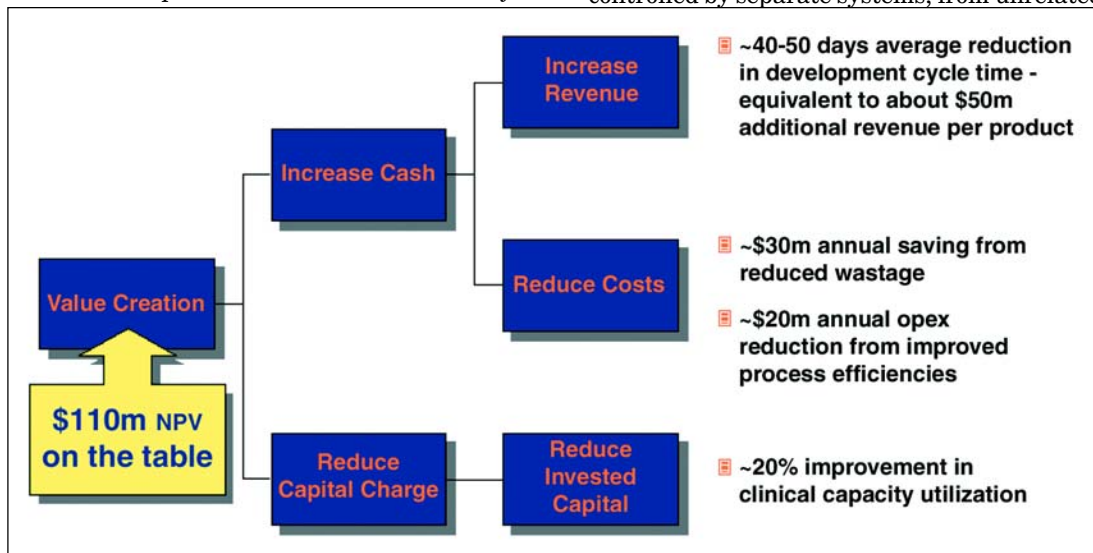
The growing importance of the clinical supply chain in drug development has resulted in the emergence of a new generation of systems, specifically designed for the clinical supply chain to support this process. With the majority of solutions available today having originally been created for manufacturing and commercial supply chains, selecting the right functionalities and integrating the operational processes within the clinical supply chain continues to be a challenge. However, these purpose-built world-class systems do exist with more undoubtedly to follow as market pressures demand such industry-

specific systems.

In a survey² conducted last year by Accenture, a provider of management and technology consulting services, it was found that achieving clinical supply excellence could reduce the speed to market by an average of 40-50 days and be worth up to \$110 million for a \$16 billion company - *Figure 2*. In a separate study³ conducted by PRTM, also a provider of strategic technology consulting services, in which the clinical supply operations practices of European and US pharmaceutical companies were surveyed, it was found that only a few companies termed 'Best in Class' (BIC) had found ways to improve efficiencies and cycle times. However, the majority of entities had been slow to adopt even basic planning tools, and had in comparison, cycle times of up to 60% more than the BIC companies, putting them at a higher competitive disadvantage - *Figure 3*. Combining the results of these two studies, it is no wonder that the effort by pharmaceutical and biotech companies to accelerate their drug development process has spurred large monetary investments in the clinical supply chain over the last decade.

Most companies currently manage their clinical supplies using an amalgam of manual and computerized processes and systems. Various parts of the clinical supply chain are oftentimes controlled by separate systems, from unrelated

Figure 1. The benefits of achieving clinical supply excellence.



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The business factors spurring the development of effective clinical supply software include providing the ability to accommodate blinded trials, increasing the speed to market, maximization of resources, and regulatory compliance.

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vendors, that have little or no integration. These systems may or may not be validated and may either be used as the source records or only to support the tracking and location of paper documents that would still be considered the source record. In their efforts to create a more efficient and effective clinical supply process, many of the large pharmaceutical companies are focusing a large amount of resources to either integrate these disparate systems or implement new, more comprehensive systems. Those companies opting to integrate their legacy systems also are being faced with retrofitting them to meet the requirements of the 21 CFR Part 11 Electronic Records and Electronic Signatures Regulations that were put into effect August 20, 1997 by the FDA.

The very nature of clinical trials, in which the packaging configurations and distribution logistics frequently vary on a study-by-study basis, has only made efforts to improve the supply chain that much more challenging. The variable dosage regimens used and frequent changes in drug formulation require a supply chain that is both flexible and able to adjust rapidly. Combined with the ever-increasing use of mega-trials and blinded studies, one can only conclude that the blend of all of these factors requires companies to seek clinical supply systems that have very unique requirements and features not available in most standard software packages. While enter-

prise resource planning and manufacturing execution systems are used successfully in the preparation and management of commercial inventory in the pharmaceutical industry, many customizations and changes must be made in order to fully accommodate clinical trial materials.

Business Drivers

The business factors spurring the development of effective clinical supply software include providing the ability to accommodate blinded trials, increasing the speed to market, maximization of resources, and regulatory compliance. Metrics around these factors may be developed in order to demonstrate the Return On Investment (ROI) when implementing such systems.

Accommodating Blinded Trials

Most standard enterprise and inventory management systems do not contain the specialized features required to run the blinded studies that are needed to gain drug approval. The system must have the ability to produce packages that are identical in appearance and description to the study personnel, but uniquely coded to ensure the appropriate subjects are given the appropriate treatment. These systems also may be used to generate randomization data as well as label supplies with

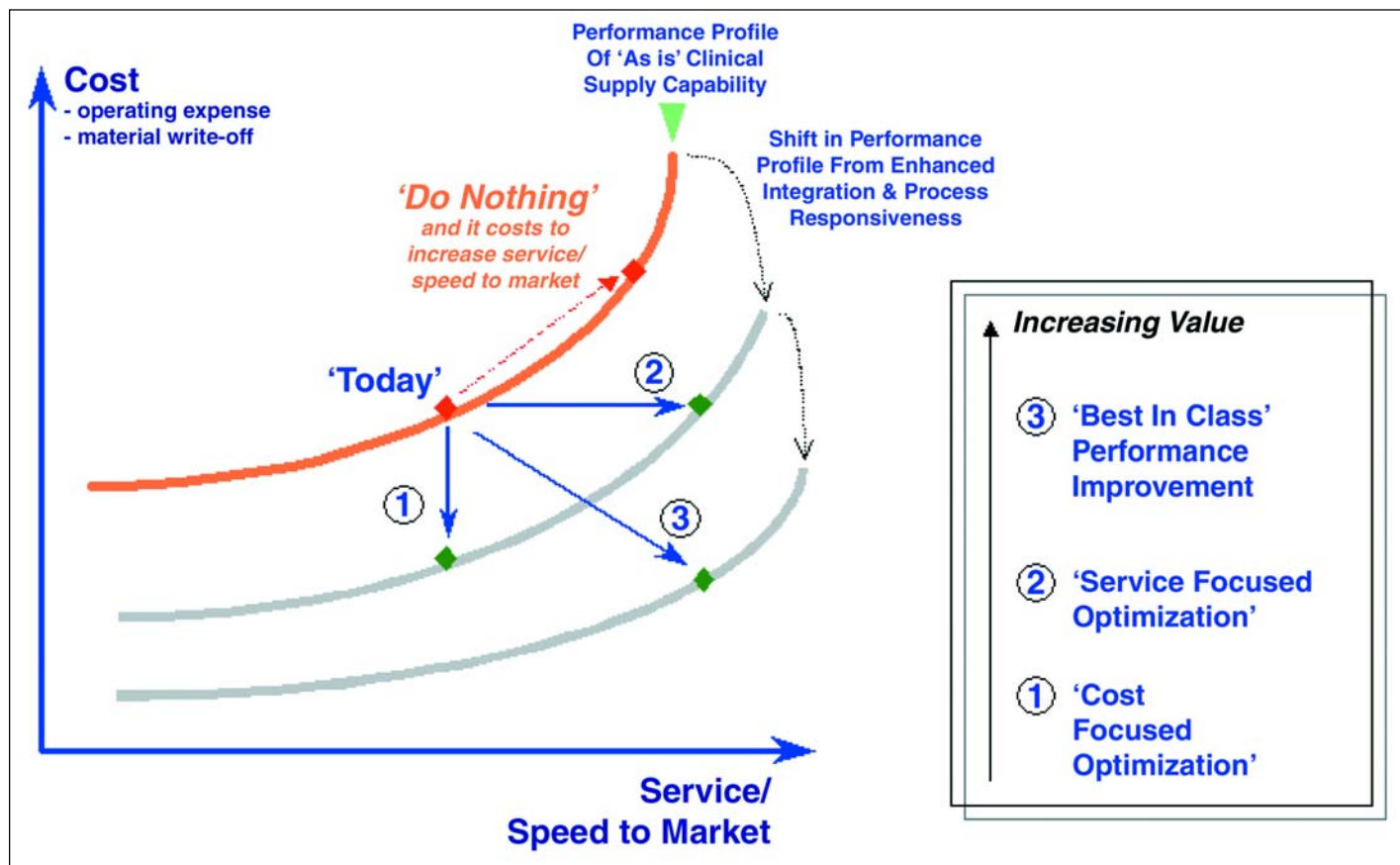


Figure 2. Enhance clinical supply performance through service improvement at reduced supply costs.

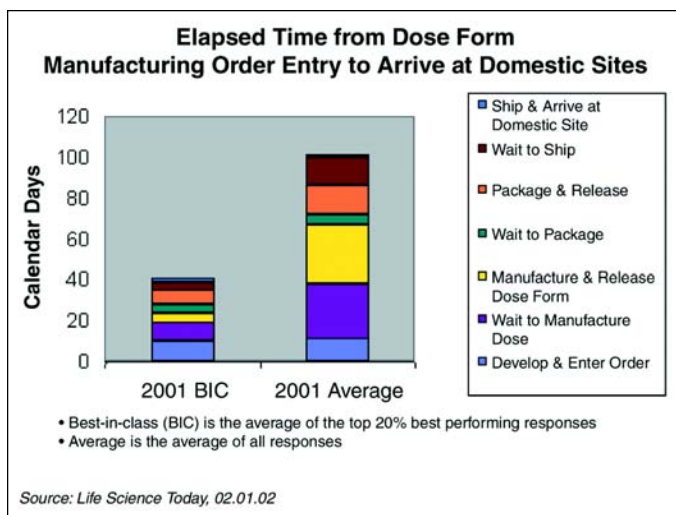


Figure 3. Elapsed time from dose form manufacturing order entry to arrive at domestic sites.

unique random identifiers. Failure to maintain traceability of blinded materials throughout the entire supply chain can put the integrity of the entire trial into question. This traceability also is required in order to effectively track the drug substance lot all the way to the study subject in the event of a drug recall or the exact opposite in case of an adverse event.

Speed to Market

A clinical supply chain system must enable an organization to efficiently manage activities from the manufacturing of active pharmaceutical ingredients through the distribution to clinical sites and the reconciliation of product at the end of the study. The focus should be on workflow tools that can reduce cycle time and minimize time between steps in the process. The dosage and treatment regimens of planned trials change rapidly in response to incoming clinical results. These frequent and often large changes require a system with mechanisms to effect changes in demand and packaging plans throughout the supply chain in a rapid manner.

Maximization of Resources

Another key function of an effective clinical supply chain package is to allow an organization to maximize the resources available in the production and distribution of clinical material. This involves enabling global organizations to route work through various facilities depending upon current capacity. It also may include tools that provide for the ability to outsource work to contract vendors at various steps in the process. It also should trigger sequential activities with multiple users across multiple locations.

Compliance

In order to ensure that the clinical supply chain process meets both internal quality standards as well as external regulatory requirements, the software must provide controls at all points. The ideal system would allow both quality and regulatory users to access the system for various approval steps. It also must maintain complete lot genealogy and traceability even if outside vendors have been used for one or more steps in the process. The system also must be able to control the expiration date management of all clinical materials. The ability of the system to meet the 21 CFR Part 11 requirements also must be

taken into account when developing a system or selecting a commercial software package.

Required Features for Clinical Supply Chain System

When selecting a software package that will be used for the Clinical Supply Chain (Figure 4), there are specific features that must be incorporated into the system to maximize the benefit. Some of the more important ones are listed below:

Handling Randomized Information

As the majority of clinical trials are blinded, a clinical supply chain system must have the ability to either create or import randomization schedules. They also must have many specific security controls around this important information. The packaging and labeling operators must have access to this data in order to ensure that the right product is dispensed to the right patient at the right time. Conversely, to ensure that no bias is introduced into the trial, controls also should be put in place so as not to expose clinical users to this information. The ability to selectively release this to authorized users and to print emergency blind break envelopes or cards is also a key feature.

Capturing and Maintaining Protocol Information

Individual protocols are designed to demonstrate specific results of one drug versus another (or placebo) in various settings, using various dosage regimens. This makes it difficult to utilize systems built for commercial product manufacturing that are based on relative fixed bills of materials and manufacturing/packaging processes. The variability of clinical research requires a supply chain system that allows for a flexible and easy-to-prepare bill of materials for individualized package configurations that may use a variety of processes to prepare the packages. The software also should include a study modeling feature to capture the different dosing regimens that a single subject may receive over the course of the entire trial. Controls should be built around this information as the integrity of the study, as well as the ability to include the trial in regulatory filings, is dependent upon the accuracy of this data.

Electronic Workflow and Routing

The clinical supply chain is often dependent upon the movement of paper documents from one actor to the next, often causing lags between each step. One powerful function of a clinical supply chain software package would be the provision of electronic work routing and automatic e-mail notifications to users of tasks to be completed. In order to maintain compliance to GMPs there are many steps in the supply process where approvals are required, e.g., label text sign-offs or QA release. A system that routes labels electronically for approval can potentially shave weeks to months off the initiation of a clinical trial. Likewise, the notification of QA that a packaging job is complete could save significant time in the release of the product. This tool, used by many automated Manufacturing Execution Systems (MES) and Enterprise Resource Programs (ERP), can be applied in numerous steps across the process from material master setup to shipment of finished packages to the clinical site. Another important component of Electronic Workflow is allowing the use of Radio Frequency (RF) scanners to allow certain warehouse activities, such as pick/pack or move inventory, to occur with little or no key punch entry by warehouse operators.

Label Printing and Generation

GMPs require the ability to identify and control product at every stage of the process from receipt of materials to dosage of the study subject to destruction. A clinical supply system should support the printing of warehouse labels to ensure this control. Many supply systems also allow the users to design and print the labels that are applied directly to the drug product. These clinical labels also must meet the local regulatory requirements of the country where the trial is to be conducted. The labels may be printed using some variable data that comes from either the randomization tables or study model.

Flexible Forecasting Tools

The nature of investigational trials involves the constant uncovering of new data relative to the activity and effects of the medication. The net effect on clinical trial material requirements for one or more studies can oftentimes be dramatic, putting stress on the supply chain to react quickly to the new demands. One way to mitigate the impact of these changes is the development of a flexible forecasting system. A system that allows the users to analyze various demand scenarios is an essential part of a proactive planning process. This is especially true in the biotech industry, where supply is often restricted and large variations in demand can cause long delays in the availability of clinical product and the ability to start and complete a trial. While many Material Resource Planning (MRP) systems provide strong analysis tools for comparing current versus planned inventory, they fall short in providing forecasting tools that allow for complex packaging and complicated dosing regimens, such as response-based dose titrations or studies with complex cross-over designs.

Global Work Processing

The recent trend in mergers and acquisitions in the pharmaceutical industry has resulted in many organizations running their clinical supply operations in large facilities across multiple regions. These facilities often had their own systems built

upon their own business processes. In order to realize the efficiencies that drove these mergers, many organizations are choosing to deploy a single clinical supply system that allows orders to be shared and executed across locations. The system should have strong warehouse security controls as well as the ability to provide inventory visibility across all distribution depots. This globalization effort is often accompanied by a re-engineering exercise and selection of the supply chain system that most closely matches the current processes. A system with a simple user interface is also a key feature when implementing across multiple countries and languages.

Inventory and Distribution Controls

A core competency of any supply chain system is to maintain an accurate inventory level for all items. This involves allowing authorized users to receive, adjust, and decrement inventory through a variety of transactions. The close controls required for pharmaceutical products necessitate an even higher level of accuracy and accountability as well as complete auditability of all inventory affecting transactions. Users should be able to reserve inventory and allocate to appropriate work orders. The system should allow the users to be able to manage product using First In – First Out (FIFO) principles. The distribution functions should allow the allocation of both composite materials as well as individually labeled packages for shipment. Users should be able to track shipments and enter returns and destruction information in the system to ensure complete traceability of inventory in a single location.

Integration Ability

Many interfaces can be developed with a clinical supply chain system and other applications to increase the effectiveness of the related systems. These systems may be other applications internal to the company as well as systems belonging to various contract service providers. One powerful potential integration would be interfacing a clinical supply chain system with an external Interactive Voice Response System (IVRS) used to randomize subjects into the trial and assign drug packages.

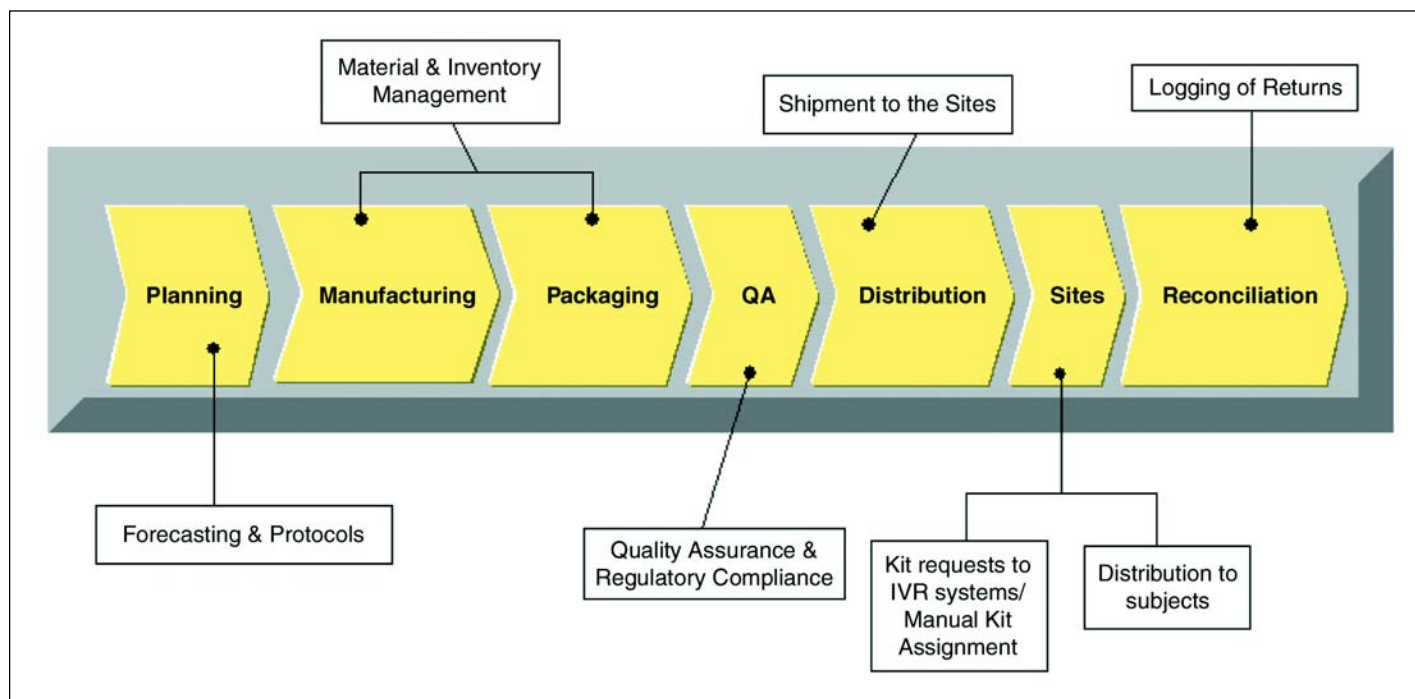


Figure 4. The clinical supply chain.

This allows real-time enrollment of subjects as well as drug package assignment at the clinical site on an as-needed basis, significantly reducing the amount of drug required to conduct the study. Functions such as automated ship orders as well as real-time expiration date and quality status sharing make integration with IVRS very attractive and allow maximum control of drug supply by the study sponsor throughout the entire trial. Another beneficial interface may involve the sharing of inventory between the sponsor company and the various contract vendors they may use for various steps in the manufacturing, packaging, labeling, and distribution of investigational materials. This type of interface may produce many workflow efficiencies for both parties as well as allow the sponsor to retain the lot genealogy, traceability, and drug accountability required to meet regulatory standards. Other interfaces may include integration with an internal enterprise or manufacturing system that would allow the movement of primary inventory into the supply chain system. This interface also could involve the preparation and processing of purchase order requests. Integration of a clinical supply chain system with a clinical site management system also may be a powerful tool in ensuring the correct and most updated investigator site information is shared. Another interface many companies utilize is between the distribution functions of the supply chain system and the automated systems offered by many of the freight carriers. This connection allows the users who place orders to track the delivery and receipt of the orders directly through the supply chain system instead of going to the carrier's Web site.

Simple, Consistent User Interface

A clinical supply chain system may have users from a large variety of functional areas, including clinical supply operations, regulatory, quality assurance, and clinical research. Many users, such as clinical research, may only utilize the system for a small portion of its functionality, such as entering a request to initiate the shipment of investigational supplies to a clinical site. This requires that the interface be simple enough for the casual user to operate while displaying the complex information needed to ensure that appropriate supplies are selected and sent to the site. As the number of users may be large for such an application, a simple yet secure process should be in place to allow a system administrator from the business side to add users and control their authorization levels.

QA Controls

Any system managing inventory in the pharmaceutical industry must meet many standard quality assurance requirements. These requirements become even more complicated when the system is used for preparing and managing packaged inventory for blinded trials. Controls need to be built into the process to ensure that the right codes are assigned to the right products as well as assuring the right label is being applied. Barcode verification of materials during assembly and shipment is crucial in facilitating these requirements. Unlike commercial products with relatively fixed expiration dates, the clinical products often have retest dates that are constantly being updated as new stability data accumulates. Combine this with the fact that most studies provide more than one drug lot in a blinded fashion and the procedures to manage expiration dating become more complex. The fact that inventory is often packaged and labeled with an individual subject or

identifier number requires that the system support the ability to control the quality and inventory status on an individual package level. This varies from many standard ERP and MES software programs that do not control quality status on a level more discrete than the warehouse or location level.

Regulatory Controls

Along with quality controls, there are several crucial regulatory controls in the clinical supply process that should be captured. The system should not allow the shipment of investigational material to a clinical site until the investigator meets all regulatory requirements. Controls also may be built in to ensure that the various lots and new processes involved in the manufacture of these lots have been filed with appropriate authorities in the destination country. In order to ensure full regulatory compliance, the system also must demonstrate ability to produce complete lot genealogy as well as reconciliation of all drug manufactured.

21 CFR Part 11 Compliance

The advent of 21 CFR Part 11 Electronic Record/Electronic Signature guidelines has had a significant impact on the industry and its use of clinical supply chain software. Companies are weighing the impact of remediating their current systems into compliance versus the purchase/implementation of a new system that has Part 11 compliance already built in. Much effort is expended by the industry to understand how these guidelines apply to every GMP and GCP system currently in production as well as developing validation processes to ensure compliance.

Validation

Like any system involved in the management of GMP and GCP activities, a clinical supply software package must pass vigorous validation testing. As the system will be used for numerous non-repetitive activities, it requires a broader range of testing than many other pharmaceutical software packages. Validation testing should include a number of scenarios consisting of both open label and blinded trials, each with unique package configurations, dosing regimens and distribution logistics. The number of applications that a clinical supply chain system may be integrated with also provides a validation challenge. The integration strategy must be designed to accommodate a rigorous validation process while allowing flexibility to connect with numerous and constantly changing contract vendors. Integration also should be accomplished in such a way that all interfaced systems are not required to undergo validation each time one of the individual systems is upgraded and requires re-validation.

Case Study⁴ - Amgen, Inc.

Amgen provides a clear example of a company that transformed its clinical trials supply function. Facing the largest series of European clinical trials in its history, the company initiated a broad strategic review of its clinical trials supply chain. It found that, while supply commitments were being met, the clinical trials supply chain was not fully prepared to accommodate the expected increase in logistics complexity and geographical reach. Amgen therefore undertook a global assessment of its clinical trials supply and demand capabilities to:

- improve process reliability and planning effectiveness
- maximize the contribution of supporting information sys-

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The demand volatility that previously risked hampering fulfillment operations is now managed ‘earlier’ through new collaborative planning processes, in effect buying more time to respond to development’s needs.

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tems and infrastructure

- establish metrics
- clarify accountabilities
- ensure continued regulatory compliance
- minimize clinical material wastage and inventory obsolescence.

Teams of expert staff from around the world conducted the review. They first benchmarked how other companies manage their clinical trials supply operations and examined leading practices from other industries. They then developed alternative scenarios and approaches before recommending a new model for clinical trials supply.

Amgen can now anticipate label requirements six months in advance, forecast the number of patients enrolled in trials three months in advance, and identify how the clinical trials supply chain will service clinical trial sites three months prior to study initiation. The demand volatility that previously risked hampering fulfillment operations is now managed ‘earlier’ through new collaborative planning processes, in effect buying more time to respond to development’s needs.

Amgen’s Vice President of Logistics is quoted as saying:

“The initiative has had a fundamental impact on the entire development organization at Amgen. Clinical trials supply has taken on a more strategic profile and is fast becoming recognized as an integral part of clinical development. Overall, we are providing a higher level of service to investigators around the globe and saving significant amounts of time and money. Integrated forecasting and replenishment practices, for example, have helped us achieve a 50 percent reduction in the number of rush orders in clinical packaging and simultaneously attain 100 percent service levels for shipments to investigator sites.”

Conclusion

Given the complexity of the current state of clinical drug development, the choice of which clinical supply system to implement is a difficult one that involves weighing many different factors. The choice should involve a detailed analysis of requirements for each key user group and should take into account the various business processes used by the company across each location of their operation. The candidate systems must be rigorously evaluated against these requirements to ensure selection of a system that best meets the needs of the organization and provides the greatest return on investment. The companies that successfully meet the challenge of implementing world-class integrated information systems to manage their clinical supply chains will be rewarded with reduced drug development cycle times and costs, increased flexibility, and competitive advantage, less product-liability exposure, and greater profits.

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About the Author



Douglas Meyer, MBA, RPh received both his BS in pharmacy and his MBA at the University of Connecticut. Prior to joining Bristol-Myers Squibb in 1993, he practiced pharmacy in hospital and high-tech homecare. Along with Bristol-Myers, Meyer has held management positions in the clinical supply organizations of Wyeth-Ayerst Research and Amgen, where he was responsible for the development

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The former Director of Manufacturing for Wyeth Vaccines talks about the changes in the industry over the past several years as well as emerging technologies.

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An Interview with Frank S. Kohn, PhD, former Director of Manufacturing, Wyeth Vaccines

by Richard Malfa, ISPE Publications/Internet Committee



Frank S. Kohn, PhD is President of FSK Associates; an international consulting company providing services to the biopharmaceutical, biotechnology, and vaccine industry. Dr. Kohn recently retired from Wyeth, where he was Director of Manufacturing at the Sanford, NC location. Dr. Kohn has more than 30 years of industry experience working in various technical and management positions for Schering Plough Corporation, Armour Pharmaceutical, Sanofi, and Wyeth Vaccines. Dr. Kohn was a board member of the ISPE Carolina/South Atlanta Chapter and is currently on the ISPE Publications/Internet Committee (PIC). He is the head of the Vaccine Interest Group for PDA and member of Technical Council for PDA. Dr. Kohn is a frequent speaker and course leader in the US and Europe, and has given more than 150 technical seminars, lectures, and publications. Dr. Kohn holds graduate degrees in environmental microbiology and operations management, and is a certified microbiologist by the American Academy of Microbiology.

and various regulatory actions. With these issues, and the after effects of September 11, one can see the dynamic shift of society's changing view of the vaccine industry.

• • •

Q Have the recent changes in the vaccine industry involved downstream processing or changes in aseptic filling?

A Several operational changes have occurred in the industry. One example is that process validation has become more critical to the industry and regulatory agencies. The increased need for improved process controls in the manufacturing process is continually evolving. This has led the industry to implement additional automation processes. In the areas of sterile filling, barrier technology has become the "state of the art" process for environmental control and sterility assurance.

• • •

Q What are the significant changes you have seen in the vaccine industry over the past five years?

A Several significant changes have occurred over the course of the past five years in the vaccine industry. These changes include the formation of Team Biologics inspections by CBER-FDA, a renewed awareness by the public of the critical need for new vaccines and therapies, a global view of quality,

Q What are some of the "key resources" and "equipment" that you foresee being implemented for future vaccine production?

A As mentioned above, automation and barrier technology are two significant advances that one would expect to see in "new manufacturing facilities." Additional equipment would include Electric Batch Record (EBR)

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Several emerging technologies are being explored in our industry. They include new vaccine administration technologies such as transdermal technology, aerosol vaccination, conjugated vaccines, and genetically altered foods containing vaccines.

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and Manufacturing Execution System (MES) for improved cGMP documentation practices.

One of the key resources in any manufacturing facility is the need for trained personnel. Recently, the industry has started to experience significant shortages in the available job market for experienced vaccines and biotechnology personnel. This has both a short and long-term impact as the vaccine industry is in a state of expansion.

• • •

Q What has been the major impact that you have seen in the vaccine industry since the September 11 terrorism attack on the US? What are the long-term effects or changes?

A The September 11 tragedy did not only change the public view of the biotechnology industry, but had a profound effect on the vaccine industry itself. The public's concern for vaccine shortages and the need for new and improved vaccines created new challenges that the industry has not experienced.

Some of the longer-term effects of September 11 are the need for improved coordination between industry, research and development and the government to set clear priorities and quick review and approval by the regulatory agencies.

Congress is currently evaluating whether to have the government develop their own vaccine manufacturing facilities. This action could have a significant effect on the vaccine industry as a whole.

• • •

Q What are the emerging technologies currently being explored by the vaccine industry?

A Several emerging technologies are being explored in our industry. They include new vaccine administration technologies such as transdermal technology, aerosol vaccination, conjugated vaccines, and genetically altered foods containing vaccines. New technologies created the need for new manufacturing processes to be able to mass produce these types of vaccines. This will result in increased need for improved filtration technology, sterile filling systems, laboratory automation, and reporting systems to mention only a few.

• • •

Q Could a technology termed barrier isolation become a standard in the vaccine industry? Or do you foresee it as only an optional method for production in the next five years?

A Specifically, I believe barrier isolation technology is one of the industry's opportunities to improve sterile filling technology within the next five years. Where applicable, form fill and seal technology is another technology that could be implemented.

• • •

Q Given the strong linkage of technology and productivity, do you have any advice for operations personnel in your industry?

A First, I believe continuous improvement and training are necessary in our industry. New technologies appear almost daily. Therefore, professional development and training are coming under increase attention by the FDA. This is an area where ISPE continues to lead the industry through their educational programs.

• • •

Q Do you think engineers have a place of prominence in a technology-based corporation?

A The vaccine industry needs an unending supply of well-trained engineers. Fields include areas such as chemical, mechanical, and quality engineers. At every level in manufacturing, qualified engineers provide the background required to not only design equipment and process, but to supervise and manage the manufacturing plant.

• • •

Q What do you see as the most important contribution a pharmaceutical engineering organization can make toward the overall success of manufacturing?

A As mentioned before, organizations like ISPE can provide the training tools and programs to help close the gap for the need for highly trained engineers and scientists for the vaccine industry. Without this initiative, personnel shortages in our industry will become magnified.

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...organizations like ISPE can provide the training tools and programs to help close the gap for the need for highly trained engineers and scientists for the vaccine industry.

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Q

How do regulatory changes impact the vaccine industry?

A

Regulatory changes can have a significant effect on the vaccine industry's ability to supply the public with safe, effective, and affordable products. Regulatory changes can cost millions of dollars to implement and can cause technological improvement to be delayed. A good example was the number of years it took the FDA to develop the approval of the electronic signature.

This resulted in the industry not moving forward with integrated electronic documentation and control systems until the agency finally defined and agreed to the methods for electronic signatures.

• • •

Q

What role do you see consultants providing to the vaccine industry?

A

As a consultant to the industry, I feel we can provide a broad view and specific area of expertise that are in short supply to the industry. Also, many times there are defined time lines for projects of limited duration. These are a few of the areas I feel a consultant could assist industry in achieving specific objectives.



This article discusses the possibilities of vaccine production through genetic mutations in virus structure.

This paper was presented at the 2001 ISPE Annual Meeting in Las Vegas as part of the Student Poster/Paper Competition held annually by the Society. Katharine Kapfer, a graduate student at North Carolina State University, was one of eight contestants in the annual contest. Previous to the Annual Meeting competition, Kapfer was runner up at the ISPE Carolina-South Atlantic Chapter local competition.

Figure 1. Graphic representation of comparative analysis of plaque forming units for BHK mutant virus on BHK monolayer.

Investigation into Protein-Protein Interactions in the Sindbis Virus Membrane Glycoproteins which Block Virus Assembly

by Katharine Kapfer

Introduction

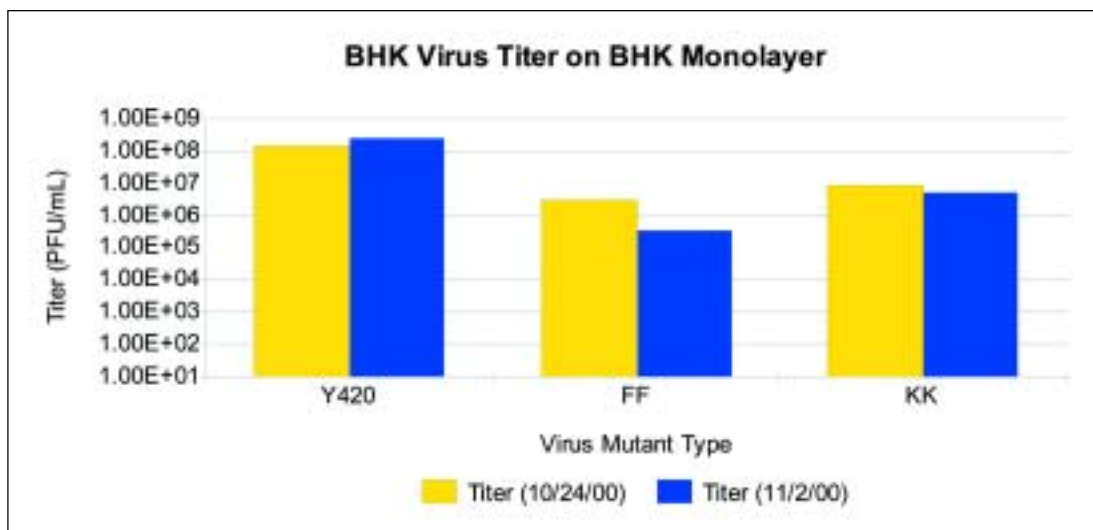
Overview of Sindbis Virus

The *Alphavirus* genus is included in the *Togaviridae* family and contains 26 species that share common antigenic determinants. The hemagglutination inhibition test has been a useful tool in segregating the alphavirus into the following seven serogroups: Western Equine Encephalitis (WEE); Venezuelan Equine Encephalitis; Eastern Equine Encephalitis; Semliki Forest, Middelburg, Ndumu, and Barmah Forest viruses. The WEE serogroup contains Sindbis virus and WEE viruses.¹

Alphaviruses are transmitted by arthropod vectors, such as the mosquito. The arthropod ingests the virus while feeding on an infected vertebrate host; the virus replicates in the gut and is transferred to the salivary glands via the hemolymph. Vertebrates are infected by the exchange of fluids during the feeding of the mosquito. In North America, Eastern and Western equine encephalitis viruses pose serious health threats to humans and animals.¹

Sindbis Virus Structure

Alphaviruses contain single-stranded RNA molecules of positive polarity.² The known *Alphavirus* structure is based on studies of the Sindbis virus and Semliki Forest virus. The RNA is enclosed in a nucleocapsid surrounded by a lipid envelope or bilayer.³ Glycoproteins extend outward from the nucleocapsid and through the envelope. Most *Alphaviruses* possess only two glycoproteins: E1 and E2. These two glycoproteins interact noncovalently to form heterodimer spikes. Cross-linking studies indicate that the heterodimer spikes (7nm long) associate with one another to form trimers.⁴ In Sindbis virus, E1, E2, and E3 glycoproteins are present, but E3 is lost into the media during the latter stages of maturation.⁵ Glycoprotein E1 is responsible for the hemagglutinating ability of Sindbis virus and contains antigenic determinants that react with related alphaviruses.⁶ E2 of the Sindbis virus, however, is the predominant neutralizing antigen, and it is antigenically distinct for each alphavirus.⁷



Sindbis virus Replicative Cycle

Replication begins after the virus delivers its genome into the host cell cytoplasm. A large macromolecular assembly is transported through the plasma membrane without destroying the cell. Virions attach to the plasma membrane and bind to cells from a variety of tissues and species.¹ While this is one model, our data suggests that the virions directly penetrate at the plasma membrane. It is believed that the entry of the enveloped alphavirus occurs via receptor-mediated endocytosis, in which a conformational change of the spike glycoproteins results in membrane fusion and release of virion RNA into the cytoplasm.³ The Sindbis virus serves directly as mRNA (positive polarity), and thus is infectious in itself.

Research Objectives

Several studies have previously been performed to analyze the infectivity of Sindbis virus after mutations have been made at specific amino acid residues along the E2 glycoprotein.⁹ In our study, mutations were inserted into the E2 tail of Sindbis at lysine (E2 K391) in order to examine the protein-protein interactions of the E2 tail with the nucleocapsid core of the virus. In the first construct, the lysine at 391 already present at the plasma membrane and the cytosol junction had another lysine inserted after it, creating a K391K392 mutant. The insertion of an additional basic residue is expected to be repelled from the membrane junction and push the rest of the amino acids further into the cytosol. The second mutation that we analyzed involved the lysine at position 391 being changed to a phenylalanine 391 with a second phenylalanine 392 inserted analogous to the first mutation; this created a F391F392 mutant. These mutations were constructed using Polymerase Chain Reaction (PCR). Infectious RNA was produced from the cDNA templates and transfected into vertebrate (BHK) or insect (mosquito) cells, and mutated viruses harvested from insect or vertebrate cells. The mutated viruses were used to infect both insect and vertebrate cells to determine virus infectivity. The two mutations resulted in significant amounts of decreased virus production.

Background

Sindbis virus is an excellent model for studying viral structure

and assembly due to its uniform icosahedral structure. Several previous research experiments have altered the structure of the virus in order to decrease its infectivity in an effort to produce vaccine strains and to prevent the spread of encephalitis. Most of those experiments have succeeded in decreasing Sindbis infectivity, yet its assembly has not been prevented (cited in 9).

In one of the more recent research projects, a single deletion was engineered in the membrane-proximal region of the Sindbis virus glycoprotein E2 endodomain.⁷ This region was targeted since previous research discovered this to be the location of virus assembly with the nucleocapsid. The assembly complex was found to consist of a hydrophobic nucleocapsid pocket which is thought to interact specifically with the TPY domain of the E2 tail.⁸ This area is the focal point of the Sindbis virus research because the plasma membrane contains the region at which the final steps of the assembly process take place. In this highly specific two-step interaction, the assembled viral nucleocapsid binds to the endodomain of the E2 glycoprotein.⁹

Keeping the assembly complex in mind, mutations in this region were constructed. Using site-directed mutagenesis¹⁰ and Taq DNA polymerase, a single mutant missing the nonconserved lysine at position 391 in E2 was created. Tyrosine was purposely deleted from the 420 position of the wild type parent, in which also served as the wild type. The Sindbis virus mutants were then amplified using PCR to create a satisfactory amount of DNA, used as the template to produce infective RNA transcripts. A cDNA template of the Sindbis virus mutants and the wild type were transcribed *in vitro* and transfected into healthy cells in an RNase free environment. This single deletion at K391 experiment successfully hindered assembly in vertebrate cells; however, assembly within the invertebrate was at wild type levels.⁷ This led to the development of a vaccine strain strategy because this eliminated assembly in the vertebrate host while assembly in the invertebrate host, mosquitoes, is not affected. This strategy enables production of infectious virus in the mosquito cells, or vector, which will infect a vertebrate host and elicit an immune response without producing a full-blown infection. This is a necessity if there are any hopes for curbing outbreaks of encephalitis.

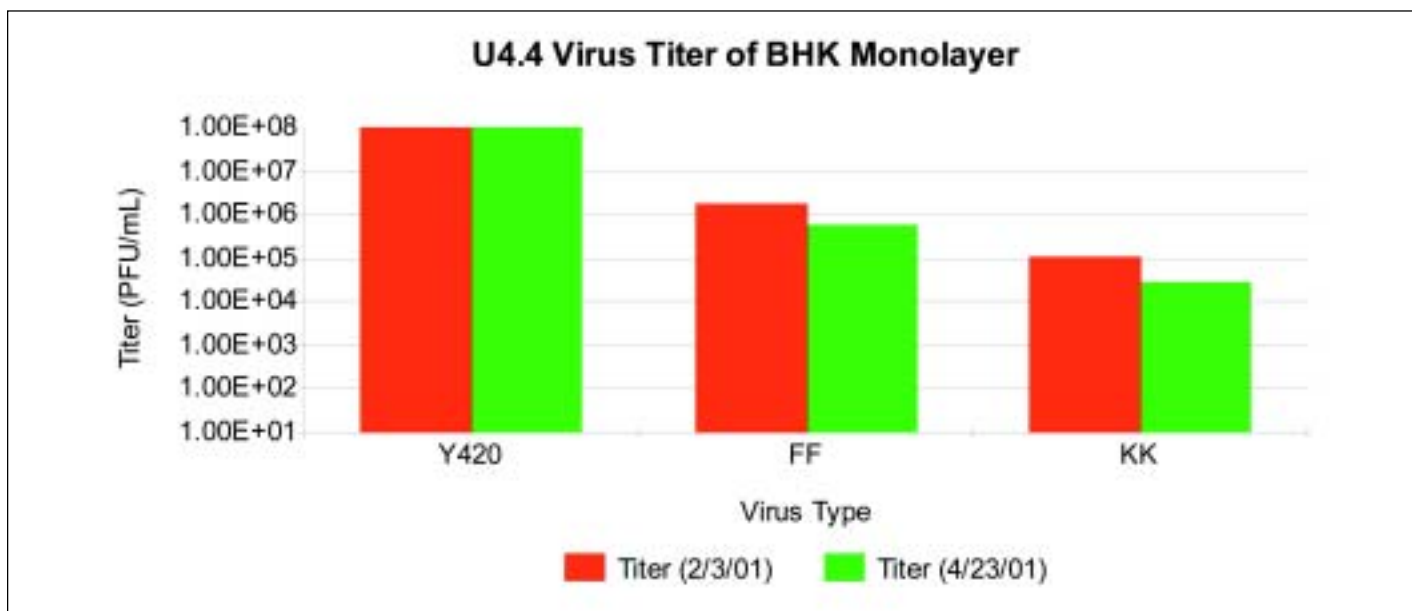


Figure 2. Graphic representation of comparative analysis of plaque forming units for U4.4 mutant virus on BHK monolayer.

Mutant Type	Titer (10/24/00)	Titer (11/2/00)	Percentage (10/24/00)	Percentage (11/2/00)
Wild Type	3.38E+09	3.85E+09		
Y420	1.40E+08	2.35E+08	100%	100%
FF	2.85E+06	3.43E+05	2.04%	0.15%
KK	8.19E+06	4.83E+06	5.85%	2.06%
U4.4 virus infected cells on BHK monolayer				
Mutant Type	Titer (2/3/01)	Titer (4/23/01)	Percentage (2/3/01)	Percentage (4/23/01)
Wild Type	2.84E+09	8.86E+09		
Y420	1.10E+08	3.00E+08	100%	100%
FF	1.71E+06	6.10E+05	1.55%	0.20%
KK	1.06E+05	2.74E+04	0.096%	0.009%
U4.4 virus infected cells on C710 monolayer				
Mutant Type	Titer (12/4/00)	Titer (1/26/01)	Percentage (12/4/00)	Percentage (1/26/01)
Wild Type	4.75E+08	1.17E+09		
Y420	3.03E+07	1.65E+06	100%	100%
FF	1.60E+04	4.00E+08	0.053%	0.0061%
KK	1.18E+06	1.50E+06	3.89%	0.30%

Table A. Plaque forming units of each mutant virus and the percent yield of each virus compared to the control.

Materials And Methods

Cells and Virus Strains

The mutated cDNA template that was used for this study was prepared by others in the lab. Baby Hamster Kidney (BHK) cells and invertebrate mosquito (C710 and U4.4) cells were used to grow virus. BHK cells, which were provided initially by Peter Faulkner (Queens University, Kingston, Ontario, Canada), were grown in minimal essential media (MEM), supplemented with 10% fetal bovine serum (FBS), 10% tryptose phosphate broth and 2 mM glutamine at 37°C under 5% CO₂ and a pH level of 7.4. The U4.4 cells were cloned from cells from Sonya Buckley (Yale Arbovirus Research Unit, New Haven, Conn.) and were grown at 28°C with 5% CO₂ in Mitsuhashi and Maramorosch (M and M) medium supplemented with 20% FBS and 5% bicarbonate. The C7-10 cells were cultured in MEM as described above at 28°C with 5% CO₂ and a pH of 7.4. These cells were provided by Victor Stollar (Rutgers Medical School, New Brunswick, N.J.).

Preparation of RNA Transcribed Using Sp6 RNA Polymerase

Many techniques and protocols were used in the investigation of the mutated viruses. Polymerase Chain Reaction (PCR) was used to prepared mutated cDNA samples from a parent virus strain; this was followed by a transcription reaction. The transcription reaction contained 2 µl of the specific cDNA sample, 11 ml deionized water, 2 µl 10X Proteinase K buffer (0.01 M Tris pH 7.5, 0.005M EDTA pH 8.0, and 1% NP-40), 2 µl NTP mixture (20mM of ATP, CTP, GTP, and TTP each), 1 µl RNase inhibitor, and 2 µl Sp6 polymerase for each cDNA sample. RNA samples were prepared from the mutated cDNA samples. PCR was used to construct mutated cDNA used as a template for RNA production. During PCR, the viral cDNA was heated to about 90°C so that the double stranded DNA separated. Along with the viral DNA present in the solution were primer pairs which were specific to certain nucleotides of the DNA, and these were then annealed. Amplification of products containing the annealed, mutagenic primers formed the mu-

tated cDNA product. Sp6 polymerase was then used to make a transcript of the cDNA. This process was repeated several times to make millions of copies of the RNA. After making the transcripts, the RNA quality and yield of each mutated virus, along with the RNA of control viruses (wild types) was assessed. A 1 kilobase ladder and a DNA mass ladder, along with the synthetic transcripts, were run on a 1% Agarose-1X TAE gel. The gel was then stained in ethidium bromide and destained in 1X TAE buffer. To ensure that the reactions were successful, both DNA and RNA from the viruses were monitored, and the gel was viewed under ultraviolet light, and a photograph of it was made.

Transfection of Vertebrate and Invertebrate Cells

The RNA of these mutated and control viruses were used to transfect BHK and U4.4 cells in a process called RNA transfection. To ensure that the RNA is infectious, this procedure was done "RNase free" under sterile conditions in the cell hood. It was very important to wash the cells being used very well, with several washes using RNase Free 1X PBS-D. This was done so that as many cells as possible can be transfected. Cells were counted to ensure 1 × 10⁷ cells/ml to successfully transfect the cells being used. The cells were then mixed with 5-10 µg of RNA of the specified viruses; this mixture was then electrophorated at 2.0 KV, 25 µF, and ¥ resistance with one pulse to produce a time constant of 0.7. This was done so that the virus was able to enter the cells more readily. Once the cell-virus mixture had restabilized for 10 minutes, it was transferred to a 25-cm² flask with 10 ml of the appropriate media for the cells for incubation at the correct temperature, 37°C for the BHK cells 12 hours and 28°C for U4.4 cells, for 48 hours. After the appropriate incubation period, the viruses were harvested from each flask. This was done by transferring the media to centrifuge tubes which were centrifuged. The harvested virus was frozen down in a solution of glycerol and HEPES at pH 7.4 for vertebrate cells, or MOPS at pH 7.4 for invertebrate cells, and stored at -80°C for later use.

Infection of Vertebrate and Invertebrate Cells

BHK cells were grown in 75-cm² flasks in 1X MEM. Once the cells were confluent, they were split into three new 75-cm² flasks after being washed in 1X PBS-D and the monolayer was resuspended with 0.01% trypsin. After the cells became confluent, they were split into the required flasks. A similar process was done for the C710 cells. The cells were grown in a 75-cm² flask, and once they were confluent, they were shaken down into their media. The cells were then split into three new 75-cm² flasks with fresh media. As with the BHK cells, once confluent, they were split into the required flasks.

The monolayers of the BHK or C710 cells in 25 cm² flasks were used to titer virus using a plaque formation assay, and the C710 are mosquito cells which display cytopathology upon infection and serve as insect indicator cells. A series of dilutions of the mutant viruses, a control mutant virus, and a wild type virus were made. The control mutant virus was used to ensure that the transfection was successful, and the wild type virus was used to make sure that the infection worked. Ten fold serial dilutions, in a range which would yield 10-300 plaques/flask, were then used to infect the indicator cells; these dilutions were made in 1X MEM complete with 10mM HEPES and 10% glycerol for BHK cells. The C710 dilutions were made in 1 ml C710P Dilution Media containing 500-μL of 1X PBS-D, 10% FCS, 10% Glycerol, 10mM MOPS, and 1.5-μL Phenol Red. The cells were allowed to infect for one hour while rocking at a constant speed. The virus was then removed from the cells by pipetting. A 1% final concentration overlay of 2% agarose and a media of 2X MEM, 20% FCS, 10% TPB, 2X L-Glutamine, and 2X Gentamicin was used for BHK cells. The C710 cells were overlaid with a 1:1 mixture of 2% agarose and 2X C710P

Media (2X MEM with 20mM MOPS pH 7.6; the resulting solution should have a pH of 7.4). These cells were incubated at 28°C for insect monolayer cells for three days and 37°C for vertebrate monolayer cells for 48 hours. After the 48-hour time period, a second overlay was made of 1% agarose, 2% neutral red and 2X PBS-D solution, which contained HEPES at pH 7.4 for BHK cells or MOPS at pH 7.4 for C710 cells. This overlay incubated for approximately 16 hours, after which the number of plaques, clearing in the monolayer formed by initial infection by one virus, were counted and their morphology was recorded as well. A calculation was done to determine the number of plaque forming units in each dilution.

Once several plaque assays were performed that yield similar data, the calculations were used to compare to previous experiments in which there were alterations to the E2 tail. Based on these comparisons, the phenotype of the mutant is determined.

Results And Discussion

After making transcripts, transfecting BHK and U4.4 cells, and performing plaque assays on BHK and C710 cells, the titers (number of plaque forming units) of each mutant virus on the two cell monolayers were compared. Percentages of the amount of virus made in each assay were calculated in comparison to the tyrosine 420 (Y420) mutant (see Table A, Figures 1, 2, and 5).

Conclusion

Our research showed that both mutations had a great decrease in the amount of virus formed; however, the results were not significant enough to produce a feasible virus mutant to be

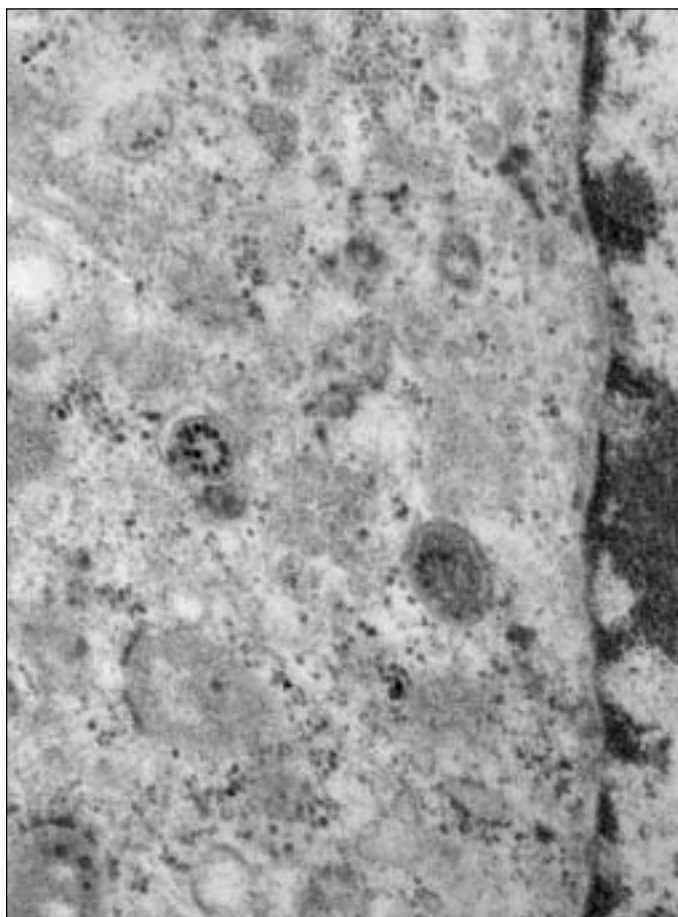


Figure 3. BHK FF (phenylalanine) virus after transfection.

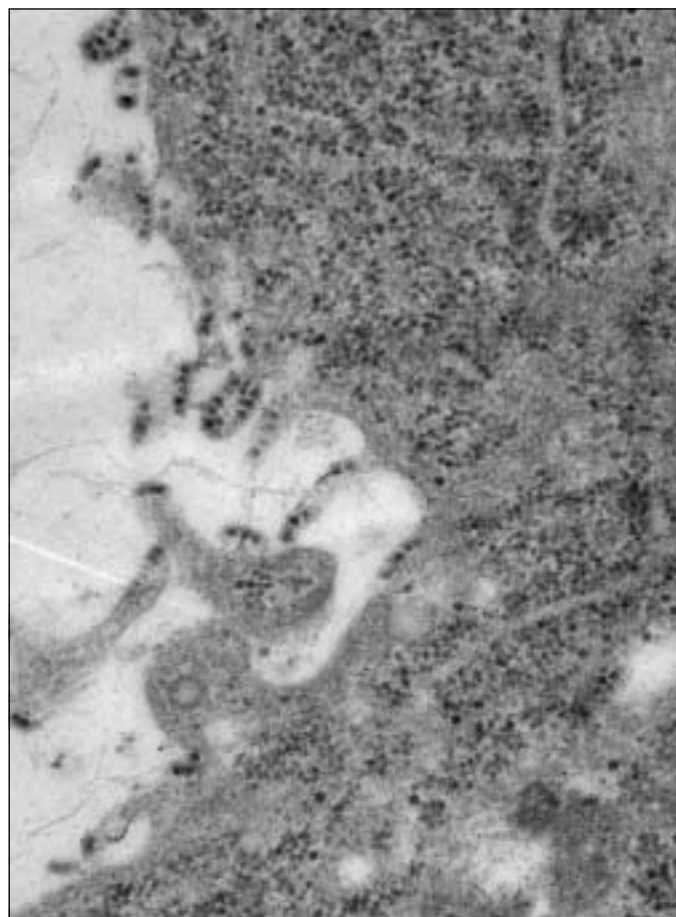


Figure 4. BHK KK (lysine) virus after transfection.

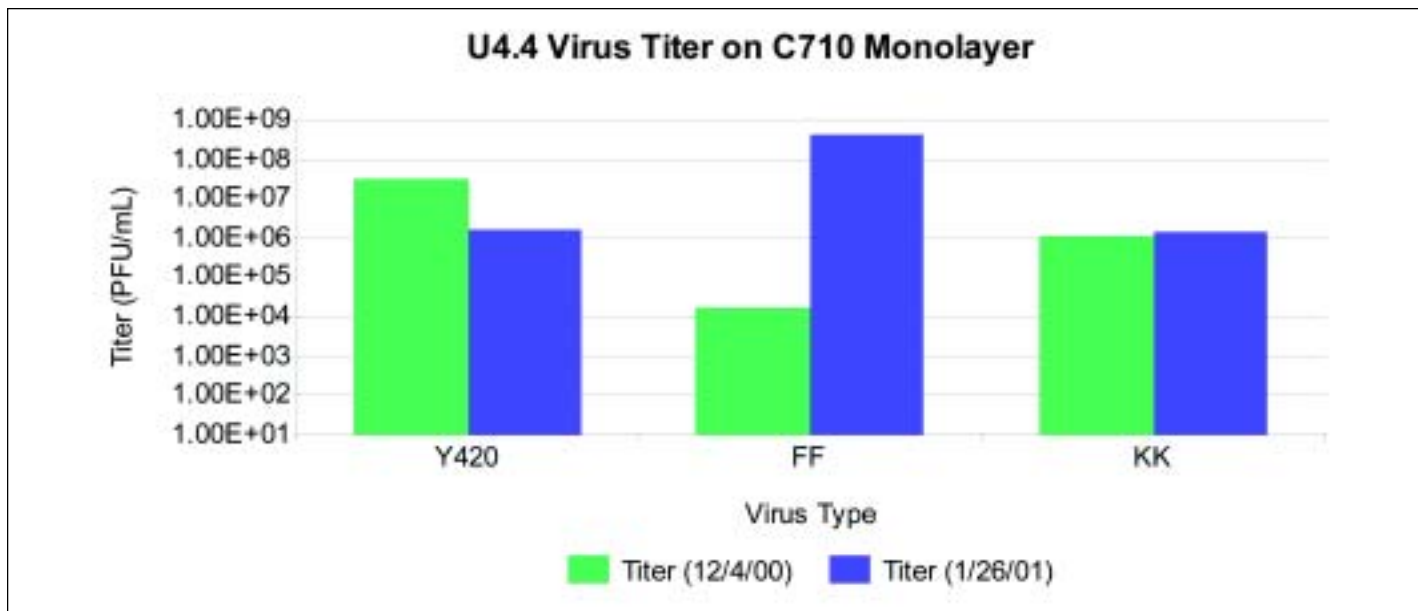


Figure 5. Graphic representation of comparative analysis of plaque forming units for U4.4 mutant virus on C710 monolayer.

used for a vaccine strain. As seen in Figure 3, the mutation involving the double phenylalanine forms a complete capsid around the virion particles; the double lysine mutation, however, shows a horseshoe shaped virus - *Figure 4*. This was not expected because our phenylalanine mutant had the largest percentage decrease in the number of plaque forming units (PFU) in comparison with to the lysine mutant (see Table A and Figures 1, 2, and 5). Because of the unexpected shape of the virus produced in the lysine mutant, further research will need to be conducted to analyze why this shape was produced in this mutant.

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Acknowledgements

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About the Author



Katharine Kapfer was born in Stuart, Virginia in 1980. She moved in 1995 to Winston-Salem, North Carolina, where she graduated in the top 10% of her class from West Forsyth High School in 1998. Kapfer received her BS in biochemistry with a minor in genetics and biochemistry from North Carolina State University (NCSU) in May 2002. She is currently continuing the research in in this article in the graduate program at NCSU in Molecular and Structural Biochemistry; she hopes to receive her MS in May 2003. Kapfer has been a member of ISPE since 2001.



Top executives from pharmaceutical, biotech, and mid-sized companies discuss their perspectives about the state of the pharmaceutical industry and predictions about the next 5-10 years.

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What Now, What Next: Pharmaceutical Executives Speak Out

by Lynn Ly Johnston

Earlier this year, ISPE interviewed top executives, including presidents and vice-presidents of the largest pharmaceuticals, biotech, and mid-sized companies. The group included the following: Frank M. Deane, PhD, Vice President, Quality, Eli Lilly and Company; Peter J. Dickinson, Vice President, Operations, Boehringer Ingelheim/Roxane Laboratories; Paul N. D'Eramo, Executive Director, Worldwide Policy and Compliance, Johnson & Johnson; Larry Kranking, Vice President and General Manager, Eisai Inc; John Mitchell, President, Global Manufacturing, Pfizer Inc; Jim Murphy, Vice President, Corporate Engineering, Alcon Laboratories Inc; Charles A. Portwood, President, Global Supply Chain,

Wyeth Pharmaceuticals; Ulrich Rudow, Vice President, Worldwide Engineering Services, Johnson & Johnson; Geoff Slaff, PhD, Vice President, Process Development, Amgen, Inc; Barrie Thorpe, Executive Vice President, Operations, AstraZeneca.

Telephone interviews conducted over several weeks probed their perspectives about the state of the pharmaceutical industry and predictions about the next 5-10 years. Not surprisingly among this group of seasoned executives, there were strong opinions about the state of operations, manufacturing, engineering, supply chain, and regulatory compliance - functions for which many have primary global responsibility and which many describe as on the brink of massive change.

Big Gets Bigger

Respondents anticipate further mergers and acquisitions with big pharmaceuticals continuing to grow. Many predict the emergence of mega-players larger than GlaxoSmithKline. Marketing, research and development capabilities are cited as the primary benefit of size, with smaller firms, stagnating companies, and research players as prime takeover targets.

At the same time, some speculate, "How big is too big?" An executive from one of the largest companies concedes there is a question of whether we can "get out of our own way" to be successful. At what point is size not productive anymore, questions more than one executive.

Most agree there is room for more than just a handful of companies at the top. "We won't be like the automobile industry with just three major players," says one respondent. Most anticipate strong niche players. "There will be legitimate, viable markets too small for the large companies. This is where we will make our money," says an executive of a mid-sized company.



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...some executives express frustration at the industry's antagonistic posture toward the FDA as a "convenient excuse" for lack of innovation. They cite the need for a more proactive, inclusive relationship.

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Changing Economics

With an estimated \$40 to \$100 billion worth of pharmaceutical patents expiring in the next few years, generic competition will intensify, coupled with greater investment in research and development in an all-consuming race for the next blockbuster.

Respondents expect greater scrutiny of drug prices from managed care firms, consumers, and government. Most worrisome to the group is the specter of price controls in the United States. While most respondents do not expect strict price controls, any shift would be significant since the United States is the only market without price regulation. The emerging European Union is another factor although few believe price controls will ease in Europe.

Executives say changing economics have made companies look for cost savings elsewhere in the value chain. Manufacturing in particular, they say, is under increasing scrutiny to become more efficient. "We have not lived in the real world," concedes one interviewee. "There's a group think," adds another, urging adoption of manufacturing techniques from chemical, automotive, and consumer goods industries. However, others caution, "Medicine is not a widget."

Continued Consolidation and Outsourcing

Respondents report excess manufacturing capacity in their companies -- one executive speculates as much as 70% to 80% under-utilization. Many anticipate massive closings and consolidation, as well as pressure to expand to 24-hour shifts and increase efficiencies of existing facilities.

"The manufacturing world is getting much smaller," with continued geographic migration to low cost and tax-friendly regions such as Ireland, Puerto Rico, Mexico, Singapore, Eastern Europe, and India.

Respondents also say outsourcing will increase although they have decidedly mixed opinions about its effectiveness. Many concede that some companies do not view manufacturing as a core competency and would rather "not be bothered" if compliance and quality can be assured. However, they say that companies have been "burned" by outsourcing attempts in the past. Some characterize outsourcing attempts as "foolish" and a "lesson learned the hard way."

Nonetheless, most agree that outsourcing will become more prevalent, as companies seek to lower head count and cut costs. The group foresees an influx of new outsource providers, as well as consolidation among suppliers to offer one-stop shopping.

Manufacturing Innovation

"We're pretty much making drugs the same way as when I started 25 years ago," says one executive. "We've had no incentive to streamline old products," explains another, citing the regulatory burden of making any process changes.

While few would dispute these sentiments, many believe that's all about to change. "The next five years will be hugely different from the last five or even 10 years," predicts one respondent who goes on to question whether colleagues are prepared.

"We're good at making lots of tablets all at once," articulates one executive. "Anything beyond that is a totally different game." The need to produce the new classes of drugs and the more targeted, potent formulations will drive innovation. "We will see real time data and validation in common use, as well as the ability to produce products on demand," say several executives although their predictions on the timeline vary from a couple of years to more than 10 years.

Emerging Biotech

Executives point to biotech as the "next big thing," while acknowledging the return on investment is still questionable. Though the investment is not likely to pay off for quite a while, many say it is "just a matter of time," pointing to the number of already established biotechs. It is not inconceivable, some respondents speculate, for biotech to change the industry almost overnight in the way amazon.com quickly emerged as a major force in the book industry.

In any case, most say biotechs will usher a new era in manufacturing requiring new facilities and techniques. Despite the emphasis on new technology, however, executives in biotech companies point to low-tech stumbling blocks such as logistics and packaging. To make up for the start up nature and lack of scale, partnerships with and acquisition by big pharmaceutical companies, they predict, will proliferate.

The State of Regulation

There are varying opinions about the regulatory process, particularly with regard to the FDA. Respondents point to increases in the regulatory process. More than one executive pointed to the need for more knowledgeable, well-trained regulators. "Even though the government wants to reduce drug prices," says one respondent, "the regulatory process only adds to the cost."

Even so, some executives express frustration at the industry's antagonistic posture toward the FDA as a "convenient excuse" for lack of innovation. They cite the need for a more proactive, inclusive relationship. Interestingly, Biotech executives say their relationship with the FDA seems more cooperative, as compared to their former interactions when employed by traditional pharmaceutical companies.

Many executives perceive "a door opening" with the FDA, signaling an era of greater collaboration. In particular, the development of "Process Analytical Technology" and harmonization of standards among regulatory bodies, particularly in the United States, Europe, and Japan, are promising areas for greater coordination.

What Next

The interviews are part of an exciting new approach by ISPE to stay on the forefront and meet the changing needs of members in a dynamic industry. Based on emerging trends and implications underscored by these interviews, ISPE leaders embarked on a new strategic planning process earlier this year that resulted in rearticulating the Society's vision for the future.

Developed and refined by ISPE planners from both North America and Europe, the strategic plan was approved by the ISPE Board of Directors in June. The plan reinforces the Society's purpose of developing professionals to bring innovation to the life sciences.

Furthermore, a chief tenet of the plan is the long-term goal that "The Society will integrate and lead industry professionals and regulatory agencies worldwide to improve the life sciences."

Implicit in this statement is the recognition of ISPE's unique position in developing and uniting industry and regulatory professionals.


As a foundation for ongoing planning and decision-making by the Society, the plan provides a consistent filter for potential ideas and actions. For example, the Board will consider proposals based on whether they support the long-term vision. When leaders from ISPE committees and staff convened in August, they developed tactics to further the plan's strategic goals. The resulting 2003 Business Plan will be summarized and developed by ISPE President Bob Best and serve as a basis for all staff and committee actions next year.

Even as tactics may change from year to year, the long-term vision will provide a clear strategic direction, challenging the Society to transform the industry and deliver more value to members.

About the Author



Lynn Ly Johnston has extensive experience in strategic planning and market development. Drawing upon her expertise in instructional design and large group facilitation, Johnston has designed and facilitated effective strategy sessions for groups of up to 500 participants. Her approach to business planning has enabled organizations to establish more direct links between broad strategies with operational plans and initiatives. She has worked with some of the most respected organizations -- including National Geographic Society, Private Industry Council, IBM, McGraw Hill, and Ernst and Young. As Managing Director of Membership for the American Management Association, Johnston was responsible for increasing AMA global reach to 100,000 members across 44 countries. As Marketing Director for the American Bar Association, Johnston guided strategic planning for 35 business units. She also was Executive Director of Community Associations Institute of Dallas/Fort Worth. She frequently speaks on the subject of strategy, management, and globalization. Her most recent presentation on "Internet Strategies for Serving Global Members" at the 2001 Annual Meeting of the American Society of Association Executives is being adapted for publication. Johnston has been cited in the Wall Street Journal, Chicago Tribune, and a number of trade publications. Committed to volunteerism, she has served on the boards of Dress for Success, Bottomless Closet, Welfare-to-Work Partnership, and Volunteer Consulting Group. Johnston earned an MBA from the University of North Texas and BA from the University of Texas at Austin. Born in Saigon, Johnston has lived in Texas, Florida, and Chicago before moving to New York City where she is now based.

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Using qualification as an example, this article will demonstrate that the work to prove cGMP compliance can be carried out efficiently and in a standardized manner with minimal documentation. This is especially applicable to Bulk Pharmaceutical Chemicals (BPC) Active Pharmaceutical Ingredients (API) manufacturing.

Figure 1. Structure of the quality management system.

Designing a Standardized System Qualification Process

by Wiebke S. Herrmann

Introduction

KISS - Keep it simple stupid. This motto evidently does not have much in common with the qualification of “complex systems” like chemical reactors or analytical equipment required within the framework of cGMP compliance programs. The often common practice of qualification processes that produce a lot of paper is proof of this.

Gossip even has it that GMP does not stand for “Good Manufacturing Practice,” but rather for “Generally More Paper.”

Qualification in Validation

Unfortunately, many people confuse qualification and validation. Qualification* is the proof

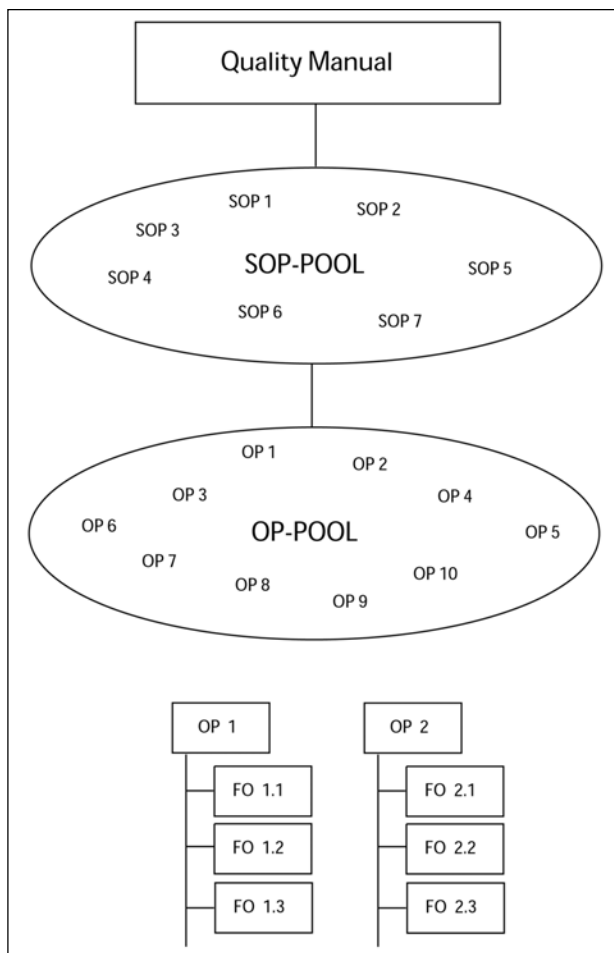
that a system is suited for its intended purpose and performs reproducibly as required. Validation is documented proof that a production process, cleaning process, or an analytical method produces consistent results that meet predefined acceptance criteria. To be able to validate a process, devices used to measure process parameters critical to quality must have been calibrated. The production or analytical systems required for the process as well as their controls must have been previously qualified.

The **qualification process** is divided into the following phases:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
- Installation Qualification (IQ): documented verification that the equipment or system, as installed or modified, complies with the approved design, the manufacturers recommendations, and/or user requirements.
- Operational Qualification (OQ): documented verification that the module, equipment, or system, as installed or modified, performs as intended.
- Performance Qualification (PQ): documented verification that the equipment and ancillary systems (in this article called production systems or systems), as connected together, can perform effectively throughout the anticipated operating ranges, including worst-case situations, based on the approved specifications.

Specifications for the systems are normally written down in the User Requirements Specification (URS). As an example, it may be defined that the jacket temperature is expected to be adjustable between -25 ± 5 °C and $+180 \pm 5$ °C. The system limits also can be determined in

Continued on page 84.



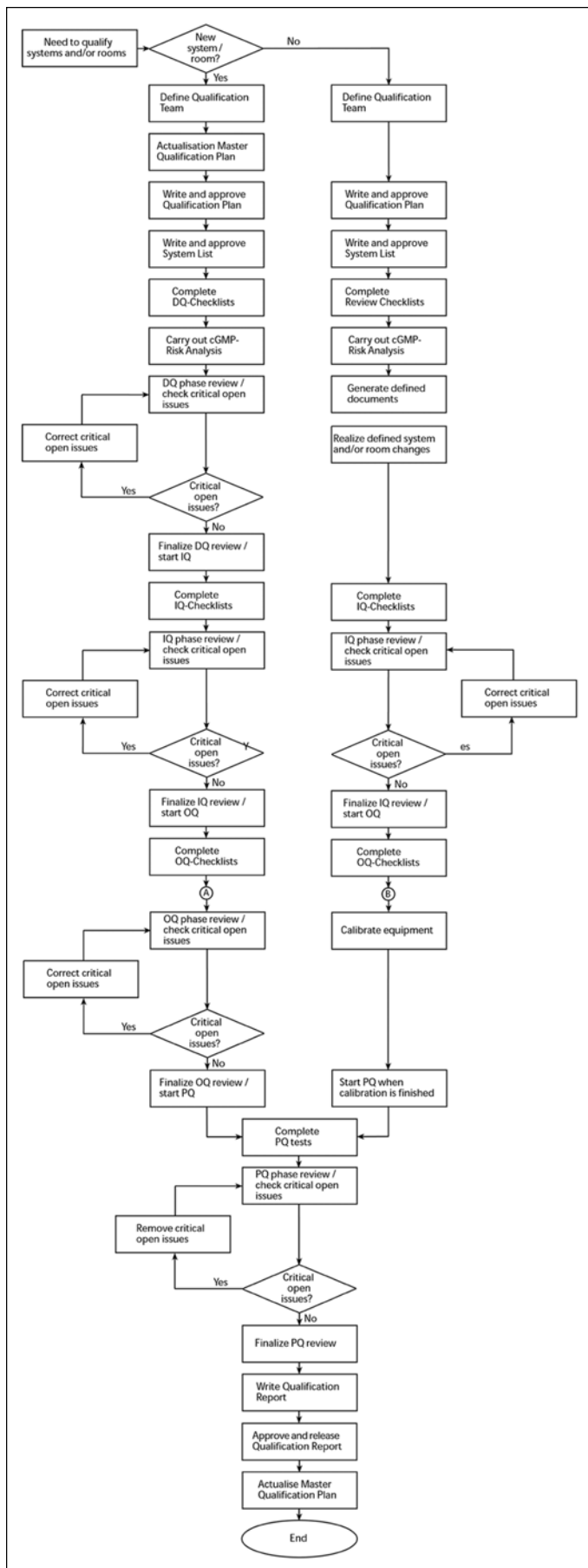


Figure 2. Qualification procedure for new and existing systems.

the PQ phase, for example, worst-case tests and achievable minimum and maximum jacket temperatures. In addition, it shows whether the software for the system performs as expected. A suitable standard test procedure can be used to perform the PQ for analytical systems.

Only when the qualification work has been successfully finished is it possible to carry out the validation for the process itself.

- Process Validation (PV) is the documented evidence that the process (production, cleaning, or analytical method), operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

A basic assumption is that systems can be used to produce several different products (multi-product systems); therefore, all these process requirements cannot be included in a single URS. The PV requirements for dedicated systems; however, already may have been defined in the URS for the system. Nevertheless, the author recommends the creation of a separate document defining the process requirements as for a multi-product system. For information systems containing no control elements (LIMS or MRPII), the product-relevant software processes such as material traceability based on defined criteria are checked for correct and reproducible functioning.

Preconditions: Quality Management System

A basic prerequisite for standardizing qualification work is an established Quality Management System (QMS) that is well thought out and structured according to the principal “Only as much paper as required, but as little as possible.”

The QMS (Figure 1) is based on a company structure with clearly defined interfaces. The departments monitor and control those work areas assigned to them and create those documents necessary for implementation or execution. The Quality Assurance (QA) Department centrally monitors the creation and revision of QMS documents and approves them.

A Quality Management Manual (QM) is created as a superordinate document. The following documents that describe and report on activities are subordinate to it:

- Standard Operating Procedures (SOPs)
- Operating Procedures (OPs)
- Forms (FOs)
- Records and Raw data

The SOPs, OPs, and FOs are prescriptive documents pertaining to activities. They are filed in a “pool” that is available to the entire company. Any work must be documented immediately after it is finished to prove that it has been done according to the prescriptive documents. The documents used to report the work are called records. Documents generated by a system, e.g., a balance or an HPLC, are called raw data. According to the top-down principle, those documents at the top of the list are created and approved first and so on down the list when the quality management system is being established.

The following will describe possible structures for and contents of the QM, SOP, OP documents, forms, records, and raw data.

Continued on page 86.

Document No and Version													
Valid from: Date													
Substitute: First Edition													
QUALIFICATION PLAN													
Process & Engineering Packages			System Packages			Qualification (DQ or Review/Q)		Qualification (OQ)		Qualification (PQ)			
REF	O&M	Description	REF	O&M	Description	REF	Description	REF	Description	REF	Description		
1.	✓	Reactor vessel	30.	✓	Reactor (1,2,3,4,5,6,7,8,9,10,12,17,31)	30.	Reactor (1,2,3,4,5,6,7,8,9,10)	30.	Reactor (2,3,9,10)	30.	Reactor (30,31)		
2.	✓	Pipework (incl. Valves)	31.	✓	Process Control System (13,14,15,16,18)	31.	Process Control System (13,14,15,16,18)	31.	Process Control System (13,14)				
3.	✓	E&I (electrical comp., wiring, cabling)	32.	✓	N ₂ - System (2,3,8,11,17)	32.	N ₂ - System (2,3,8,11,17)	32.	N ₂ - System (2,3,8,17)	32.	N ₂ - System (32)		
4.	✓	Receiver	33.										
5.	✓	Separator	34.										
6.	✓	Chiller	35.										
7.	✓	Header	36.										
8.	✓	Filter	37.										
9.	✓	Pump	38.										
10.	✓	Load cell	39.										
11.	✓	Tank	40.										
12.	✓	Dedicated vacuum	41.										
13.	✓	Programmable Logic Controllers (PLC)	42.										
14.	✓	Supervision, Control and Data Acquisition (SCADA)	43.										
15.	✓	Server	44.										
16.	✓	CPU	45.										
17.	✓	Firmware	46.										
18.	✓	Computer Hardware	47.										
*Tick off if needed ✓													
Qualification Plan Revision			00										
Author			Approval			Release							
Name		Date	Initial		Name		Date	Initial		Name		Date	Initial

Table A - Part 1. Example of a qualification plan.

Quality Manual (QM)

Top management is responsible for the quality manual. The basic quality principles that must be adhered to are defined in the QM. The activities and areas of responsibility, the superordinate applicable laws, guidelines, standards, and the delegation of responsibilities required to achieve and maintain those principles are defined in the QM for each department.

A particular activity can be carried out in more than one department. However, in each case, only that department designated in the QM is responsible for creating the prescribed documents. All the other departments must adhere to the contents of those documents.

Standard Operating Procedures (SOPs)

An SOP contains general information, instructions, and requirements. There is only one SOP for each responsibility

listed in Table A. This is made available to the entire company in the so-called “SOP POOL” and must always be used to carry out the described activity. It describes, wherever possible in flow chart form, which jobs must be carried out in which order according to which OP. It also assigns responsibilities for initiating or carrying out the tasks. In this article, those people responsible are referred to by their job titles.

Operating Procedures (OPs)

An OP describes in detail how the work must be carried out and is a support document to an SOP. The OPs pertain to the work to be carried out and not to the individual departments. Every person carrying out work described in the OP must adhere to the instructions in it.

The OPs also are placed in the “OP POOL” where they are made available to the entire company.

Document No and Version													
Valid from: Date													
Substitute: First Edition													
SYSTEM LIST													
REF (QP)	System No	System Name					Supplier Audit REF (QP)	FAT REF (QP)	SAT REF (QP)	OP No System QP			
30	000.111.001	Reactor 111					---	1,3	---	OP001			
31	000.222.001	Process Control System 222					13,14	13,14	13,14	OP001			
32	000.333.001	N ₂ - System 333					---	---	---	OP002			
System List Revision													
00													
Author			Approval			Release							
Name		Date	Initial		Name		Date	Initial		Name		Date	Initial

Table A - Part 2. Example of a system list.



... to standardize the qualification, an SOP must first be created which includes all the general information necessary for carrying out qualification, names the associated documents, and describes those procedures that always must be adhered to for qualification work.



Forms (FOs)

Forms are always attached to an OP. They are standard reports for the work carried out according to the OP. However, they also can be used as plans, e.g., project plans, master plans, or as a template.

Records and Raw Data

As soon as work is reported in a document, the document becomes a verification document or record, such as completed forms and documents used to report tests. Raw data are printouts, chromatograms, etc.

Standardized versus Non-Standardized Qualification

A non-standardized qualification system often contains a variety of less than optimum methods. For example, a Qualification Master Plan (QMP) is created for each individual qualification, which includes a lot of general information about the company and only a small part dedicated to the actual planned qualification. If something described in those various QMPs is changed, they have to be adapted accordingly, which is a lot of unnecessary work. To go into more detail what qualification work is actually planned, a Qualification Plan (QP) is usually written. Often this document contains a lot of general information concerning the structure of the quality management system or the planned project execution, such as the qualifica-

tion timetable included in the QP and the project plan. If something changes, the corresponding documents need to be adapted. In such a case, the really important information is almost impossible or at least very difficult to decipher. Next, pages and pages of documents from the system's planning phase are copied into the qualification documentation for the execution of the qualification work. These planning documents usually already contain all the information required to carry out the qualification work.

This frequent practice leads to the "Generally More Paper" mentioned at the beginning of this article, and it also produces many possible sources of error. For example, when something is changed on the system and the qualification documents are not updated, errors may occur in copying text.

In contrast, it is assumed that a standardized qualification system already basically meets the requirements for the cGMP compliance, for example, concerning training, maintenance, calibration, change control, and validation. Information on these points can be taken from company's quality manual, and thus do not need to be repeated in the qualification documents as is done during non-standardized qualification work. If required, the QM can be submitted to the authorities.

In addition, in a standardized qualification, all the work follows a general pattern. The work that needs to be carried out for the qualification of a new system, for example, is planned, the design determined, and finally the installation, function,

Document No and Version							
Valid from: Date							
Substitute: First Edition							
DQ - CHECKLIST PROCESS TECHNOLOGY							
System Name						REF (QP)	
System No							
No	Document Name	Available check appropriate	Document No Revision No Revision Date	File	Comments	Date	Initial
1.	P&ID Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
2.	Process flowsheet Approved (N/A for multi product plants)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
3.	Functional Specification Process Technology Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
4.	List of equipment Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
5.	List of fittings Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
6.	Specifications for all parts mentioned in lists points 4./5. Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
7.	List of equipment fabrication drawings Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
8.	Equipment fabrication drawings mentioned in point 7. Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
9.	Piping Isometrics and/or "Spool Drawings" Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
10.	Recommended Spare Parts List Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					
11.	Recommended for Lubrications List Approved for execution	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A*					

*Not Applicable - document reason in the comment area.

Table B. DQ checklist from the process technology module.

and performance tested. To standardize the work this procedure only needs to be written once in an SOP, which must always be followed. All the other work to be carried out can be written into standardized OPs. This is possible because the system is broken down into units, thus allowing the requirements for these units to be standardized. The requirements of the authorities must be taken into account when the work to be performed is determined.

This point reduces the amount of work and ultimately paper because the procedure and the work to be carried out is only written down once.

The requirements for a new system are also written down in predefined documents usually as part of a project. These documents can, in turn, be used for testing. However, the prerequisite is that how the test is to be carried out and reported on using the documents is defined in OPs.

Thus, the standardization requires increased effort at the beginning because interfaces must be exactly defined and the processes unified. In addition, the work processes for the system units and the reports made on them must be standardized as much as possible. However, once employees have been initiated to and trained on the process, the standardized qualification takes less work during the qualification itself as no documents need to be copied. This means that less paper is produced long-term because documents that are created as part of the normal work process are used to carry out the qualification. A side effect is that less archive space is required.

Thus, in order to standardize the qualification, an SOP must first be created which includes all the general information necessary for carrying out qualification, names the asso-

ciated documents, and describes those procedures that always must be adhered to for qualification work. Various OPs also are required to describe the different tasks. An example of the SOP Equipment Qualification and the OPs required for qualification are provided below.

Example of SOP System Qualification

As mentioned before, a basic assumption is that a system can be used to produce several different products. Thus, a clear distinction is made between the qualification of the system including its control computers (hardware) and software, and the validation of the processes. The control (Category 4 and 5 software according to GAMP) is tested for functionality and performance during the qualification. These tests are made during the software-specific Factory Acceptance Tests (FAT) as part of the IQ phase for the system and the software-specific Site Acceptance Tests (SAT) during the OQ phase for the system. The hardware is qualified during the IQ for E&I. The coordination between the software and the computer hardware is verified by the SAT at the latest. Finally, tests are made during the PQ phase to see if the software works correctly in connection with the production equipment and if the software and the equipment together (production system) perform as specified in the URS. Thus, the tests made in the PQ phase show if the software can be validated as part of a production process. (Author's note: The features that are tested during the validation of the production process are: first, if the control works reproducibly during the manufacture of the product. Second, if consistently good results are achieved according to the acceptance criteria in the product specification. Third, if

Continued on page 90.

Document No and Version					
Valid from: Date					
Substitute: First Edition					
DESIGN QUALIFICATION REVIEW REPORT					
System Name			System No		
Building No			Room No		
Reviewed by			REF (QP)		
No	Review of	Acceptance criteria	Accepted Yes / No / N/A*		Comments
1.	cGMP-Risk Analysis	Completed, issues implemented into DQ documentation			
2.	DQ-Checklist Process Technology (incl. Documentation)	Completed			
3.	DQ-Checklist E&I (incl. Documentation)	Completed			
4.	DQ-Checklist Room (incl. Documentation)	Completed			
*Not Applicable.					
Critical open issues for quality or safety		<input type="checkbox"/> Yes, #: _____ <input type="checkbox"/> No, proceed approval and release for execution			
DQ-Review Chairman (Name)					
Date		Sign			
Critical open issues removed		<input type="checkbox"/> Yes, proceed approval and release for execution		Date: _____	Initial: _____
Approval			Release for IQ		
Name	Date	Initial	Name	Date	Initial

Table C - Part 1. DQ review report.

the control is suited for the production of the specific product.)

All commissioning work, which also is needed during qualification, is carried out in accordance with Good Engineering Practice (GEP). During procurement, all needed actions and documents for qualification have to be included into the order forms. The order is written in accordance with the procurement

SOP by Logistics. The documents created during the system design are the basis for the qualification work. The following eight sections describe an SOP-Example:

Introduction

The qualification procedure described is used for multi-product

Document No and Version					
Valid from: Date					
Substitute: First Edition					
OPERATIONAL QUALIFICATION REVIEW REPORT					
System Name			System No		
Building No			Room No		
Reviewed by			REF (QP)		
No	Review of	Acceptance criteria	Accepted Yes / No / N/A*		Comments
1.	OQ-Checklist Process Technology (incl. Documentation)	Completed			
2.	OQ-Checklist E&I (incl. Documentation)	Completed			
3.	OQ-Checklist Room (incl. Documentation)	Completed			
4.	Copy of actual change controls from list	Available			
5.	After IQ started change controls from list	Completed			
6.	Commissioning checklist	Completed			
7.	Preventive maintenance checklist	Completed			
8.	System log book	Available			
*Not Applicable.					
Critical open issues for quality or safety		<input type="checkbox"/> Yes, #: _____ <input type="checkbox"/> No, proceed approval and release for execution			
OQ-Review Chairman (Name)					
Date		Sign			
Critical open issues removed		<input type="checkbox"/> Yes, proceed approval and release for execution		Date: _____	Initial: _____
Approval			Release for PQ		
Name	Date	Initial	Name	Date	Initial

Table C - Part 2. OQ review report.

and dedicated systems. Because the work to be carried out is not the same for new and existing systems, a general distinction is made between two different types of qualification:

- Qualification of New Systems
- Qualification of Existing Systems

The different phases of the qualification take place according to the defined procedure:

- Creation of the Qualification Plan (QP)
- Either the Design Qualification (DQ) for new systems or a Review Phase (Review) for existing systems
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)
- Creation of a Qualification Report (QR)

Specific Guidelines and Standards

Good Automated Manufacturing Practice (GAMP 4) Guide for Validation of Automated Systems in Pharmaceutical Manufacture, Version 4.0, December 2001 is used to qualify computer systems. (Author's note: I use the GAMP as a guideline for computer system qualification; however, GAMP does not

make a clear distinction between production processes and processes that take place within the software. Because production processes are validated and the control software is a component part of the production system, the control software also is qualified. The activity described under PQ in the GAMP takes place during the validation of the production process).

In addition, the ISPE Baseline® Guide for New and Renovated Facilities, Vol. 1 Bulk Pharmaceutical Chemicals, June 1996 is used.

Definitions

For definitions of DQ, IQ, OQ, and PQ see Qualification in Validation.

Tasks and Responsibilities

The Engineering Department is responsible for carrying out the qualification. When the qualification work has been completed and the system qualified, the qualified system is handed over to the production department. (Note: the production department is responsible for producing and carrying out validation work on qualified systems.)

The composition of the qualification team and who is responsible for what is defined in the project management SOP.

Basics

A system should be capable of operating in a reproducible manner within the defined limit values and tolerances. The tests should be repeated often enough during the qualification work to prove this is the case. The cause of any detected errors and deviations must be found and corrected. After this is done,

Continued on page 92.

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Once the qualification work has started, any changes must be made according to the Change Control process. As for new systems, standard forms described in OPs are used to report on all the tests that are carried out during Review Phase, IQ, OQ, and PQ.



the tests must be repeated to make sure that the specification is met. Tests, e.g., FAT, SAT, and Performance Qualification, are witnessed by the user and they are considered to have been passed when the results lie within the predefined acceptance criteria. After the tests have been carried out and before the phase review, the test documents are checked by the specialists responsible and approved when the requirements have been met.

A qualification phase can only be finished and the next started when the documents created have been reviewed and no critical quality or safety issues have been found. All qualification documents are filed and archived according to the requirements of the document management department. Figure 2 shows the sequence of the qualification process for new and existing systems.

Qualification Procedure for New Systems

For new systems, the system design is determined in the DQ phase. (Note: the key document to start work is the URS, based on this the functional specification and all other needed documents are created.) To ensure that all cGMP requirements are implemented, a cGMP Risk Analysis is performed and the findings are implemented into the system documentation. During the DQ phase, a change management and document management system are in place. As soon as the design has been approved for execution and/or the Design Qualification Review has been carried out, any further changes must be made according to the established Change Control process. During IQ, tests are made to check if the system has been

installed according to the requirements. When required, an FAT is carried out for Category 4 and 5 control software. In the OQ phase prior to the parameter adjustment, any required calibration is made.

The used components are tested to see if they function according to the functional specification. The SAT for Category 4 and 5 control software is also part of the OQ phase. Finally, in the PQ phase the entire system is tested to see if it performs as expected by the user as given in the URS (remember: no process validation requirements therein). The tests are written down in a corresponding OP. For dedicated systems, the first production phase with placebo or product after OQ can be designated as the PQ phase.

Qualification Procedure for Existing Systems

Once the qualification work has started, any changes must be made according to the Change Control process. As for new systems, standard forms described in OPs are used to report on all the tests that are carried out during Review Phase, IQ, OQ, and PQ. Existing systems usually show through their many years of use that they function according to variable requirements, but be ready for problems. Do not make any attempt to qualify the unqualifiable. The qualification work focuses more on the documentation (“documented evidence”), showing that the system and its control are suited for the intended purpose.

The intended purpose and the required/existing performance are written down during the Review. In addition, as well as for new systems, a cGMP Risk Analysis is carried out. In this case, the analysis evaluates the existing system and its envi-

Document No and Version					
Valid from: Date					
Substitute: First Edition					
PERFORMANCE QUALIFICATION REVIEW REPORT					
System Name			System No		
Building No			Room No		
Reviewed by			REF (QP)		
No	Review of	Acceptance criteria	Accepted Yes / No / N/A*	Comments	
1.	PQ test according to OP	Tests passed		OP #: _____	
2.	Copy of actual change control list	Available			
3.	After OQ started change controls from list	Completed			
4.	OP for system cleaning	Available		OP #: _____	
*Not Applicable.					
Critical open issues for quality or safety		<input type="checkbox"/> Yes, #: _____ <input type="checkbox"/> No, proceed approval and release for execution			
PQ-Review Chairman (Name)					
Date		Sign			
Critical open issues removed		<input type="checkbox"/> Yes, proceed approval and release for execution		Date: _____	Initial: _____
Approval			Release		
Name	Date	Initial	Name	Date	Initial

Table C - Part 3. PQ review report.

Document No and Version								
Valid from: Date								
Substitute: First Edition								
System No			System Name			OP No		
OVERVIEW PQ TEST RESULTS								
PQ Test No	Feature/Operation	Variable	Target Requirement	Acceptance Limits/Criteria	Observed Result	No of tests	Pass or Fail*	Comments
1	Vacuum test	Pressure	Max. vacuum	Less than 40mbar	32mbar	2	Pass	---
2	Jacket temperature	Temperature	1. Setpoint achieved -25°C, -10°C, 80°C, 140°C, 180°C 2. Min./max. Temp.	1. ±5°C of each setpoint 2. For information only	1. -26°C, -8°C, 80°C, 142°C, 178°C 2. -29°C, 186°C	1.1 2.1	1. Pass 2. Pass	---
*Result from last test number								
System is qualified		<input type="checkbox"/> Yes <input type="checkbox"/> No	Comments					

Table D. Simplified overview of PQ test results as an integral part of the QR.

ronment for its cGMP compliance (cleanability, materials, etc.) and sets any measures necessary to achieve compliance. Further, reports are made on what system documentation is available and on any documentation that must be created or procured. Often supplier audits, FAT, and SAT cannot be made for an existing system, or can only be made under limited conditions. The requirements to qualify the system are defined during the review phase.

In the IQ phase, the existing documents are compared with the built system, and any missing documents defined in the Review Phase are created or procured. The defined measures from the cGMP Risk Analysis will be implemented during the IQ. The redlined documents are part of the IQ documentation.

Because existing systems have usually been in use for many years, the calibration is performed and the functional tests during the OQ phase are skipped (but remember: better safe than sorry). The system documentation must be “as is” and available in approved form. The PQ is carried out in the same way as the PQ for new systems. The Qualification Master Plan (QMP) update only may be made when the qualification work has been completed.

Re-Qualification

All systems must be re-qualified within a given period of time. During re-qualification, checks are made to see whether the system has been altered and that any alterations have been handled according to change control procedures, whether the documentation corresponds to the “as is” status and whether the system continues to perform as required. Parts of the IQ and the entire PQ are repeated according to the applicable OPs. The PQ test results are compared against URS. If the re-qualification is prompted by a planned alteration, then it must be carried out according to the procedures for qualifying a new system.

Operating Procedure Qualification Master Plan (QMP)

The QMP is not, as often described, a project management tool that must be created anew for each planned qualification. It is rather an overview document that records which systems will be qualified by when, which systems are already qualified, and when the re-qualifications are planned. It also names who is responsible for the systems. It is an aid for planning the qualification work as a whole. If a system does not need to be qualified, the rational must be entered in the QMP.

The OP Qualification Master Plan describes how and by whom the QMP is to be maintained, and what responsibilities concerning the qualification those responsible for the system have. The QMP itself is linked to the OP as a form.

Operating Procedure Qualification Plan (QP)

The Qualification Plan and the System List in Table A reflect the modular design of the systems. The modules and their link with the type of system are defined in the Qualification Plan. The System List gives all the systems to be qualified and is used to determine for which system modules a Supplier Audit, a Factory Acceptance Test, and/or a Site Acceptance Test must be carried out.

Concludes on page 94.

The QP form and the System List are designed as templates, which are linked to the OP as a form. They are completed and approved by the responsible persons.

Operating Procedure System Qualification

Systems and rooms can be divided into units, and the requirements on these units or modules can be standardized. Three modules are defined: Process Technology, E&I, and Room. The Process Technology module covers all the requirements on the mechanical part of a system. The E&I module contains all the components from this area including the software and hardware for the control. Because the process technological requirements on the room are very different to the requirements for a system the checklists are defined separately, but according to the same principles.

The following explanations are based on the qualification of a new system. Checklists are created for the three modules. These checklists contain all the standardized qualification requirements for the DQ, IQ, and OQ phases. The question to be asked during DQ: Is the document approved for execution available? During IQ: Is the document checked? During OQ: Is the document "as is?" Table B shows the checklist for the Process Technology module as an example. (Author's comment: all the requirements from the GAMP concerning the qualification of the control must be included into the checklists for E&I). The main difference between the DQ, IQ, and OQ checklists is that in DQ the documents are approved for execution. During IQ, the test documentation, called "checked," and for OQ the end-version, called "as is," is approved and available.

During the qualification phase, the checklists are completed by the responsible specialists. The PQ phase does not need a special checklist because the operations to be carried out are defined for every system specifically in individual OPs (system specific test protocol). During the phase review, the qualification team checks again whether the cGMP requirements have been met and whether all formal aspects of the qualification have been implemented. Each phase review also is carried out with standardized forms. An example is given in Table C.

A list of "Open issues" is written during each Phase Review. This list contains all discovered deviations as well as open points and the measures defined for corrective actions. Every open issue is classified by the qualification team if it is uncritical, moderate, or critical for quality and/or safety. A person is defined and made responsible to carry out the work by a given deadline. If there are critical open issues concerning quality or safety, the phase review can only be approved and released after the corrections have been implemented.

The checklists and forms for the review phase, IQ, and OQ for the qualification of existing systems vary somewhat from those for new systems as the requirements placed on old systems are similar. The procurement or creation of some documents is hardly or not at all possible once the system has been commissioned and has been used for a certain period of time.

Operating Procedure Qualification Report (QR)

The qualification report is written when all the qualification work has been finished. A separate report can be written for each system, or a single report can be written for all the systems according to the System List. However, for later use,

it seems a good idea to write a separate report for each system soon after the qualification work has been finished. If a single report is written, the time between finishing of the work and finishing of the QR could be very long depending on the number of systems involved. The report must contain the statement on whether the system is qualified or not. It also should contain an overview of all the tests and their results. An example for this overview is given in Table D. The overview is, among other things, an important document for deciding whether or not a system is suited for a production process.

Synopsis

In this article, a standardized system for qualifying new and existing production systems is presented. The advantage is minimized paper, comprehensive, clearly structured, same procedures for every system through standardized modules and ease of use. It is especially applicable to BPC/API manufacture.

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*The definitions about Qualification, Validation, and Performance Qualification used in this article represent the author's opinion only.

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