

This article provides a summary of the Standard Operating Procedures according to VDI/VDE 3517, part 4.

Operation and Maintenance of Process Control Systems in the Pharmaceutical Industry - Standard Operating Procedures according to VDI/VDE 3517, Part 4

by Dipl.-Ing (TH) Volker Teuchert

Introduction

Since 1994, the GMA/NAMUR Committee "Validation of Control Systems" has worked on validation of process control systems as a joint activity of the European pharmaceutical industry and process control industry. The first results were presented in this journal in 1997.¹ The members of the GMA/NAMUR Committee are shown in Figure 1. The activities are continuing and as a further result, the VDI/VDE-guideline 3517 "Validation of Control Systems"² has been published covering the field of process control systems validation. The guideline is addressed to system planners (engineering), constructors, vendors, and users of control systems. It consists of five parts which are shown in Figure 2.

The GMA is a specialist society of the two engineering associations Verein Deutscher Ingenieure (VDI) [Association of German Engi-

neers] and Verband Deutscher Elektrotechniker (VDE) [Association of German Electrical Engineers] with approximately 14,000 members. The scope of work includes process control systems, sensor and actuator technology, computational intelligence and information processing, and related areas. The GMA performs its tasks by:

- organizing congresses, specialized conferences, discussion days, etc. to promote the flow of information concerning new processes and developments
- preparation of publications, recommendations, and guidelines
- scientific preparation for standardization
- representing the special field in international organizations (IFAC, IMECO)
- participation in the planning and implementation of training and further training measures
- promotion of the exchange of information between companies, industry, authorities, engineers (catalytic effect)
- publication and promotion of technical and scientific literature

About 1,000 specialists work on a honorary basis on the more than 80 specialist committees and sub-committees of the GMA.

NAMUR is the User Association of Process Control Technology in Chemical and Pharmaceutical Industries. It is:

- an international association in the field of process control technology (1/3 of the members do not originate from Germany, the rest from Germany)

Figure 1. GMA/NAMUR Committee on Validation of Process Control Systems.

GMA/NAMUR Committee on "Validation of Process Control Systems"	
Pharmaceutical Industry (NAMUR)	Process Control Industry (GMA)
<ul style="list-style-type: none"> • Aventis • BASF • Bayer • Boehringer Ingelheim • Degussa • Hoffmann LaRoche • Merck • Novartis • Schering 	<ul style="list-style-type: none"> • ABB / Hartmann & Braun • AEG • B. Braun Biotech • Fisher Rosemount • Foxboro-Eckardt • Honeywell • Propack data • Siemens • Yokogawa
<small>NAMUR is the user association of process control technology in chemical and pharmaceutical industries</small>	<small>GMA is the Society for Measurement and Automatic Control in the VDI/VDE</small>

VDI/VDE-Guideline 3517: Validation of Control Systems

- Part 1: Principles of Validation and Qualification of Control Systems
- Part 2: Execution of Process Control Projects subject to Validation
- Part 3: Retrospective Validation
- Part 4: Operation and Maintenance of Validated Systems (Ongoing Validation)
- Part 5: Validation Support by Applications of Process Control Systems (DCS/PLC)

Figure 2. VDI/VDE-Guideline 3517: Validation of Control Systems.

- a German speaking association (the working language is German, publications are in German, in some cases in English)
- an association of users from the chemical and pharmaceutical industry as well as related branches of industry (representatives of vendors and public authorities are only allowed to participate in sessions as guests)

The main goal of NAMUR is to increase added value for member companies by exchanging experiences for the use of inter-corporate synergies, adjusting requirements for further technical development and influencing authorities, supervision organizations, and standardization bodies in a coordinated manner. The actual NAMUR-structure and areas of work can be seen in Figure 3.

A close partnership between the GMA/NAMUR Committee and the GAMP initiative on validation of computerized systems has been established. The GMA/NAMUR guidelines have been integrated into version 3 of the "GAMP-Guide for Validation of Automated Systems in Pharmaceutical Manufacture"³ as examples for best practices. A preliminary version of the VDI/VDE 3517, Part 4 on Operation and Maintenance of validated process control systems in the Pharmaceutical Industry can be found here. This article provides a summary of VDI/VDE 3517, part 4.

Guideline on Operation and Maintenance of Process Control Systems in the Pharmaceutical Industry

Structure

For optimal applicability, the guideline is structured as a set of generic Standard Operating Procedures (SOPs). However, these SOPs should be adapted to project-specific or system-specific needs. For example:

- control system aspects may have to be integrated into general purpose SOPs or existing, other company-specific, regulations
- the SOPs must be adjusted to reflect organizational responsibilities in a company
- greater detail may have to be integrated into SOPs

The following 11 principal SOPs for control system operation and maintenance are included in VDI/VDE 3517, part 4:

SOP 1: Structuring and Updating the Process Control Documentation

SOP 2: Preventive Maintenance and Change Management

SOP 3: Controlled Access and Access Rights for Process Control Systems

SOP 4: Software Backup and Software Archiving

SOP 5: Modem Operations

SOP 6: Audits

SOP 7: Risk Analysis

SOP 8: Requalification

SOP 9: Procedure for the Event of System Malfunctions and System Failures

SOP 10: Change of Release, Upgrade of Hardware, Update of Firmware

SOP 11: Training

These SOPs are cross-referenced. Therefore, the cross-references should be observed when applying the SOPs to a specific project or company. All SOPs are subdivided into the following sections:

1. Scope
2. Objective
3. Procedure
4. Responsibilities
5. Documentation/Records
6. Review
7. Supplemental Documents
8. Abbreviations, Definitions
9. Attachments, Forms, Examples

In the following part of this article, a summary of objectives and procedures of the 11 SOPs is given. It has to be taken into account that the original paper goes into greater detail – additional flow charts, forms, examples, and tables can be found there. If VDI/VDE 3517, part 4 is used as guidance for creation of SOPs, the original version should form the basis. It is expected to publish the full version in English within the next few months.

Standard Operating Procedures SOP 1: Structuring and Updating the Process Control Documentation

Objective

To determine structure and extent of and responsibility for creation of documentation for new process control systems. To determine that part of documentation which has to be updated during system life cycle.

Procedure

Technical documentation for new process control systems consists of three principal parts:

- hardware documentation for field instrumentation and switch room
- hardware and software documentation for the control system
- documentation of system tests and qualification

It is recommended to define a scheme for required planning documents in compliance with current design standards like VDI/VDE 3517, Part 2: "Execution of Process Control Projects Subject to Validation." Documentation updating service during system life cycle should be defined for those parts of the planning documentation. Table A through C present a recommendation for these documentation parts. These plans should be available during the life cycle of the system and updated in case of system modifications.

SOP 2: Preventive Maintenance and Change Management

Objective

- to define maintenance activities and change management system characteristics to keep the process control system in a validated state

Procedure

It is assumed that the system has been established as a validated system and that the documentation is updated regularly during system life cycle (as described in SOP 1). Three different possible actions can be distinguished:

- Planned Maintenance
- Repair
- System Change

Planned maintenance includes maintenance and inspection measures and covers calibration of critical instruments. For these measures working instructions and time schedules are necessary for definition of maintenance actions and cycle times. Appropriate feedback and documentation after finalization of the measures are required.

Repair of validated equipment requires special actions. A failure report has to be written describing the repair carried out and the materials changed (if applicable). The report has to be distributed and analyzed. It has to be decided whether a requalification of equipment is necessary.

System changes are defined as planned modifications of the projected status of the control system. Changes of validated systems require a change control procedure including a written description of the intended modifications and a documented decision process about system change release. It is assumed that a company wide change control procedure is in place. This procedure has to be followed for changes of process

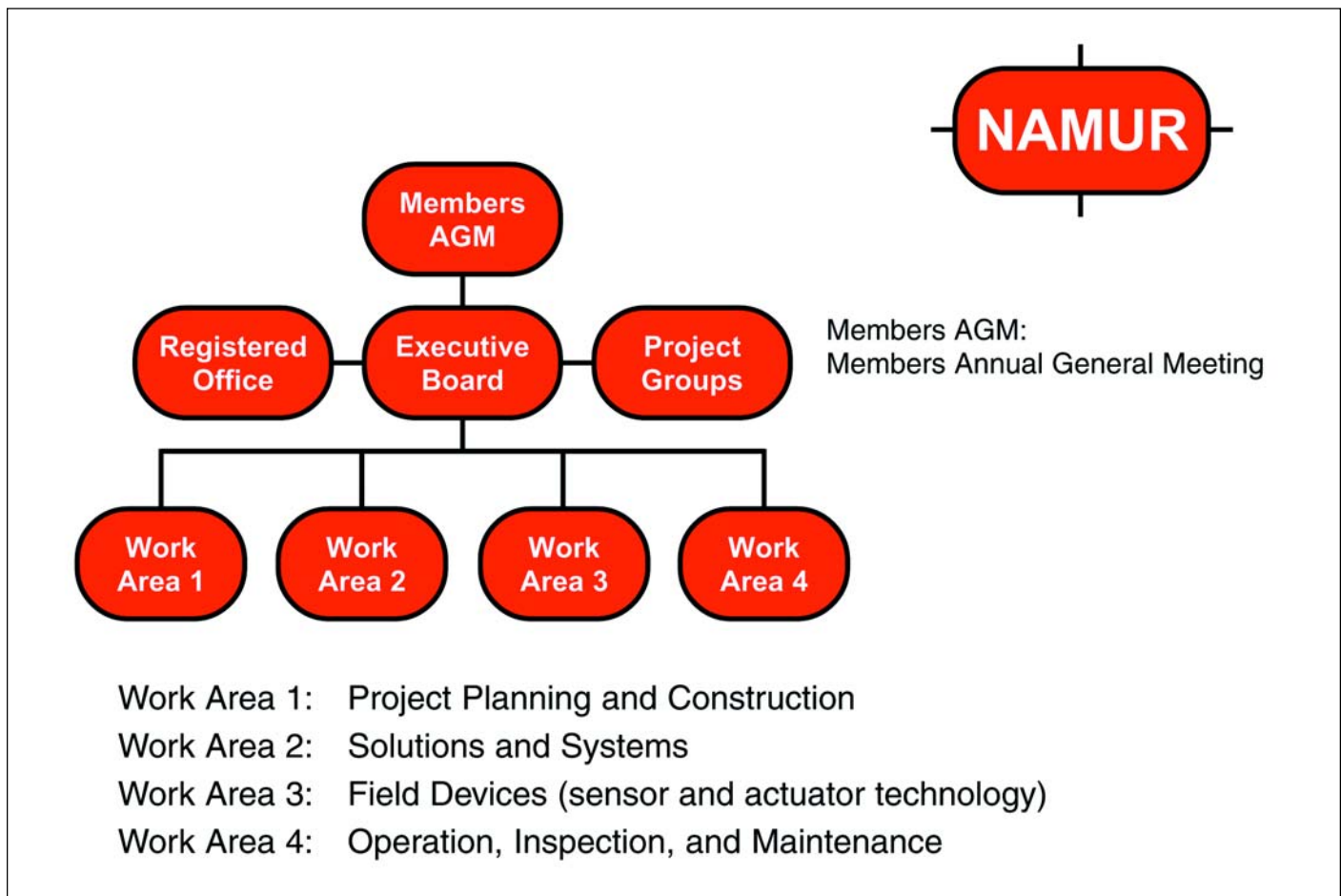


Figure 3. Structure and work areas of NAMUR.

DOCUMENT
P+I flow charts
Loop list
List of quality relevant loops
Instrument specifications and certificates
Loop sheets
Loop function sheets
Load list
Circuit list
Package unit documentation
Field instrumentation documentation
Service cabinet documentation
Wiring list
Power supply scheme
Switch room documentation

Table A. Hardware documentation for field instrumentation and switch room.

DOCUMENT
User requirements specification
Control system architecture
Supplier's documentation on system standard software (operating system, firmware, configuration tools...)
Supplier's documentation on system hardware
Supplier's manuals for system service
Software structure plan
Documentation of equipment modules, control modules, typicals
Function plans, documentation of automatic locking
Documentation of sequential control
Documentation of recipe structure
Documentation of records (incl. batch records)
Realization of system access rights
Realization of software archiving
Operator manuals

Table B. Hardware and software documentation for the control system.

Test plans Hardware and Software
Test protocols Hardware and Software
Protocol of finalization of assembly check
IQ test plan
OQ test plan
IQ protocol
OQ protocol
Protocols of requalification tests

Table C. Documentation of system tests and qualification.

control systems. Figure 4 shows an example for planning and execution of system changes.

SOP 3: Controlled Access and Access Rights for Process Control Systems

Objective

- to avoid unauthorized operation and maintenance actions on validated control systems

Procedure

Controlled access to process control systems is supported effectively by current system technologies. Thus, in modern plants, the access can be arranged by control system functions. A personal identification can be defined and is supervised by the system. Dedicated functions are connected to different personal identifications. User groups with similar qualifications and tasks should be combined to common access profiles to make access management more transparent.

Existing plants may be equipped with control systems that do not carry these features. In these cases, it is possible to ensure controlled system access by structural or organizational measures (controlled physical access to control rooms).

SOP 4: Software Backup and Software Archiving

Objective

To establish methods for software backup and software archiving (data and programs) of process control systems. **Note:** Software backup means short-time protection against physical loss or inadvertent deletion, archiving means long-term protection of data and programs on an external data carrier; archived software can be deleted from the original system.

Procedure

Data of a process control system are:

- Raw Data
- Evaluated Data

Programs of a process control system are:

- System Software (Operating System, Firmware, Configuration Tools)
- Application-Specific Programs.

1. Data Backup

Data usually are backed-up automatically by the process control system, e.g. on hard disks. If necessary, the hard disks can be designed redundant or mirrored. Additional cyclic backup of data on external media may be recommendable. Data backup can be limited to cGMP-relevant data.

2. Data Archiving

Data archiving assures the availability of cGMP-relevant data during the legally required period of time, e.g. 10 years after release of product. Data are being archived on an external data carrier and have to be checked regularly for correctness. It may be advantageous to copy data on this occasion to a new data carrier. The following items need to be defined:

- responsibility for applications for and execution of data archiving
- type and labelling of data carrier

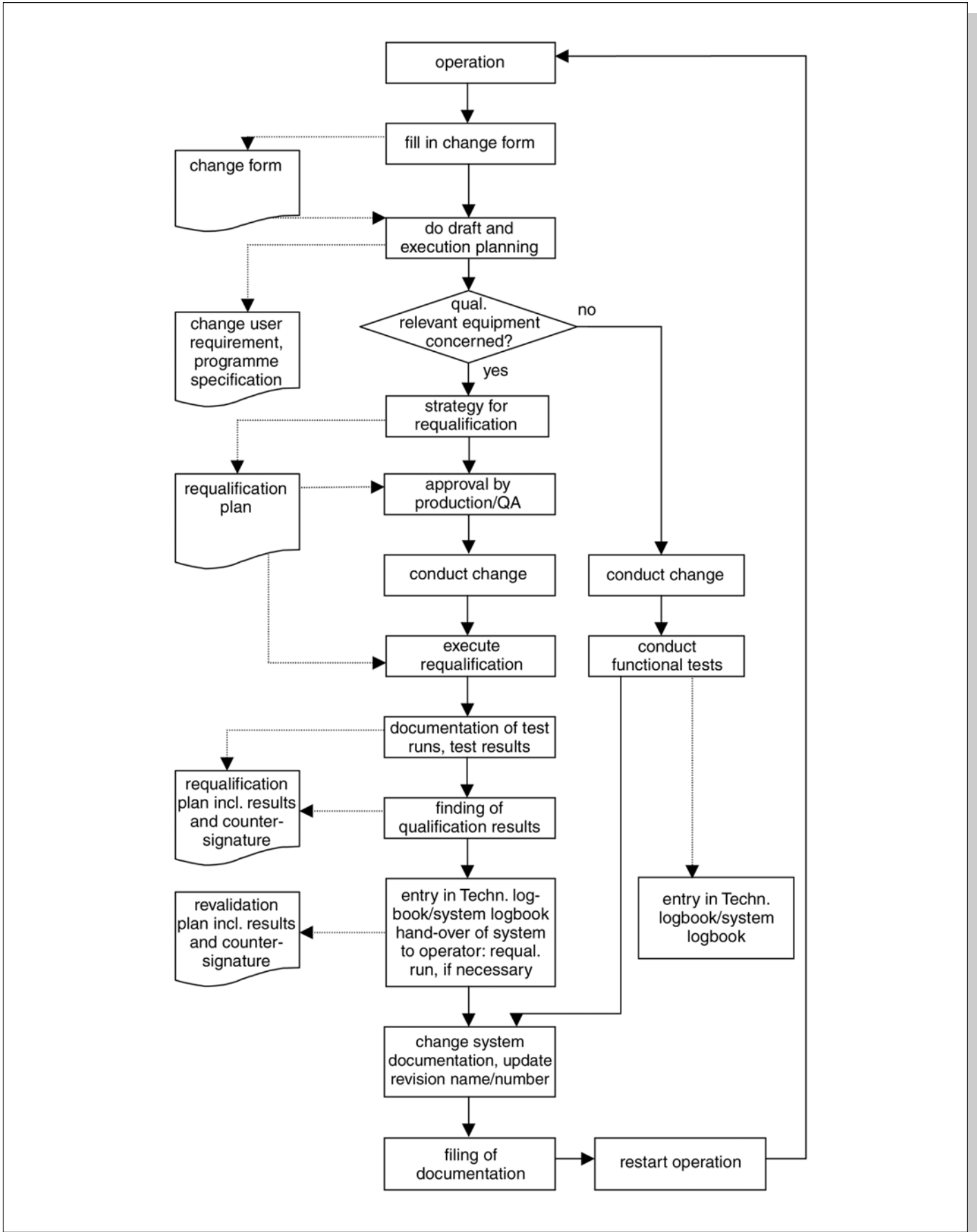


Figure 4. Flow chart for system changes.

- software used for archiving and data format
- software and hardware necessary for data reading and printing
- storage conditions and storage place for data carrier
- responsibility for maintenance of archiving conditions
- archiving period
- checking method for archived data

3. Backup and Archiving of Programs

Backup of programs is carried out to guarantee availability of the latest program version in case of system failures (e.g. memory failures), or in case of malfunctions in the controlled plant as a result of programming errors in the application-specific software. It is recommended to backup programs on a cyclic basis, e.g. once a year, or after every program modification (in the latter case, incremental backup of the modified code part is sufficient). Programs are backed-up on external data carriers twice, if possible. The backup copies are to be stored at different places in different fire-risk areas. Program backup has to be performed up to the end of the system's life cycle. In exceptional cases, it may be necessary to store the latest program version even longer for analysis and assessment of archived data (recipes, batch control, etc.). In these cases, the program versions need to be handled and archived like data.

SOP 5: Modem Operations

Objective

- to protect data communication with process control systems via public networks for the purpose of remote trouble detection and system service

Procedure

System access, data exchange, and finalization of communication have to be controlled.

By access control, it needs to be assured that no unallowed callers be able to enter data or programs of the process control system during usage of remote service lines. This can be achieved by different measures, e.g. call-back modems and/or installation of modems in access-controlled areas.

Start-up of data exchange needs to be released by authorized personnel of the control system operating company. The identification of the external communication partner has to be checked and the modem interface must be compatible to the process control system. Upon fulfillment of these conditions, transparent data exchange normally will be guaranteed.

After completion of modem operation, a controlled connection clear-down needs to be performed.

SOP 6: Audits

Objective

- to ensure the required reproducible quality of internal and external suppliers by means of audits on the field of process control technology

Procedure

An audit should be performed by an internal audit team mainly representing Engineering, Quality Assurance, and Production Departments. As an introduction, a questionnaire should be prepared and sent to the audited supplier. A written answer to this questionnaire is expected. A sample for typical questionnaire items can be found in Figure 5, an example for an audit flow chart in Figure 6.

After evaluation of the completed questionnaire, it has to be decided whether a local audit at the supplier's site needs to be performed and which areas are to be looked at closer during the following parts of the audit.

In the audit report, a summary of the final results can be found. Be it necessary, correction measures should be checked by adequate means, e.g. self-declaration or a repeated audit.

SOP 7: Risk Analysis

Objective

- to identify quality relevant functions of a process control system, including control loops and further functions like batch records, data records, dosage control etc.

Procedure

1. Risk Determination and Classification

At the beginning of the process, those risks that may impact quality attributes of the product will be determined. In this phase, not only process control system-based risks are being analyzed, but also risks caused by process, plant, operating conditions, or operator actions. The identified risks are being classified in an appropriate way. The classification forms the basis of the effort to risk management.

2. Risk Management

Measures of risk management will be analyzed and defined. These include process or plant modifications or additional organizational measures for plant operation. With respect to process control technology, the following measures are suitable for quality-related risk management (examples):

- redundant design of process control equipment and/or software
For fault determination, usually double copies are sufficient, for automatic fault correction, triplicate copies are necessary.
- implementation of plausibility checks into control system software (e.g. watchdog timers)
- integration of quality-relevant control loops into a recalibration program

For quality related risk management, all those measures that are used for ensuring plant safety are suitable.

3. Documentation

It is recommendable to carefully document the results of the quality risk analysis. The documentation can be structured as follows:

- list of identified risks
- risk classification
- measures for risk management
- list of quality-relevant functions of the process control system, including calibration-relevant control loops, redundancy determinations, plausibility checks, and further determinations

SOP 8: Requalification

Objective

- to define criteria for process control system requalification including recommendations for scope and execution

Procedure

The validated state of process control systems needs to be maintained during the system's use. Assumed that the system has been validated prospectively prior to production start up, it has to be analyzed whether a requalification is necessary after system modifications. It is recommended to perform modifications according to documented standards (e.g. SOPs) and corresponding with change control programs to reduce requalification effort.

1. Requalification Criteria

Extensive or GMP-relevant modifications and enlargements may cause the need for requalification. Especially in the following cases, these conditions may be fulfilled:

- System Software Update
- System Hardware Upgrade
- Extended Modifications Concerning the System's Structure
- Modifications Following Serious System Breakdowns
- Considerable Modifications of Environmental or Operational Conditions

2. Extent/Range of Requalification

The following points can be addressed during requalification:

- System Software Update/System Hardware Upgrade
 - Following of Documented Procedure (e.g. SOP 10)
 - Installation in Conformance with Supplier's User Manual
 - Supplier's Statement on Features of the New Version
 - Updated Documentation (Hardware, Software)
 - Service Staff Training
 - System Start-Up Test
 - Modified System Functions Test
 - Quality Critical Functions Test
 - Communication to Related Systems Test
 - Realistic Test of Emergency Scenario (e.g. Power Failure, CPU Breakdown)
- Extended Modifications Concerning the System's Structure
 - Following of Change Control Procedure
 - Updated Documentation (Hardware, Software)
 - Safe Archiving of System Software
 - Service Staff Training
 - Operating Staff Training
 - Modified System Functions Test
 - Quality Critical Functions Test
 - Communication-to-Related-Systems Test
 - Realistic Test of Emergency Scenario (e.g. Power Failure, CPU Breakdown)
- Modifications Following Serious System Breakdowns
 - Following of Failure Procedure (e.g. SOP 9)
 - Service Staff Training
 - System Start-Up Test
 - Quality Critical Functions Test
 - Communication-to-Related-Systems Test
 - Realistic Test of Emergency Scenario (e.g. Power Failure, CPU- Breakdown)
- Considerable Modifications of Environmental or Operational Conditions
 - Following of Change Control Procedure
 - Keeping to Supplier's Specifications
 - Monitoring of Modified Environmental and Operational Conditions
 - Updated Hardware Documentation

General information:

- Information on company history
- Current organization chart including responsibilities for system quality
- Staff qualification in System Development, Marketing and Sales and other relevant departments
- Information on commercial / financial situation of audited company
- Market distribution of supplier's products
- Experiences in pharmaceutical industry applications
- Experiences in validated applications
- Existence of written standards or operation procedures
- Existence and qualification of service department
- Local service sites in acceptable geographical distance to pharmaceutical company's site
- Third-party service available for system maintenance
- Existence of training centre
- Supplier's attitude on and support of this audit
- Preparedness to display documents, e.g. source code

Information regarding Quality Management (QM) System:

- QM organized as an independent department?
- Existence of a documented QM system
- Existence of a certified QM system
- All necessary areas covered by the QM system?
- Regular performance and documentation of internal audits guaranteed?
- Existence of internal standards for technical documentation and project documentation
- Third-party supplies covered by QM system?

Project-related Information:

- Existence of a Validation Plan for the project in question
- Necessary documents covered by validation plan?
- Project documentation list available?
- Input / Output of all project phases clearly defined?
- Technical standards current and documented?
- Version history of used products available?
- Can supplier provide their in-house project documentation?

Figure 5. Sample for audit questionnaire items.

- Service Staff Training
- System Start-Up Test
- Quality Critical Functions Test
- Communication-to-Related-Systems Test

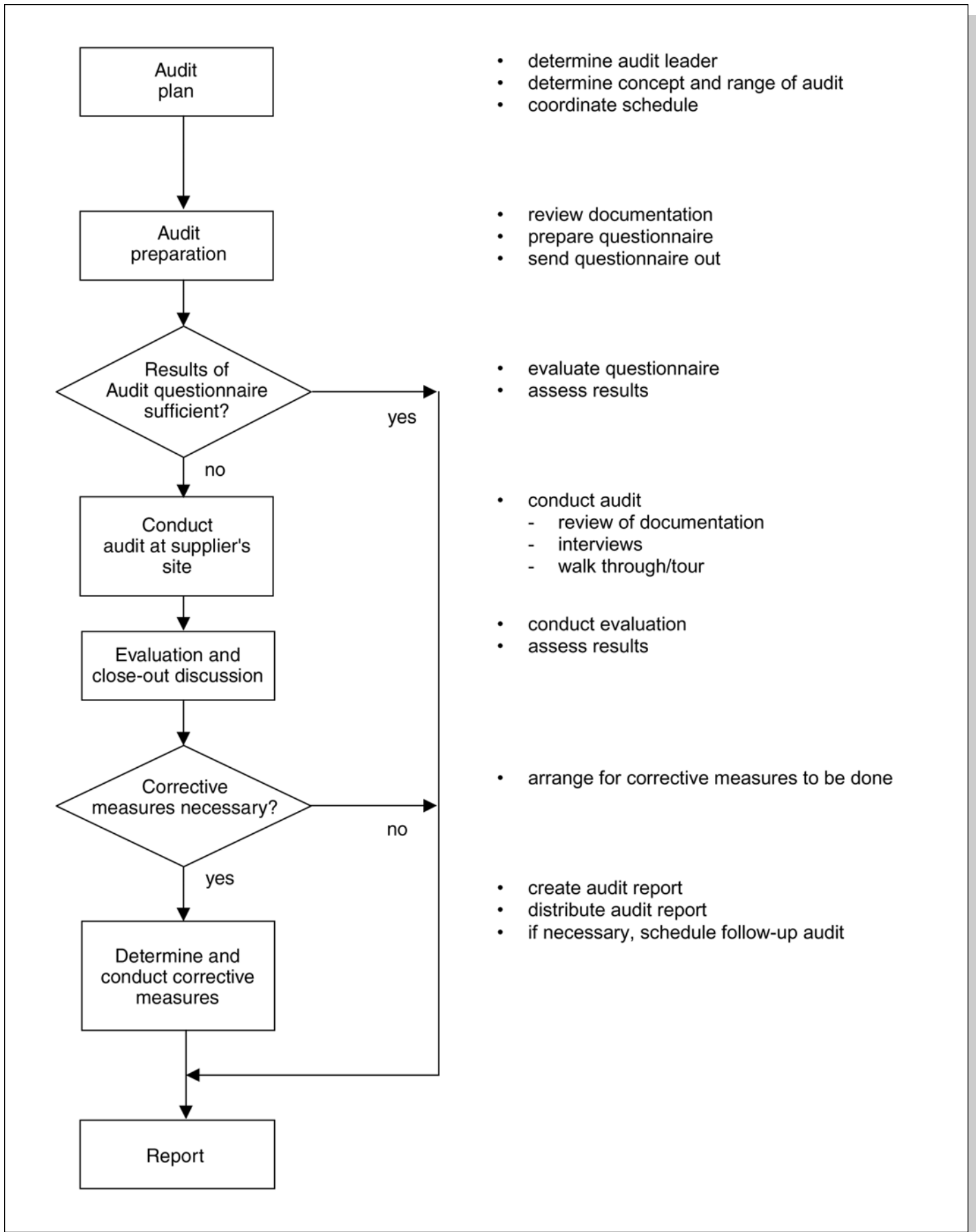


Figure 6. Example for an audit flow chart.

SOP 9: Procedure for the Event of System Malfunctions and System Failures

Objective

- to define strategies and measures for systematic detection, classification, mastering, and documentation of failures and malfunctions of process control system components

Procedure

The following principal steps are being passed:

1. Fault Detection and Identification

Fault detection and identification can be supported effectively by self-diagnosis tools of process control systems. Failures that are not detected by these tools have to be identified by trained personnel.

2. Classification

Fault classification shall support a quick evaluation of possible consequences. Examples for criteria are:

- Hardware/Software Failure?
- Critical/Not Critical Fault ?
- Consequences for Process, Personnel, Environment or Batch Release ?

Further criteria may be added in correspondence with existing alert plans.

3. Fault Mastering

In this part, only immediate actions are described. These can include:

- Reduced Operation
 - Manual or Semi-Manual Operation of Plant
 - Fault Treatment Delay to a Later Point of Time
- Immediate Fault Clearance Actions During Running Operation
 - Switchover to Redundant Systems
 - Switchover to Emergency Power Supply
- System Restart
 - Observing Start-Up Sequence
- Initiation of Repair
 - Initiation of Immediate Repair
 - Feeding in of Backups
 - Exchange of Components

4. Documentation

All activities are documented in the system logbook or by another appropriate documentation system.

SOP 10: Change of Release, Upgrade of Hardware, Update of Firmware

Objective

- to keep the validated status of the process control system in accordance with release changes, hardware upgrades, and firmware updates

Procedure

Changes of the system software and standard hardware are covered. Application-related changes are controlled by SOP 1: "Preventive Maintenance and Change Management."

Release changes (including software patches), updates, and upgrades have to be performed in compliance with service recommendations of the manufacturers. It has to be observed:

- if they can be carried out during operation of the process control system, or if a system shutdown is necessary, and
- if application-related software has to be modified (in this case, an independent development system should be used, or an appropriate system shutdown has to be scheduled).

In all cases, detailed information by the system supplier has to be provided and analyzed. Figure 7 shows typical supplier's information for support of release changes, firmware update, and hardware upgrade.

SOP 11: Training

Objective

- to ensure the appropriate information and training status on process control technology for staff involved in system design and operation

Procedure

Definition of qualification profiles for operators, project engineers, maintenance staff, external personnel, and key personnel. It is recommendable to set up qualification programs for

Information supporting release changes and firmware updates:

- Hardware requirements for new software version
- Description of all new features
- Description of corrected failures
- Confirmation
- Confirmation of compatibility with predecessor-version and with non-updated parts of firmware
- Confirmation of compatibility with application-related software indication of those parts of the application-related software that have to be checked after firmware update especially
- Confirmation of compatibility with archived and backed up data formats (if necessary indication of data format conversion)
- Installation manual

Information supporting hardware upgrades:

- Description of all new features
- Description of corrected failures and function restrictions
- Confirmation of compatibility with predecessor-component and with non-upgraded parts of hardware
- Installation manual
- Updated standard documentation of hardware

Figure 7. Recommended information for release changes, software updates, and hardware upgrades.

the different groups of people and document the training activities.

Summary and Outlook

A set of 11 generic SOPs for operation and maintenance of process control systems in the pharmaceutical industry is presented in this article. These SOPs are the outcome of a European joint committee "Validation of Control Systems." According to the committee, the subjects dealt with in these SOPs should be covered for process control systems in the pharmaceutical production. However, it is possible that company or project specific additional aspects have to be handled or aspects can be omitted. If, for instance, change control management, document management, or requalification are controlled by existing regulations, there is no need for specific process control SOPs. Complete information can be found in the original version of VDI/VDE 3517, part 4 that will be published in English.

The complete guideline VDI/VDE 3517² is a first important result of the work of the GMA/NAMUR Committee. The guideline is being used in practical business; members of the committee are reporting regularly on current applications, e.g. on ISPE/GAMP3-seminars in Zürich and Amsterdam (1999) and in Zürich (2000). The further direction of the committee's work is being discussed intensively at present. Topics of interest include the validation of control systems in package units, the validation of manufacturing execution systems (MES) or GMP requirements of asset management tools and CAE systems.

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This article addresses a case study of the development of a fluid bed spray drying process for a protein for agricultural uses.

Fluid Bed Spray Drying of a Protein Formulation - A Case Study

A Possible Alternative to Spray Drying and Freeze Drying for Production of Solid Dosage Forms

by Orapin Rubino

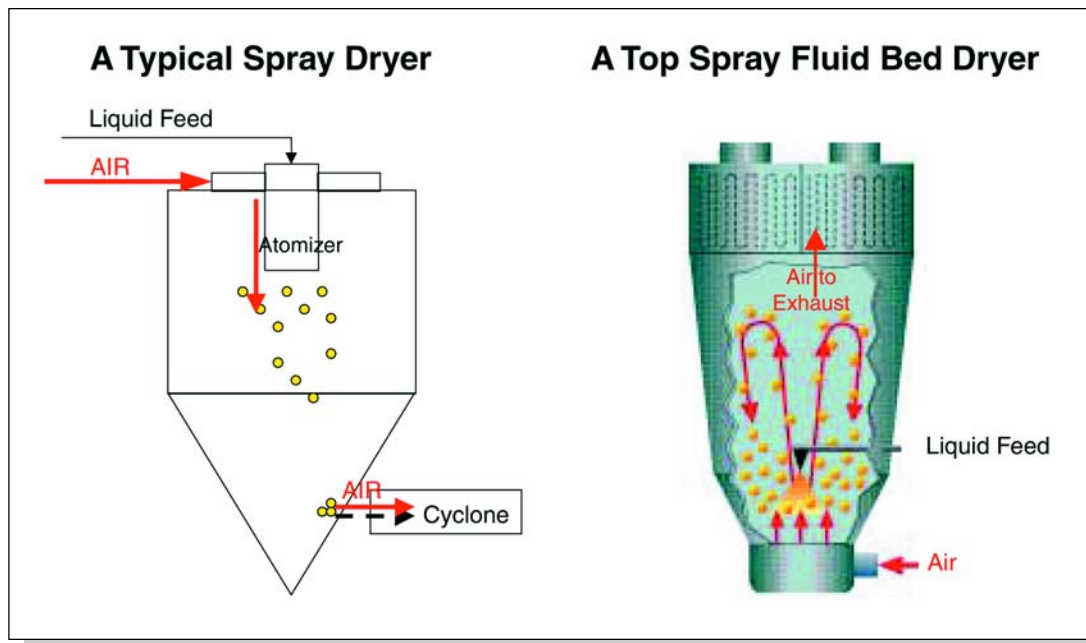
Introduction

The trend in the pharmaceutical and chemical industries in recent years has been toward the use of biological molecules. Advances in molecular biology, analytical and separation techniques have led to significant advancements in uses of proteins and biological products in the agricultural (such as fertilizers, insecticides, or fungicides), pharmaceutical, and other industries. Proteins also are widely used in the food industry. Some examples include dairy products such as milk, baby formulas, and nutritional supplements.

This article addresses a case study of the development of a fluid bed spray drying process for a protein for agricultural uses. The protein in this study was dried using freeze drying and traditional spray drying process initially; however, the dried protein obtained from spray drying exhibited poor dispersion characteris-

tics. Dispersibility is the ability of dried product to get wetted throughout and dissolved in water. It is an important characteristic for applications where the finished product is mixed with water at point of use. Examples of products that require good dispersibility include milk and milk products, instant drink mixes, and dried medication powders. For this particular product, good dispersibility is required because the users need to disperse and dissolve the product in water before applying the product to the plants. The freeze-drying of this particular protein also was performed on a small scale. However, the cost of the freeze-drying process was too high for commercial production of this product. The fluid bed spray drying process was investigated to determine the feasibility of drying and agglomeration of powders to achieve desirable dispersibility at reasonable manufacturing cost while maintaining biological activity.

Figure 1. A schematic diagram of a typical spray dryer and a top spray fluid bed dryer.



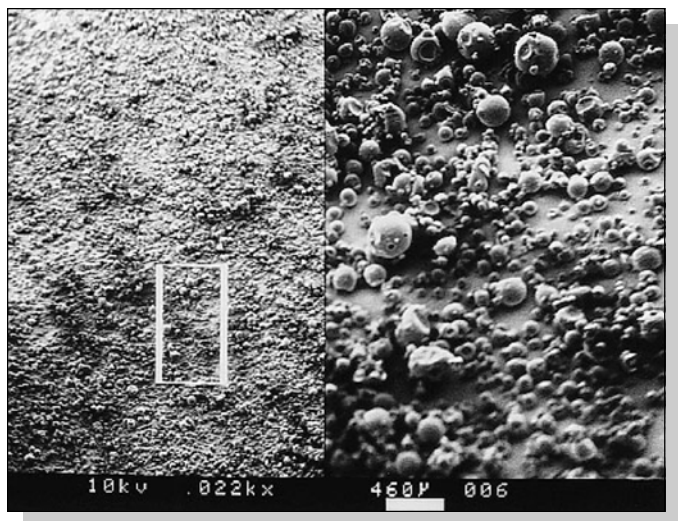


Figure 2. Scanning Electron Micrograph of dried protein particles obtained from a traditional spray drying process.

The development of a formulation and process scale-up of a protein solution from a lab scale (< 400 g) to a production scale (> 100 Kg) is discussed. The desirable product characteristics include good dispersibility, low moisture content (~ 2 - 3 %), and good flowability. A comparison between fluid bed spray drying and traditional spray drying also is reviewed. Finally, an evaluation of three drying processes (top spray fluid bed spray drying, traditional spray drying and freeze-drying) including operating cost, capital cost, and product quality also is presented. The focus of the comparison of the three drying methods of proteins was for solid dosage forms.

Protein molecules are composed of several amino acids in a specific sequence.¹ In solution, protein molecules are in certain conformation (folding) stages. The folding of a protein molecule is responsible for its stability in solution. High temperatures can cause proteins to unfold, expose hydrophobic groups and form aggregates or precipitates. This phenomenon is called thermal denaturation.² The temperature of denaturation (T_d) of a specific protein in solution can be determined using a simple capillary melting point device to look for a "cloud point" or via a more sophisticated thermal analytical device such as a differential scanning calorimeter (DSC). Proteins are generally more stable in a dried or solid form than in liquid form.^{1,2}

Traditionally, proteins are dried by freeze-drying.³⁻⁶ Freeze-drying has been used mainly in the pharmaceutical industry to produce proteins for parenterals. The freeze-drying process has been long recognized as a "safe" process for drying of proteins, especially those that have low T_d . The main disadvantages of freeze drying are the high capital and operation cost. A typical freeze drying cycle of a protein solution can be as long as several days. Protein formulations and process conditions during freeze-drying can play an important role in stability of the finished products.^{5,6}

Spray drying of proteins has been used as an alternative to freeze-drying, especially in the food industry for the drying of dairy products. In some cases, protein denaturation during the spray drying process has been reported.^{7,8} Protein denaturation in a fluid bed processor also was reported.⁹ Each protein has a unique amino acid sequence and has a unique conformation. Thermal denaturation and shear denaturation are probably the two main degradation pathways during spray drying

or fluid bed drying. For proteins that have some heat and shear stability, selecting optimal process conditions that minimize the denaturation are a key to achieving success in spray drying or fluid bed drying of a particular protein solution.

Traditional spray drying is known to have low thermal efficiency. Thermal efficiency is defined as the fraction of total heat supplied to the dryer used in the evaporation process. Overall thermal efficiency increases when inlet air temperature increases for fixed outlet and ambient conditions.¹⁰ Typically, a spray drying process requires a high inlet air temperature, in many cases exceeding 200°C^{10,11} to improve thermal efficiency. The product temperature during processing is lower than the inlet temperature due to evaporative cooling. Residence time in a spray dryer is short, in the order of 5-100 sec.¹⁰ However, the chance for thermal denaturation of a protein could be a concern when operating at an extremely high inlet temperature.

Fluid bed processes operate on the principle of air suspension of particles using high operating air volume. Therefore, thermal efficiency of a fluid bed process is significantly higher than that of a spray drying process due to dynamic heat and mass transfer of the fluid bed process. Typical inlet air temperatures of fluid bed processing are below 100°C, which is significantly lower than typical inlet air temperature of spray drying.

In general, powders obtained from a traditional spray drying process are small and have poor flowability.^{12,13} A post drying agglomeration step is often required for good dispersability. Masters¹⁰ described several layouts of two-stage spray/fluid bed drying systems to overcome the disadvantages of a traditional spray dryer as compared to fluid bed. However, such a two-stage system tends to be more costly than a simple fluid bed system.

A top spray fluid bed process has been widely used for agglomeration, granulation, or coating of particles in various industries for more than 30 years.¹⁴⁻¹⁷ An instantizing process is an agglomeration process that uses water as the spraying medium. It is a process that is generally utilized to achieve good dispersability of powders.¹⁸ A fluid bed spray drying process is a combination of spray drying and an agglomeration process using air suspension technology.

Figure 1 shows a schematic diagram of air and material flow

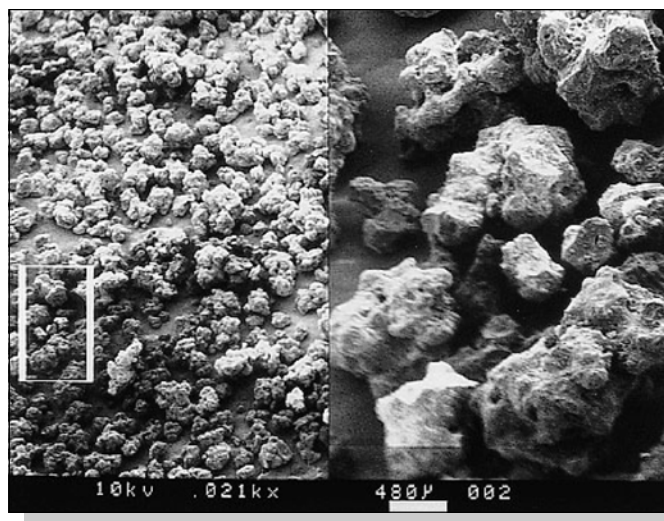


Figure 3. Scanning Electron Micrograph of dried protein particles obtained from a top spray fluid bed spray drying process.

Property \ Protein:Carrier	1:2 ratio	1:4 ratio	1:6 ratio
Protein solution weight (Kg)	15	7.5	7.5
Run time (min)	158	77	63
Product Temperature (°C)	~ 52	~ 50	~ 51
Max Spray rate (g/min)	120	120	160
Yield (%)	88.9	102	95
Final Moisture (%)	0.9	1.2	1.1
Dispersibility (compare to spray-dried powder)	+	+++	++
Biological Activity of finished product	Yes	Yes	Yes

Table A. Summary of process conditions and results of feasibility studies to determine an optimal ratio of protein:carrier.

through a typical spray dryer and a top spray fluid bed dryer. There are variations in spray dryer models that can offer different air flow pattern and spray nozzle position.¹⁰ One main advantage of a fluid bed dryer over a traditional spray dryer is ability to further dry the product to a certain moisture level. For a fluid bed process, product is fluidized and remained in the chamber. For a spray dryer, product is removed from the drying chamber to cyclone for collection.

The characteristics of granules prepared using a fluid bed process are loose and porous, which also allows for good dissolution. In addition, products obtained from a fluid bed process are generally larger in size and have better dispersibility and flowability when compared to those obtained from a traditional spray drying process.

Development of a Fluid-Bed Spray Drying Process

Feasibility Studies

The protein solution in this study was purified using conventional protein separation methods. The molecular weight was about 40 KD. The final solution contains 3 - 5 % protein (dried weight). The dispersibility of finished product is a desirable characteristic. Traditional spray-drying of this protein solution resulted in a powder that had poor dispersibility. The fluid bed process was evaluated because of its ability to improve dispersibility of products through agglomeration or granulation of powders.

Incorporation of "Seed" Material

In general, formulations of proteins contain some stabilizers. Sugars, especially di-saccharides, have been used to stabilize proteins in solution.⁶ Using sugars or other inert materials as "seed" materials allows the initial stage of the fluid bed spray drying process to occur relatively fast. Maltodextrin was selected as seed material for this application based upon compatibility in the formulation and good dispersibility characteristics. Maltodextrin is a commonly used excipient in solid dosage forms. Its use as a stabilizer for protein also has been reported.¹⁹

At constant process conditions, the more seed material introduced at the start of the process, the faster the acceptable rate of liquid (protein solution) addition. The ability to spray rapidly leads to high productivity. However, increasing the quantity of seed material results in the need for a larger



Figure 4. Dispersibility of the protein powders produced by spray drying (left) compared to the protein powders prepared by fluid bed spray drying process (right).

quantity of the finished product in order to obtain an effective dosage of protein. It is necessary to determine an optimal ratio of protein to seed material for a particular application (to achieve good dispersibility at high productivity). In the present study, the ratio of protein to seed material was varied from 1:2 to 1: 6.

Results

Table A summarizes the conditions and process parameters used for three batches of product at the ratio of protein to seed material of 1:2; 1:4; 1:6. Preliminary data showed that the



...products obtained from a fluid bed process have better flowability than those obtained from traditional spray drying.



protein solution is stable at ~ 50°C and below for up to two hours. Thus, the process parameters (inlet temperature, spray rate, etc.) were set to control product temperature at ~ 50°C.

When compared to spray-dried powder, all three fluid-bed batches had significantly improved dispersibility. Figure 2 and Figure 3 are scanning electron microscope photographs of dried protein particles obtained from the traditional spray drying and from the top spray fluid bed spray drying, respectively. Figure 4 demonstrates good vs. poor dispersibility of the dried protein powder. The batch with protein:carrier ratio of 1:4 has slightly better dispersibility than the batch with a ratio of protein:carrier of 1:2, and 1:6. This may be related to two observations. For the 1:6 ratio batch, the liquid spray rate was increased to 160 g/min to maximize productivity. This resulted in larger granules that tended to sink to the bottom of the dissolution vessel when dispersed in water. The 1:2 ratio batch had a small amount of starting material (maltodextrin) in the product container. Initial fluidization was somewhat erratic due to a small product load. In summary, the ratio of protein:carrier of 1:4 was identified to be optimal for this application.

The results from laboratory runs suggested that it is possible to dry this particular protein using a top spray fluid bed approach. There was no loss of biological activity of the dried protein.

Scale-Up Studies

The next step was to scale-up the batch size to approximately 100 Kg of the protein solution. Placebo runs using maltodextrin and water were used for the initial scale-up study since the protein concentration was low (3 - 5 %) and the viscosity of the protein solution was very close to that of water.

One desirable goal for this application was to maximize productivity (dry as many liters of solution in as short a process time as possible). There was no particle size specification of the finished product, as long as good dispersibility could be achieved. For the production scale equipment, a three or six-headed spray nozzle can be used. In general, the six-headed nozzle may allow operation at a higher spray rate vs. the three-headed nozzle as long as there is sufficient drying capacity.

A study to evaluate the three vs. six headed nozzle by comparing particle size distribution as a function of spray rate was performed. The product container was charged with 36 Kg of maltodextrin. Using a three-headed nozzle, water spray rate was started at 600 g/min. At 15-20 min intervals, spray rate was increased. The range of spray rate studied was 600 to ~ 1000 g/min. Total water sprayed was 55 Kg. Particle size analysis of samples during the process was determined using sieve analysis. The experiment was repeated using a six-headed nozzle.

Results

Figure 5 illustrates the relationship between spray rate and average particle size (calculated from sieve analysis data).

Both three and six-headed nozzles showed similar relationships between spray rate and average particle size. The faster the spray rates, the larger the average particle size of granules. For this application, either three or six-headed nozzle can be used (drying capacity was not an issue). The six-headed nozzle was chosen to maximize productivity.

The next step, a scale-up batch using the protein solution was produced (Trial 1) using a six-headed nozzle. The total weight of protein solution was 188 Kg. The product container was charged with 36 Kg of maltodextrin. This equated to 1:4 ratio of dried protein:carrier. Samples were removed at various times. Particle size analysis was performed throughout the run.

Figure 6 illustrates the average granule size as a function of process time at a fixed spray rate (1100 g/min). As the process progressed, average granule size slightly increased, possibly due to an increase in exhaust air relative humidity at fixed process conditions (inlet air temperature, process air volume, and spray rate). However, the particle size range through the process was still acceptable since the finished product had good dispersibility. In addition, these large granules were easily broken down to smaller size during drying. The yield was 98.1%. Final moisture was 2.6 %

Note: For an application that required maintaining average particle size, it is possible to control the process conditions to minimize granule growth. Increasing inlet air temperature or increasing process air volume can typically accomplish this.

Reproducibility of a Production Scale Drying of the Protein Solution

To validate the process, four additional production-size batches of protein solution were spray dried (labeled Trial 2 to 5) using conditions similar to Trial 1. The ratio of dried protein:carrier was (in the range of 1:4 to 1:6) adjusted based on activity of protein in each lot.

Results

Process conditions and parameters including product characteristics are summarized in Table B. Protein solutions were effectively dried using a top spray fluid bed process. The drying rate was close to 1 kg of protein solution per minute (0.86 to 0.97). The yields of four production lots were 93.5 - 99 %. Finished products retained biological activity and had desirable dispersibility characteristics.

Considerations for Selection of Production-Scale Drying Process

There are three processes that can be used for drying of a protein solution in production scale: freeze-drying, traditional spray drying and top-spray fluid bed spray drying. As a first consideration, a drying process has to retain biological activity of the finished product. For this particular protein, all three drying processes can be used.

A comparison among the three drying processes for protein solution in the study, based upon several criteria are summarized in Table C.

- Yield (weight finished product recovered to theoretical weight based upon protein concentration). Yield of the product obtained from top-spray fluid bed process was high (93.5 to 99 % as seen in Table B) which is typical of a fluid bed system. Typically, yield from freeze-drying is high (> 90 %) while yield from traditional spray drying was lower. In

some other studies, lower yields (60 to 70%) for spray drying of other protein solutions have been reported.^{8,20}

- Process time. Both the top spray fluid bed and the traditional spray drying have significant advantages over freeze-drying. Top spray fluid bed processes demonstrated the ability to dry approximately 100 liters of protein solution in less than 2 hours (data in Table B). The process time of freeze-drying is generally days instead of hours.
- The equipment size for both fluid bed and spray drying can be selected according to the capacity required. However, large-scale traditional spray drying equipment generally requires a very tall chamber. This can present a problem when installing the system into an existing facility. The top spray fluid bed processor is generally compact, when compared to the spray dryer of approximately the same capacity. The freeze-dryer equipment does not pose any issues with equipment height.
- Ability to further dry the product.
 - The top-spray fluid bed spray drying presents an advantage in the ability to further dry the product to the desired moisture. During the fluid bed drying process, it is possible to take samples for moisture analysis. If the moisture is higher than desired, the drying process can be continued without further operation steps. The top-spray fluid bed process has high drying capacity because of high air volume. For the product used in this study, additional time to reach 3% moisture was only 10 to 30 min (under a certain set of process conditions).
 - The freeze-drying process also allows additional drying if moisture is too high. However, freeze-drying processes operate under vacuum and do not have dynamic airflow. Additional drying time of 8 hours or more are typically needed to achieve desirable final moisture levels.
 - The traditional spray drying process does not allow for additional drying since the product is removed from the chamber and collected in a cyclone.

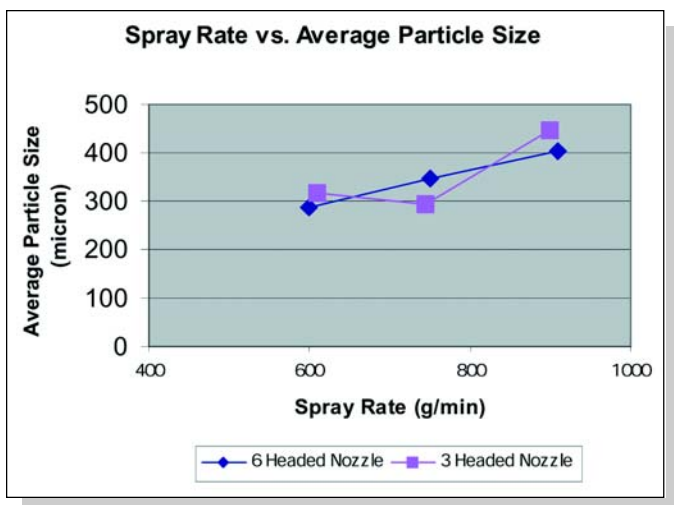


Figure 5. Liquid spray rate vs. average particle size of placebo runs using a three or six-headed nozzle.

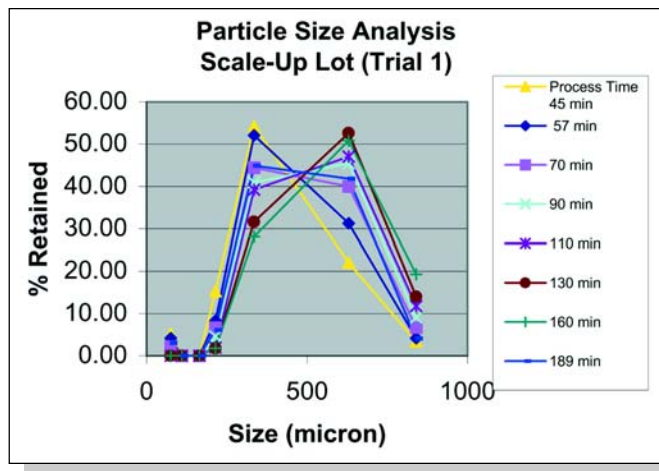


Figure 6. Average particle size of a protein drying, scale-up lot (trial 1) as a function of process time at a fix spray rate and other process conditions.

- Product dispersibility. Both fluid bed process and freeze-drying process provide product with good dispersibility, significantly better than traditional spray drying process. The sample from traditional spray drying of this particular protein was unacceptable for use due to poor dispersibility.
- Cost. One major disadvantage of freeze-drying is high cost (both capital and operating cost). Top-spray fluid bed and traditional spray drying processes are much more cost-effective than freeze drying process.

Summary

Fluid bed spray drying has been shown in this study to effectively dry a protein solution, even at a very low concentration of protein (3 - 5%). By combining the concept of instantizing and fluid bed drying/agglomerating, a dried form of protein with desirable dispersibility and biological activity was achieved. Compared to other drying processes such as freeze-drying and traditional spray drying, fluid bed spray drying provides an attractive alternative. The keys to success depend upon protein stability, thermal characteristics of each particular protein, physical characteristics during processing (i.e. stickiness of protein to equipment surface), and protein-carrier compatibility. Thus, this process may not be appropriate for all proteins.

The protein in this study has very good stability and did not lose biological activity during the fluid bed process. When considering a fluid bed spray drying of a protein, it is necessary to focus initial efforts upon the effect of process conditions on protein stability. Processing factors need to be evaluated. For example, high air volume may be a problem for proteins that are easily oxidized, atomization air pressure may cause some shear denaturation, temperature of denaturation under a certain process condition needs to be defined. The use of laboratory scale fluid bed systems for feasibility testing to understand the effect of processing conditions on chemical, biological, and physical stability of each particular protein is extremely important for a successful fluid bed drying application, especially for pharmaceuticals. Fluid bed processors with more sophisticated designs also are available for specific process needs. For example, nitrogen gas in a closed-loop system can be used instead of air for highly oxidized com-

pounds.

Although the top spray fluid bed process has been used in many industries for more than 30 years, the concept of fluid bed spray drying is not widely explored. It can potentially be an alternative drying process for some proteins. Thus, top spray fluid bed spray drying can be used to achieve one-step drying and granulating of some liquid proteins or biological actives for solid dosage forms. At this time, the design of a top spray fluid bed is suitable to achieve the particle size of dried products in the range of approximately 100 to 800 microns. It is not intended as a process to produce very small and very narrow particle size as required for inhalation. The particle size of finished product obtained from the fluid bed process can be controlled to be in a suitable range for tableting.

In addition, products obtained from a fluid bed process have better flowability than those obtained from traditional spray drying. Furthermore, the cost effectiveness of a fluid-bed process (due to its high drying capacity) provides an attractive choice for drying of compounds on a large production scale for certain applications.

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Property	Top Spray Fluid Bed	Traditional Spray Drying	Freeze-Drying
Yield	3	2	3
Process Time	2 or 3	2 or 3	1
Equipment Size	3	1	3
Ability to further dry to desired moisture	3	1	2
Product Dispersibility	3	1	3
Capital Cost	2 or 3	2 or 3	1
Operation Cost	3	3	1

Table C. Comparison of the three drying processes for production scale (where 1 = least desirable and 3 = most desirable).

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Property	Trial 2	Trial 3	Trial 4	Trial 5
Total weight of Protein solution (kg)	94.4	149	63.1	107.2
Process Time (min)	109	154	73	123
Drying rate (kg/min)	0.87	0.97	0.86	0.87
Final Moisture (%)	2.4	2.8	3.1	2.3
Yield (%)	94.4	98.7	93.5	99.0
Ratio (dried protein:carrier)	1:5	1:6.4	1:4	1:4
Dispersibility	Good	Good	Good	Good
Biological Activity	Yes	Yes	Yes	Yes

Table B. Summary of process conditions and results of large scale drying of the protein solution.

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About the Author

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This article will discuss the tools, techniques, and practices that top pharmaceutical performers use to turn their trial supplies operations into a competitive advantage. The information was compiled from a database of clinical trials operations management benchmarks, as well as from field experience in helping drug companies assemble faster and less wasteful supply chains for clinical trial materials.

Figure 1. Clinical Supplies Effectiveness Map.

Using Clinical Supplies Operations as a Competitive Advantage

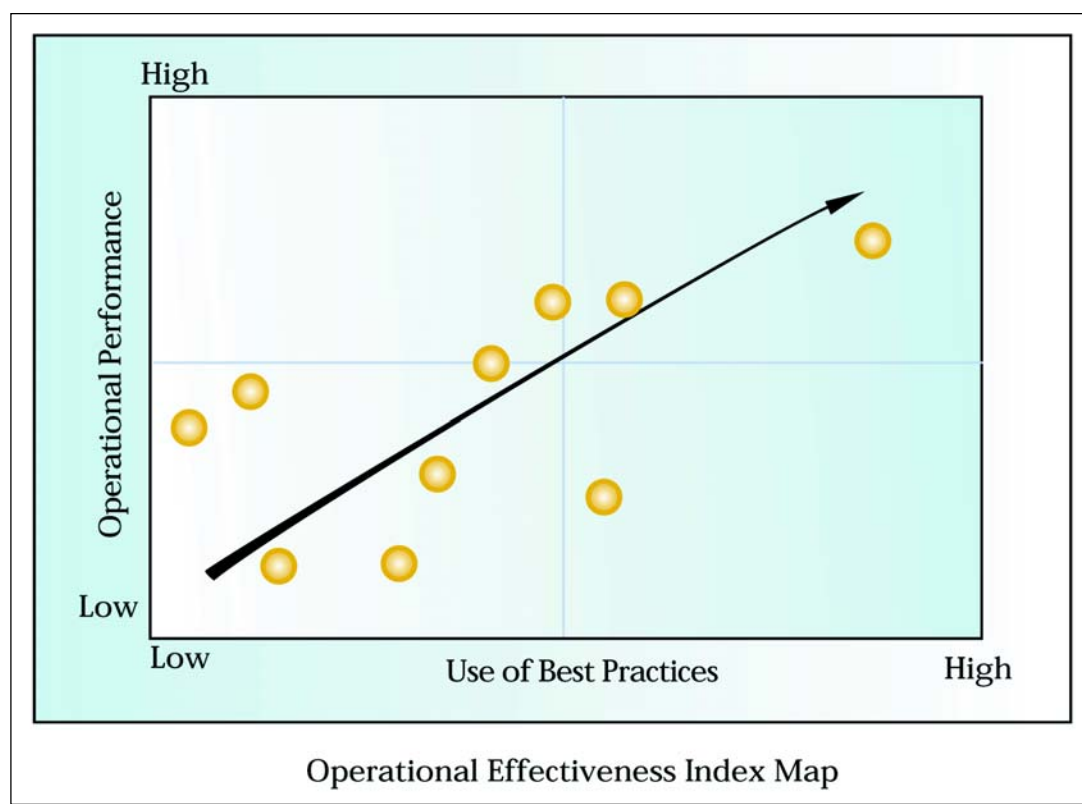
by Mark Stesney and Maheshwar Singh

For clinical supplies groups, the time is now to step-up and deliver results. At a time when some are struggling to keep pace, internal and external changes require more from these groups in terms of flexibility, speed, and cost control.

As competition increases and technological advances accelerate the discovery of new chemical lead compounds, pharmaceutical companies face mounting pressure to develop effective and innovative new drug compounds and bring them to market more quickly and cost-effectively than ever before. Companies are spending large amounts of resources on improving the clinical trial management processes, and an increasingly critical aspect of the trial management process is the management of clinical trial supply operations.

This focus upon clinical trial management processes is beginning to dramatically shrink the time that compounds spend in the clinical phases of development. Companies are using leading-edge technology to provide value to both themselves and the clinics and researchers they serve. Protocols are being written and approved collaboratively with research partners. The Internet is being used to recruit and match patients to trials. Clinics are being provided upstream inventory and delivery visibility. Data are being collected by wireless handheld computers and e-mailed to central collection databases. These practices, in-turn, are forcing the clinical supplies operations groups of these companies to respond aggressively.

Clinical supplies operations groups are not necessarily moving away from their traditional



roles of ensuring that the correct compounds are manufactured, packaged, labeled, and delivered to trial sites on time and in the quantities required. They are redefining themselves to support the new clinical trial management approaches so as to provide a competitive advantage to the company. These competitive advantages are typically centered around reliability, responsiveness, speed, and cost.

Learning from the Best

A comparative survey of pharmaceutical companies' clinical supply operations practices reveals clear opportunities for enhancing pharmaceutical development efficiency:

- *Best-in-class companies deliver materials to clinical trial sites 56% faster than average companies.* This added speed can help reduce total drug development time by weeks or even months.
- *Leading companies waste significantly less investigational drug material.* They require 15-20% fewer subject kits than average companies. The use of Interactive Voice Response (IVR) systems and clinical supply planning coordinators appears to have the greatest impact upon minimizing inventory requirements and waste.
- *Clinical supplies operations have been slow to adopt basic software planning tools.* Only 25% of the companies surveyed used material requirements planning, advanced planning, and execution systems, while 33% used no systems at all.
- *Performance metrics are significantly underutilized in managing clinical supplies operations.* In contrast to most operations environments in other industries, clinical supplies operations rarely use metrics to evaluate and improve their overall performance.

Speed, Reliability, Parsimony

There appear to be three key performance indicators in clinical supplies operations management. First, how rapidly can clinical supplies be prepared, packaged, and shipped? Second, how reliably can supplies be delivered to sites so that trials can be launched and enrollment maintained? Third, how effectively can inventory and overage requirements be managed to avoid wasting limited investigational drugs or comparators?

To understand the payoffs from adoption of best practices, the performance of the companies in the database were mapped against the use of industry best practices. An operational performance score was calculated based upon the cycle time to prepare, package, and deliver clinical trial supplies, on-time delivery performance, and supplies overage. A best-practices score was then calculated based upon the use of management processes and tools such as cross-functional planning teams, performance metrics, and software applications. The Clinical Supplies Effectiveness Map attests to the fact that as companies invest in and implement industry best practices, their operational performance improves accordingly - *Figure 1*.

Tightening the Cycle-Time Loop

A pharmaceutical organization's ability to start a clinical trial quickly and on schedule depends upon both the protocol development and the clinical supplies cycle time, the latter being defined as the time from start order entry for the manufacture

of bulk dosage material to delivery of the packaged kits to the trial sites. Best-in-class companies command a 56% advantage in delivery cycle time over average performers - *Figure 2*.

Starting a clinical trial requires more than simply getting the clinical supplies to the study site. Those conducting the clinical research need to develop the protocol, prepare systems for data collection, and obtain site and agency approvals. These activities typically occur in parallel with the manufacture and packaging of clinical supplies. As measured from draft protocol to protocol approval, and from approved protocol to commencement of the clinical trial, best-in-class companies achieve 45-75% shorter times than average performers, depending upon phase - *Figure 3*.

It is critical for pharmaceutical companies to get their clinical trials started on time and to keep subjects enrolled throughout the entire trial. On-time delivery measures the ability to deliver clinical supplies to the trial sites by the requested date. The average on-time delivery performance for the companies sampled is high - 95%. However, that figure slips slightly as the number of shipments increases. As companies grow, their planning functions and operations become more complex. Clinical supplies organizations must understand these complexities and appropriately modify their processes to maintain high on-time delivery performance.

A good deal of uncertainty surrounds the planning and execution of clinical trials. Factors contributing to this uncertainty include late changes in protocol design, the need to alter the trial based upon preliminary results, insufficient enrollment, and unexpected discontinuation rates among enrollees. All this uncertainty, combined with the common need to provide all treatment group kits to all sites, leads the average company to package 15-20% more patient kits than it expects to dispense during the trial. Best-in-class companies have reduced this overage to 5% in all trial phases by investing in planning processes that promote flexibility in delivering supplies.

Practicing Best Practices

Best practices in clinical supplies operations fall into three broad categories: commonly used, selectively used, and underutilized. Commonly used best practices, such as the deployment of cross-functional planning teams, tend to be relatively straightforward. Selectively used best practices, such as the use of Interactive Voice Response systems, tend to be more complex, and require a good deal of cross-functional support and process changes. The best practices that have been conspicuously underutilized by clinical supplies organizations, such as the use of software planning tools, demand serious attention, since they can immediately improve operational performance.

All the companies in our database employ cross-functional planning teams. These teams are involved in the planning of clinical supplies, and are usually created during the early phases of compound testing. Typical functions represented on these teams include formulation development, planning, manufacturing, packaging, and shipping. Ninety percent of the companies examined include clinical research personnel - the primary customers of clinical supplies operations—on their cross-functional planning teams. Since these teams are involved in evaluating the tradeoffs between demand requirements and supply constraints, clinical research involvement is crucial to the timely delivery of clinical supplies.

Another common best practice in clinical supplies planning



Best practices in clinical supplies operations fall into three broad categories: commonly used, selectively used, and underutilized.



is the use of planning coordinators. These coordinators, who are present in 50% of the companies surveyed, focus upon planning and orchestrating all operational aspects of clinical supplies. Planning coordinators also closely interact with clinical research to determine demand requirements and the necessary responses of the operational functions in order to ensure the timely processing and delivery of clinical supplies. Planning coordinators also can help reduce overall material wastage by pooling the excess planned material across multiple trials and projects when possible.

IVR systems are used in many industries, from air carriers to credit-card companies, and are selectively used by pharmaceutical organizations to manage the quantities and distribution of clinical trial materials. IVR systems allow clinical supplies operations to postpone the assignment of subject kits to specific individual patients until the last possible moment. (Once assigned and labeled, a kit cannot usually be reassigned to another subject.) This postponement ability allows the organization to maintain its subject-kit supplies in a generic form at a central location, minimizing overall inventory requirements and accommodating last-minute design changes in clinical trials. Using real-time information on subject enrollments and discontinuations, IVR systems can limit material overage to less than 5%.

More than 63% of the companies in the database studied use IVR systems. Their use is more widespread in Phase II and III

trials, where the availability of material may be severely limited. Best-in-class companies have reduced their planned kit overage, to 5%, through the use of IVR systems. These systems, in other words, can enable a company to complete a clinical trial even when the bulk active is truly scarce. In addition, material saved in one trial can be used to start other required trials concurrently, thus reducing time-to-market. Companies also can dramatically reduce the cost of comparators by using IVR systems, to the tune of millions of dollars.

While remaining a selectively applied practice, successful clinical supply operations have begun to leverage the highly specialized competencies of third-party providers to help manage peak workloads and expand capabilities. The strategic outsourcing of key activities, such as manufacturing, packaging, shipping, distribution, and customs clearance, has enabled these organizations to increase their production while keeping pace with accelerated drug development objectives. By building long-term relationships with reliable third-party providers, pharmaceutical companies can establish effective satellite operations that can be counted to deliver product quickly as the demand arises - *Figure 4*.

The use of planning and execution software tools is a best practice among technology-based companies. These tools can help identify and resolve demand and supply imbalances, thus ensuring the timely delivery of product. Only 25% of the companies in survey use all three types of these software tools:

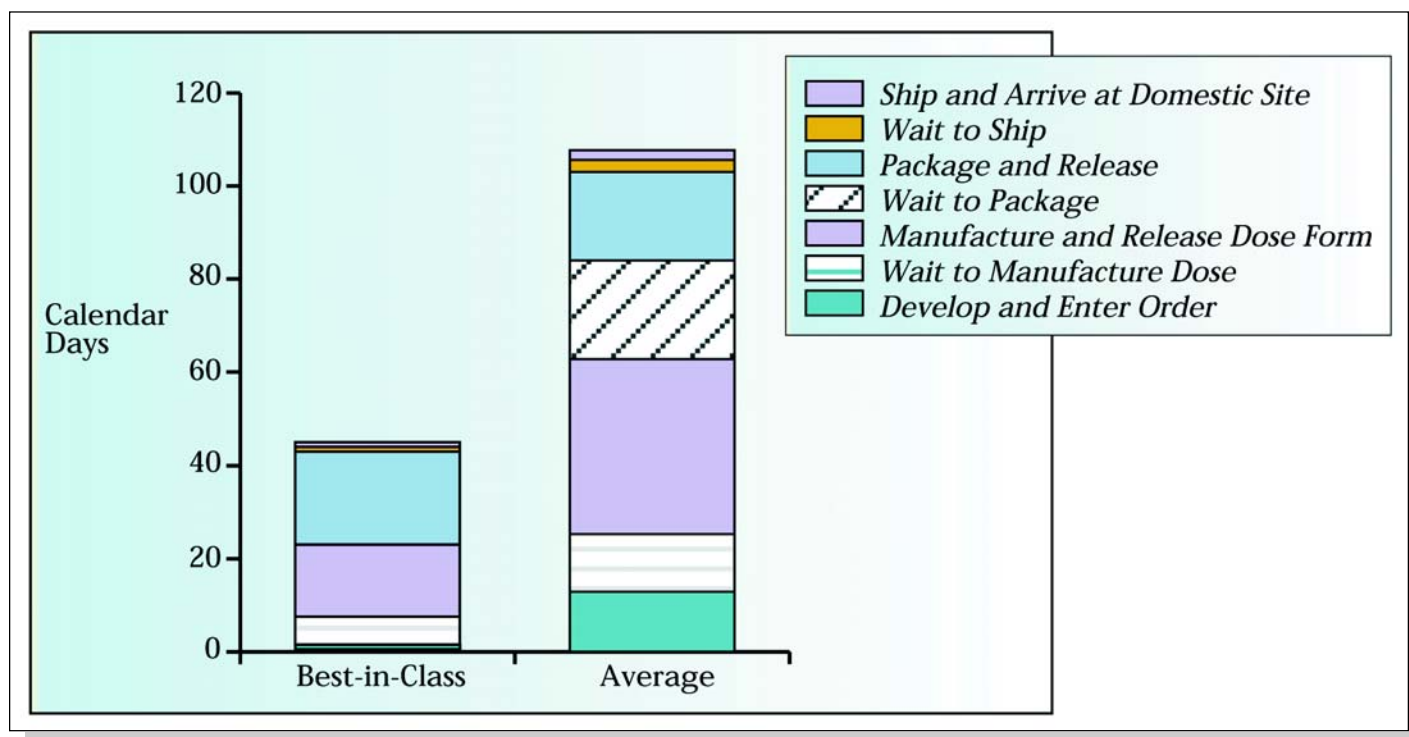


Figure 2. Elapsed time from start order entry to arrival at domestic sites.

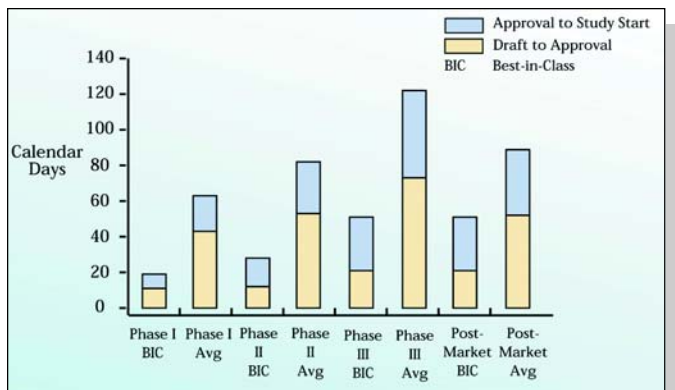


Figure 3. Cumulative elapsed time from draft protocol to study start.

manufacturing requirements planning, production scheduling, and advanced planning systems. A third use none of them.

Measuring Performance

The use of metrics to measure performance and drive process improvement is a basic tenet of operations organizations, yet the average clinical supplies organization measures only one or two metrics, most commonly delivery performance and cycle times. Of the companies sampled, 75% concede that they don't measure enough metrics to give them a full picture of their performance. In clinical supplies operations, measuring cycle times can help identify opportunities for reducing manufacturing, packaging, and shipping times. For an overall reduction in clinical trial cycle time; however, it is essential to coordinate this effort with clinical research so that the protocol cycle times can be reduced accordingly. Only a handful of companies measure a cross-functional portfolio of metrics taking into account delivery, flexibility, costs, and asset performance. This type of "balanced scorecard" approach is essential to ensuring that all the functional groups involved in managing clinical supplies operations are pursuing common goals in a coordinated way.

A comprehensive quantitative and qualitative assessment of *all* functional areas involved in the planning and delivery of clinical trial supplies should be conducted to identify all potential areas of improvement before any specific improvements are pursued in isolation. The assessment should measure performance across a balanced set of indicators. A comparison of current performance against industry benchmarks will then establish the gap between the organization's performance and best-in-class performance standards, providing a cogent baseline for improvement.

The next step is to use the findings of the assessment to create a value proposition for the organization. The value proposition, which is a quantitative justification for driving process improvement, should be used to secure top management's commitment to the improvement initiatives, and to communicate the initiatives to the rest of the organization. Best practices need to be carefully reviewed, and the right set of such practices must be selected and scrupulously followed if overall performance is to improve.

Millions of dollars in increased revenue and cost savings are within the grasp of pharmaceutical organizations that identify their performance gaps and correctly implement the right practices in their clinical trials and supplies management processes. By using industry benchmarks, such as those illus-


trated in this article, along with an integrated supply-chain management approach, clinical supplies organizations can achieve dramatic improvements and meet the internal and external requirements of greater flexibility, speed, and reduced costs.

Note: If your organization is interested in participating in the 2000/2001 refresh of PRTM's Clinical Supplies Benchmarking Study, please contact Mark Stesney (email: mstesney@prtm.com). There is no cost to participate and all respondents will receive a custom analysis and report.

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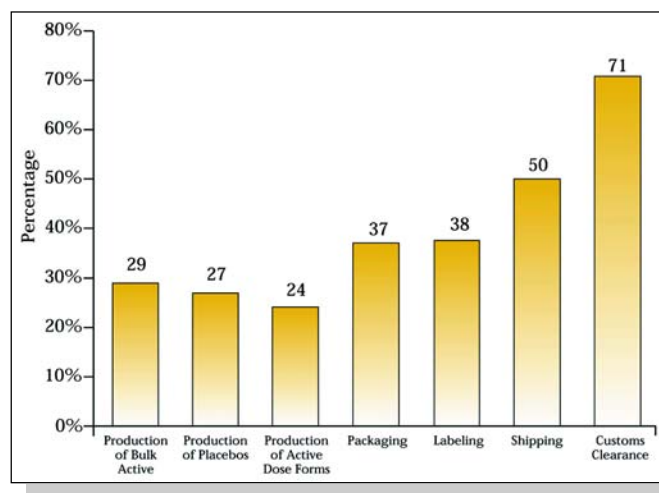


Figure 4. Average percentage of activity outsourced by companies.

This article discusses how advance planning can maximize the benefits obtained from FATs, and demonstrates how optimizing the time and money spent on FAT can result in a smooth transition from design to installation to validated production.

Factory Acceptance Testing (FAT) of Pharmaceutical Equipment

by Matthew G. Roberge, PE

With the growing demand for validated computer controlled processing systems, testing of new equipment has become a large portion of the costs associated with a pharmaceutical project. However, there are several ways to optimize the time and money spent on equipment acceptance testing.

The General Need and Approaches that can be Taken

There are two objectives of a FAT equipment: 1. to ensure that you are getting what you pay for, and 2. to begin the execution process of the validation plan. There are numerous testing

philosophies that can be used to carry out the FAT ranging from a cursory physical inspection to a detailed physical and operational verification. All have their place depending upon the circumstances.

Decide on the Testing Approach to be Taken for FATs at the Beginning of the Project

All parties involved in selecting a testing approach for the FAT must agree upon the testing program philosophy at the start of a project to allow for the best use of resources. This philosophy should be outlined in the validation plan and/or quality plan for the project. Knowing and

understanding the degree to which a design will be challenged serves several practical purposes, but perhaps the most important is defining the objectives and deliverables to the project team. As the project team procures equipment and services, it will have the ability to align the project's expectations with the vendor's deliverables.

Reputable vendors have quality-testing programs and an assembly of documents that they supply as a standard package to demonstrate that their product is suitable for the given application. If the vendor's standard is different from the objectives outlined in the validation/quality plan, changes can be made to correct this discrepancy. An early understanding of the required testing will ensure that any changes to the vendor's approach will be made with minimal schedule or monetary impact.

For the purposes of illustration, consider the following hypothetical example: If a large PC/PLC-controlled equipment system (Figure 1) with numerous ancillary items and utility requirements has been ordered and is to be tested, the vendor will usually include a 3-5 day factory inspection and review of related documents. These tests usually entail a



Figure 1. Example equipment setup for FAT testing.



Figure 2. Load testing equipment with placebo.

physical inspection with limited functional tests. The size of the equipment, the amount of setup time, and the availability of utilities limit the functional tests. If the FAT is to include detailed functional tests with placebo, it will take prolonged setup time, some simulation of operating plant conditions, and the connection to suitable (possibly rented) utility sources as well as arrangements to obtain the placebo material. In some cases, equipment can be too large or in multiple pieces, limiting the functional test and making it impossible to perform placebo tests. Since overcoming these issues will take more time than is standard, there will be monetary implications for labor hours in setup time, as well as a schedule impact for the time associated with the setup, disassembly, and extra testing involved. With a tight budget or schedule, these effects can be significant. It is important to note that the success of the testing will be directly related to the early efforts establishing the project's testing philosophy.

Components of an FAT

This is a guideline based upon Good Automated Manufacturing Practices¹ (GAMP) and the author's experience in planning and executing these types of tests. Expect to make modifications based upon circumstances.

The equipment vendor and the project team should agree upon the documentation deliverables at the time the Purchase Order (PO) is placed. A list of documents and their required submittal dates should be attached to the PO. This list should include all drawings, specifications, and test protocols that will comprise the design, installation, and validation deliverables. Examples of the required documents are helpful and will cut recycle time if provided to vendors. The drawings and specifications will be reviewed during the project life cycle and approved by the project team as part of the equipment manufacturing process. In theory, the approved drawings and specifications should be complete before any manufacturing starts. Unless time permits (which it normally does not), approval and manufacturing will have to take place concurrently to meet aggressive project schedules. Approvals will start on the general items and work toward the specific details by the end of the manufacturing phase, but final approval on all details should be done before the start of testing. These approved documents will form the basis of the testing and define the pass/fail criteria of the acceptance test.

FAT Documentation Summary

The actual FAT protocol should have the following basic sections.

The first section consists of a minimum of general arrangement drawings, P&IDs, detail drawings, specifications defined by the project, electrical and pneumatic drawings, a user requirement specification, a functional specification, and software specifications as defined by the project.

The second section of the FAT protocol consists of the manufacturers' cut sheets as supplied by the vendor and subcontractors to support the validation plan. In general, these support documents consist of material test certificates, weld certificates for each product contact weld, ASME or equivalent certificates if dealing with a pressure vessel, passivation certificates, surface finish certificates, and a parts list which indicates the part number, wear items, product contact, and location on the component as a minimum. If the vendor is not based in an English-speaking country, a translated cross-reference list also is helpful for the vendor, project team, and end user.

The third section of the protocol contains the test certificates that pertain to product contact and process critical parts. The respective test methods, procedures, and calibration certificates for the testing instruments, along with the appropriate reference back to a traceable standard also should be supplied. Any procedures should be provided in writing and approved up front and provided in this section. (For example, passivation of stainless steel is done by a wide variety of methods from "air passivation" to hot dipping in nitric/hydrofluoric acid solutions. The method chosen may or may not yield the required results although you will get a certificate in either case.)

The third section also will contain physical inspection test protocols, sometimes called quality inspections. These protocols will verify the mechanical dimensions against the approved drawings, weld quality, wiring quality, and electrical hardware functions (point to point, Input, and Output tests). There also will be a certification by the vendor that the equipment in question has been supplied in accordance with the vendor's standard supply in matters of general finish and safety.

The fourth section will contain the unexecuted portions of the protocol, which consist primarily of functional test, batch report verification, interlock testing, alarm verification, system functionality (security access, data management), disaster recovery, and a review of the operating screens. A placebo test, if conducted, also will be contained in this section. Figure 2 shows a high shear granulator being load tested with placebo.

The last section should contain a blank section to describe in detail any deviations or exceptions that were noted during the test along with the resolution and retest results. This section also should contain a list of the people who executed the tests along with their title, company, signature, and initials written in at the time of the FAT.

FAT Execution Summary

Step 1

To ensure that the required documents are available and accurate, the first step at the FAT is to perform a documentation review. This should consist of two parts: 1. confirmation of



The execution time for the FAT will depend upon the level to which the vendor and the project FAT team have prepared and the end user's documentation and testing requirements.



the availability of the approved design documents and specifications, and 2. confirmation that all support documentation is available and accurate.

Step 2

The execution team should form groups to perform the next step, a physical inspection of the electrical hardware, and the mechanical inspection concurrently (unless there is a safety or manpower issue). Figure 3 shows a remote control panel being checked against wiring drawings. Any notes or markups to the approved drawings should be added to the original documents from the FAT protocol.

As previously mentioned, the third section contains physical inspection (quality test) protocols. The vendor can execute this section prior to the customer's arrival on site, or the project team can execute these protocols with the vendor, depending upon how much time was budgeted for testing. It is generally more efficient to have the vendor do this prior to the testing team's arrival. During the FAT execution, the team will preferentially spot check those tests performed by the vendor, spot-checking those items that are critical to the project, ie, building interface dimensions and non-standard I/O. Assuming that the results are satisfactory, testing can continue. If the results are not satisfactory, full checking (100%) of the pre-executed work should be performed with appropriate deviations/resolutions being noted. If the resolution is to be performed at a later date, this also should be noted in the appropriate section. It is not common practice to include nuts/bolts and small electrical conduits on arrangement drawings. For this reason, floor, ceiling, and wall intersections with the equipment should be marked with string or tape to assess the impact of these elements upon the eventual architectural finish.

Step 3

Once the electrical and hardware checks are completed, the functional testing can begin. The physical checks usually cannot be performed concurrently with the functional checks since the electrical and mechanical checks may involve personnel exposure to unprotected moving or electrical parts that may start or become energized automatically during the functional test. Further, the physical checks involve a certain amount of disassembly of the equipment, which could render the unit non-functional.

The functional tests should proceed as outlined in the protocol. Any tests that require support documentation can be supported with printouts of data from the PC that is controlling the equipment. If deviations from the approved protocol occur or if the end-user requests changes, these deviations should be reviewed by the project team, agreed upon, and then hand-marked in the original protocol with an initial and date. Deviations should be noted and corrective actions listed. Time can be saved during this portion of testing if the computer screens and screen layouts are reviewed and the comments are sent to the vendor before the actual FAT.

Step 4

At the conclusion of testing, the team reviews the FAT results and specifies any corrective action that the vendor should take. The FAT team has the option of specifying how and when the corrective actions will be made. In the worst case, the testing team can return at a later date to retest the resolutions (or the entire FAT). More typically, the resolutions and required due dates can be agreed upon with acceptance being given conditionally, or the resolutions can be implemented as they occur with the equipment being accepted and shipped at the end of the FAT.

Examples of deviations that could be accepted conditional upon the vendor correcting the deviation are missing paperwork, wording changes in the functional specification, or the polishing out of an external scratch. More significant deviations that involve electrical or software modifications have to be retested in a subsequent FAT addendum or in the Site Acceptance Test (SAT). It is a project decision when the retest



Figure 3. Electrical hardware check.



Figure 4. Example equipment being installed.

should occur. The severity of the deviations and time required to resolve these issues determines the direction to be taken.

FAT Deliverables

At the end of the FAT, a series of deliverables is handed over to the project team. The end user is given the original copies of all the signed and executed test documents and attachments. The vendor will maintain copies of the executed FAT, and the project team will distribute copies at its discretion. As the executed protocols tend to be large documents, consider sending selected sections to people or groups on an “as-needed” basis. For example, the electrical team should get copies of the marked-up wiring/pneumatic drawings to form the basis of the installation, and so on. It is of primary importance to distribute copies of the marked-up functional specifications to the validation section of the project team since this will refine and aid in the definition of the site testing.

If time permits, new document revisions that are labeled “as shipped” should be submitted formally after the FAT. This will assist the installation crews, particularly if the mark-ups are numerous. “For Record” (or As built) documents will be issued after the installation and commissioning activities are complete. Direction regarding what will be done with the FAT deliverables should be clearly stated to the vendor at the end of the FAT, but at a minimum the FAT team should leave with copies of all of the above and the understanding that it will be sent the originals.

The team, or the team’s designee, should produce a closeout report that defines any issues that arose, the agreed direction to resolve the issues, the person responsible for the resolution, and the date by which the resolution is due. The report also should list the severity of the deviation and whether or not the issue must be resolved to accept the equipment. All participants in the test should sign and date the closeout report.

Time and Personnel Requirements

It would be misleading to suggest guidelines for how long the preparations and testing for a typical equipment package should take, as there are no typical systems, equipment, or projects. The point to emphasize is not to underestimate either the preparation time and effort for the FAT or the usefulness and payoff to the project derived from the proper execution and documentation of the FAT. For the hypothetical equipment system referenced earlier, and only for the project team, plan

for about three revisions of the functional specification with three man weeks review and defending time per revision to develop a document that is approved for manufacturing.

The execution time for the FAT will depend upon the level to which the vendor and the project FAT team have prepared and the end user’s documentation and testing requirements. The following steps will ensure that the execution time is kept to a minimum. The vendor should have performed dry runs of all the tests that will be run for the FAT team to ensure success when the team arrives. As a starting point using the same hypothetical system as depicted in Figures 1-4, plan on one week (5 days) for the FAT assuming the testing is properly staffed and the vendor is prepared for the testing. Less complicated packages will require less time, but not proportionally less due to the time associated with getting up to speed on the test execution.

The project FAT team should be kept to a minimum number of required people. The core team should consist of a mechanical or process engineer, a controls engineer, and a validation engineer. Staffing from the vendor side should be technical in nature to properly support the focused and detailed project FAT team. More people can be added based upon system complexity, but attention will need to be given to certain areas. If only one engineering discipline can attend, this should be the controls engineer, as this comprises the largest portion of the work. If possible, the construction or installation supervisors should participate in the later activities of the FAT to oversee the packaging of the equipment and inventory ancillary items and spare parts - *Figure 4*. Rigging and unpacking knowledge also can be transferred from the vendor to the construction team at this point.

The project’s FAT execution team should consist of personnel who are thoroughly familiar with the project and the documents associated with the FAT. It is likely that some unforeseen issues will arise. Being well prepared gives the team the ability to focus upon the minimum requirements for the test (approved protocol), while at the same time prioritizing, evaluating, and implementing solutions to any new needs that arise. The project team members also should be empowered to make decisions regarding the potential issues that can arise during the FAT, such as non-acceptance and the consequent direction to be taken.

Finally, the execution team should allow time on the last day of the test for reviewing the test results. The acceptance or rejection of the results should not be a surprise by this point, but there may be some points to review. This may be the last opportunity to get the same group of people together. This time should be used to develop and document the consensus.

If the test results are considered very weak by the team and there is considerable schedule pressure to ship the equipment, more time could be required to approve the direction as more people will need to have input into the decision, agree with the FAT team on the FAT results, and allow the decisions to be made based upon those documented facts.

Merits of a FAT

The results of the FAT can have benefits in two areas. First, provided the results were properly documented (in accordance with cGMP² and GAMP requirements) and that items were not taken apart for shipping from the factory to site, the FAT does not have to be redone. The second benefit is that the FAT familiarizes the project and process engineers with the nuances of the equipment and installation particulars based

upon the experience of the people who built the equipment. This will benefit the project at the installation end as the FAT team will have a detailed and tangible understanding of the operating needs and special requirements of the package that can be communicated to the construction crafts, ultimately quickening the installation process.

Another FAT benefit is that it is the first time project and process people get a hands-on inspection of the equipment. Some projects send operations personnel to the FATs for key pieces of equipment, as the user's perspective is invaluable in assessing usability type issues. This will be the first chance to verify that the design and the end results perform as expected. If the results are not as required, it is easier and less costly to have the original manufacturer correct problems in its own shop, rather than on site.

Leading up to the FAT, mechanical/equipment people have been the most involved in the equipment design development on a day-to-day basis. The FAT serves as an opportunity to get the process and validation personnel involved in the system to transition the involvement from the project to the operations group.

Validation

Regardless of the decision to reuse data from the FAT for the Site Acceptance Test (SAT) or Operational Qualification (OQ), the test protocols and specifications developed for and executed at the FAT can be used as the basis for the writing of the SAT and OQ protocols. Electronic copies of these documents are usually obtainable from the vendor. Much of the protocol can be cut and pasted from the electronic files. Additions to the FAT are made taking into account that the equipment is now connected to the intended utilities and interfaces with the building and other systems are now permanent. Priority can be placed on areas that were not considered adequately tested at the FAT.

The FAT results can be re-used via reference in the SAT (meaning the actual test will not be performed again) provided the results remain valid (no disassembly has taken place) and the documentation was done in a manner consistent with cGMP and GAMP. This means that the validation plan at the beginning of the project has to include data reuse as an option and that the various design specifications and drawings go through a proper review cycle and are approved by the project's representatives. Further, all test results must be signed and counter-signed by approved personnel, and all testing equip-

ment must have calibration certificates demonstrating traceability against a national standard.

The point concerning no disassembly pertains to the fact that items are often assembled at the factory, disassembled for shipping, and reassembled at site. The reassembly at site has to be verified. For example, if a remote control cabinet with interconnecting wires was installed at the factory for testing, then had the interconnecting wires removed and reinstalled at site, the interconnections need to be checked to ensure they were performed in accordance with the design.

Limitations of FAT Results

Although FATs have a definite purpose in the project life cycle, they also have limitations. Understanding these will aid in the process of deciding how much emphasis to place on the FAT. The size and complexity of the equipment will determine the amount of time required to construct the system in the factory to the point where it can run as intended. There also will be time associated with taking the system down and packaging it for shipment. In the case of a large system that can take several weeks just in setup time, a limited FAT should be considered. This type of FAT will still have the elements previously mentioned; however, the functional tests will be limited to what can run and what can be simulated. Figure 5 shows a simulated air handling unit where the control flaps and valves are mounted to a bench and wired back to the control panel for testing.

Test PLCs can be setup to simulate other systems that interface with the package being tested. If the expense of a test PLC is not justifiable, a manual switch box can be used. However, since simulation of the tests will have to be redone in the field, this portion of testing will only minimize the risk of gross non-performance in the field. Simulation is not as reliable as testing under real conditions, therefore caution should be exercised in reviewing this data for schedule improvement vs. cost. If non-standard functions have been added to the equipment, there will be a benefit to simulation of these items. There will be limited benefit from simulating standard machine options.

Since many large systems cannot be shipped in whole, the degree to which the system must be disassembled can limit the reuse of data. Although the control system can be well wrung out, the tests themselves would have to be re-executed to verify the new installation. This is a good way to reduce the possibility of failure during on-site testing, and there can be a high degree of expectation of success if only the installation needs to be checked. The controls system check should go very quickly with limited deviations.

Conclusion

Addressing the following five points will minimize the time commitment and maximize the benefits obtained from the effort put into the FATs. This will result in a smooth transition from design to installation to validated production.

1. In the project-planning phase, decide upon the emphasis that will be placed on the FATs for the process equipment. This will vary depending upon the size and complexity of each system.
2. Incorporate the FATs and related data into the project's validation plan, and plan on reusing FAT data wherever possible.



Figure 5. Simulated air handling unit at an FAT.


3. Send a minimum number of people to the FAT who are familiar with the project and who have the ability to produce the deliverables required to support the remaining project activities.
4. Allow enough time for protocol review and FAT execution including contingency time to address surprises. The time allocated for each system will vary with complexity and experience with the vendor.
5. Disseminate the information obtained at the FAT in a timely fashion.

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This article discusses the management of R&D projects with a global perspective toward creating a product and process responsive to change.

Meeting the Challenges of R&D Facility Design in a Dynamic Technology Business (Part 2)

by Joseph M. Phillips, AIA, and Jay Shoemaker, AIA

Introduction

This two part article identifies how evolving trends and current patterns effect both the process and result. Part 1 dealt with design strategies and specific solutions which support the emerging trends in pharmaceutical R&D (September/October 2000 PE). Part 2 considers the management of the R&D facilities project with a global perspective toward creating a product and process responsive to change.

In pharmaceutical and biopharmaceutical organizations, management has recognized that whatever supports good scientific process favorably impacts speed and quality of product discovery, development, and release. Simplistically, the equation is time and knowledge are money. For R&D, the flow and relationships among ideas, people, materials, equipment, etc. play a beneficial role in the time-to-market cycle. The challenge architects and engineers continuously face is to provide the research community with physical environments that are safe and effective tools for supporting optimized R&D activities. The challenge comes with a catch: design and construct the most responsive research facilities, but do so at the lowest cost possible in the shortest cycle time.

Identifying Needs and Costs: The Facility and Its Relationship to the Business

The first challenge is to determine what performance outcome is needed and what is the reasonable cost to provide it. Part 1 described significant trends in the sciences highlighting the need to develop new design prototypes. Doing so and assigning costs are not always on convergent paths. There is frequently an assumption that facility costs should always be lower than the previous project. While innova-

tion and improvement need not carry a higher price tag than previous projects, implementing new ideas applying old cost solutions, and lower cost assumptions comes with the risk of short-changing the science or guaranteeing cost overruns when it becomes apparent what is genuinely needed was not in the initial budget.

Attention to cost is understandable if over emphasized. Facility projects are tangible. Projected revenue from an investment in a facility innovation is not. Costs are readily quantifiable, therefore, novel designs with non-quantifiable justifications become easy targets in any debate of value. Resisting innovations solely on the basis of cost, however, carries high risk of adversely affecting the science that will eventually generate market-responsive products and the income stream. Put another way, money saved is not money earned.

Is there a cost-benefit analysis reckoning the cost of the "best" tools, techniques, and environments with the value of the scientist's work afforded by these improvements? This is not an easy metric to establish, but the question is persistent in R&D facility design. To address this question one has to perform a thorough comparative analysis. Such an analysis requires an in-depth understanding of cost, basis of design, operating assumptions, and scope for both existing and new facilities. This simple, but demanding comparison will articulate assumptions of R&D activities and management embedded in cost models for facilities and identify *why* costs differ among projects. The technology origins of assumptions for costing solutions which match scientific needs has been covered in Part 1 in the discussion of benchmarking and design solutions. It is sufficient here to re-emphasize the issue by pointing out the general trend is to provide each scientist with more technical resources to enhance productivity.

Increased automation and information technology tools have a strong record of translating into more productivity per person so it is reasonable to anticipate some justifiable cost escalation simply for technological developments.

Set Budgets Based on Performance Needs

The primary source of conflict in R&D facility projects arises from establishing a rigid cost model and expectations of population before technical trends, possible solutions, and business-responsive scope are well understood. When cost is established first in isolation from trends, the task becomes designing to the cost model as opposed to providing the appropriate business tool. Near the end of such a project, it will become readily apparent that there is an imbalance between cost, scope, and quality. Something must change, but human and organizational factors make such change uncomfortable or impossible. If cost remains fixed, the unintended consequences are significant. The end result of such a process is that the design and construction of facilities creates de facto R&D policy decisions for the company, either in the quality of the R&D environment or in the number of personnel housed, perhaps both.

The issue of whether to follow a new trend requires R&D management involvement. The facility ramifications of the new R&D trend require articulation early in the process, absent directives from senior R&D administration. Debate of the application of resources can become impassioned when those charged with administering a project and keeping it "under control" and those users who will work in the proposed new facility view the project's objectives differently. To make matters more difficult, the discussion usually gets caught up in a circular debate centering on the fundamental dichotomy of facility perspective: empirical proof – cost – versus theoretical gains – performance. One side "knows" how much a change in the lab will cost while the other can only speculate, regardless of the types of evidence described in Part 1, on how much science can gain by implementing the change. Nonetheless, each side is passionate and each has important expertise.

Conflicts Highlight Essential Issues

To complicate the debate, most design and construction schedules are fairly tight. Time to gather input and accommodate the future occupants is often viewed as a necessary evil. It is seen to slow the simple process of getting a building built, and it is a catalyst for organizational discussions about the allocation of resources. How this process is handled is important to project performance. Where and how people provide for housing their needs can be the source of deep, sometimes acrimonious debates. From our observations, these discussions are essential to establish understanding of what works and what does not. The discussions establish shared expectations. Unless conflicts surfacing in these discussions lead to the disintegration of a longstanding relationship, it is absolutely essential to recognize that how people react to where and how they are housed comes from personal perspectives. Individual personnel are compensated by their contributions to the organization. The facility project is one of the tools they have to demonstrate their worth. If users perceive that facility decisions will compromise their ability to contribute, they will respond vigorously. It is important to carefully unpack these responses to determine expectations and needs accurately.

Corporate organizational dynamics need to be recognized as well. A well managed open debate in the planning stages is rife with personal overtones, but avoids disastrous conflicts later in the project.

Establish Understanding of Perspectives and Subjective Terms

Is there an easier way to get through planning and design quickly and with minimal personal and economic cost? Experience has shown that maximum value and good designs result from the confluence of contrary needs and the forging of win-win solutions. But it takes the right attitude to make great solutions out of differences. The planning and design process for the project should start with the participants understanding and challenging each other's issues, agendas and goals. Some of these are quantifiable and some of the softer ones can't be fully defined or measured. So be it. Initially, agreement is not necessary as long as each understands how they and others see the situation and the project's real opportunities and probable limitations. Recognize at the out-set all perspectives have value and validity.

Once started, keep the dialogue going toward the selection of definable criteria for success. One essential activity is to define subjective terms with limits. Readily quantifiable criteria are easy to achieve, but subjective criteria without some level of interpretation have the potential to lead to questionable decisions. For example, *flexible* should be defined by what is expected to change, what is the degree of change anticipated, and what will not change. This gives the project team an identifiable metric allowing comparison of physical design with performance expectations. It also provides a means for evaluating new information about needs that arises later in the project. With this attention to articulating expectations, the dialogue about project needs will move quickly and result in a credible decision making process within a defined schedule.

Basic Activities in Sequence Map a Successful Process

It pretty much goes without saying that managing the process of developing good solutions begins with mapping out the major events from inception to occupancy, determining who the real "stakeholders" are, etc. While each project has and will have a different map, different participants, etc., there are four sequential questions that have helped guide the process and aim it toward successful occupancy.

What must be Achieved?

All facilities are different. What objectives do you need to achieve for the current business climate and situation? Define business goals linking desired effect with some facility influence. A facility complete with all its components is a means to an end. What, therefore, are the business, regulatory and/or scientific purposes that the new facility must support? In turn, what are the results the project must facilitate? Clear, well-documented directives defining these are critical in defining scope of the project, the principles that are to guide it, and the method by which its success will be measured. At the outset of the design process, value should be assigned to such issues as people's expectations or the improvements in productivity. As with other criteria, each solution should be evaluated as to its success in meeting the soft criteria. In the end, a project's success and economy must be measured by both the hard and soft criteria.

Remember: facilities are only part of the means to achieving these objectives, and never the objectives themselves. Experience indicates that this is seldom a one-way, top-down, single pass process. Both the crystallization of the objective then the development of the solution goes through iterative stages that require ongoing dialogue with those who initially set the objectives.

Rare are the pharmaceutical scientific processes or laboratory design and construction projects that do not demand great effective responses to the scientific needs, speed, and rigid cost containment. Therefore, to make good decisions it is important to establish the scientific, scheduled, cost criteria, and other critical criteria against which solutions will be judged. All subsequent design options must include information on these criteria. For example, if cost is a major controller, then the evaluation of each option must include a cost comparison with the other options as well as with the original budget criteria. It is best to hit these issues straight on.

Soft issues also must be evaluated. It is a continuing theme in this article that these may have a greater impact on the overall economic issues a company may be facing than the actual cost of building and operating R&D facilities. At the heart are issues about people and how they work together and what they want their environment to be. As these were covered in Part 1, it is sufficient here to note that any programmatic statement of needs should describe and diagram these more subjective requirements in explicit terms. Some, access to natural light and a view of the outside, for example, can be highly controversial issues that will impact the shape of labs and influence where people gather. Therefore, design options should be evaluated as to their relative effectiveness in meeting these softer criteria.

What are the Current Conditions?

What is the starting point for this project? These are the facts and assumptions that exist at the point in time when decisions are made. It is essential to document these facts and assumptions for later reference. Over the lengthy period of a construction project, conditions generally change. What once was a perfect solution may be completely wrong if the operating conditions change. For example, a construction schedule and budget may be adversely influenced by the introduction of another project competing for local resources within the same geographic region. If the assumptions about labor availability were established with the initial budget, it is easier to understand the forces which may lead to bid escalation.

How Can Creative Solutions to Meet These Needs be Fostered?

Predetermination of the "right" solution must be avoided. Like the scientific process, untested assumptions and preconceived ideas inevitably get in the way of good work. Architecture and engineering requires a creative leap backed by a lot of hard work. Design is the process of seeking alternative solutions for bridging the gap between current reality and desired future outcomes. Workable concepts are saved while rationally filtering out weaker possibilities.

Good solutions arise from testing alternative ideas against the objectives and requirements of the project. And for each, alternative ways to obtain the same result should be identified. In a cGMP process development facility, the objective of maximizing return on investment leads to the need to turn over fewer rooms. A similar response may maximize the use of

equipment, which, in turn meant limiting fixed equipment. This had the added advantage of allowing the equipment to be sent to a specialized area retooling. At the end, a concept survives that coalesces need with limitations and restrictions.

As with any criteria, it is essential to define subjective terms. *Workable concept* has many perspectives. Along the way it is important to do a reality check: Are the concepts and what it takes to implement them possible? For example, does the cost outweigh the gain? Does the proven technology exist to support a new approach? A project won't get very far until the objectives and what is needed to achieve them are in alignment.

A useful sorting process to develop workable solutions is to look at each issue in a comprehensive way that is a microcosm of the overall approach. First, each issue seeks its own level of application in a project, from broad, non-scalar issues such as business mission to narrow, highly refined performance details. Second, each issue should be examined for its own set of starting conditions, future goals, workable bridging concepts, and implementation needs. Finally, each concept is tested against the considerations of budget, schedule, form, and function.

The disciplined search for alternative solutions has an additional advantage in that hereto-unrecognized problems or other probable solutions may surface.

What are the Specific Needs to Make a Concept Work?

It is essential to understand what needs to happen to achieve the objectives via a specific concept. What are the activities, functions, equipment, relationships, flow, codes, regulations, etc. that need to align to produce the desired result? Each should be challenged to confirm the validity of its contribution to the initial objectives. The result is both a catalogue of constituent activities and an enlightened understanding of opportunities for intervention. This becomes the statement of needs for the project. It is well documented, supported by business objectives, and identifies the simplest and most direct route to implementation.

To achieve a well defined needs statement, begin with an examination of the constituent parts and understand their relationships and interactions. It is important to test each requirement as you progress. Successfully converting objectives into needs requires a careful understanding of how the project will work: what size, processes, flow, activities, skills, special equipment, documentation, etc. are required. At this point, it is now possible to identify all the components of the organization who can verify their needs will be addressed.

The lessons learned from this exercise will identify what needs have changed from the previous generation of design solutions. This knowledge of current and potential facility use activities helps to anticipate change and push off obsolescence.

A Summary of Management Basics for Implementing Emerging Trends

Here are some basic tools for successfully implementing projects in a dynamic technology business. While most of these have application to every project, they are essential for projects with continuously evolving needs.

- Be objective. Define requests and needs as justifications, not simply as requirements.
- Define subjective terms with limits and specific expectations.

- Plan and continuously update the plan using the best available information, noting differences from the initial expectations.
- Continuously monitor the project against the key success criteria.
- Identify who has responsibility for what and what they need from others to successfully complete responsibilities.
- Identify the decision-maker(s), what they need to make decisions, and the timing for decisions.
- Identify the shareholders and the input they will want to have to the project process.
- Allow for change; assess all changes for their impact then manage the associated risks.
- Communicate directly, simply, promptly, and inclusively.
- Document the project from inception, noting changes to direction and scope.

Conclusions

“Always design a thing by considering it in its larger context”
Eliel Saarinen – Architect

Technology development and demands for economy and productivity are forcing change in nearly every facet of facility design and management of pharmaceutical facilities. Innovative design solutions and processes are appropriate investments when engaged as part of the process of generating value. Design has the potential to favorably influence product and technology development. In order to capitalize on the power of innovative design, it is necessary to make the time and intellectual investment in the process. Commitment to both is required to fully synchronize facilities with R&D. To this end, simply put, successful projects depend on an understanding of what the business, regulatory, or scientific objectives are, what is needed to achieve them, and how the design of new or renovated facilities can best meet these within clear criteria.

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This two part article describes the steps from the purchase and sales agreement, through qualification and capability studies, to setting in-process control specifications.

Application of a Capability Study to a Syringe Filling Operation

Part I of 2: Validation, Capability Theory, and Protocol Design

by Peter A. Hugunin

This two part article describes the steps from the purchase and sales agreement, through qualification and capability studies, to setting in-process control specifications. It ties the purchase and sales agreement as well as manufacturing specifications, through the study design, execution, and analysis, to the mission of validation as well as to manufacturing and regulatory affairs requirements.

Part I offers several organizational and philosophical perspectives and tools including a clear and meaningful distinction between machine and process capability as well as between short term and long term studies. The value of equipment qualification is discussed as it relates to process validation. Part I concludes with the discussion of an actual protocol designed for a typical filling machine.

Part I: Validation, Capability Theory, and Protocol Design

Introduction and Justification for Capability Study

The focus of all qualification and validation efforts is the generation of productive knowledge, i.e. knowledge useful in the understanding, and where economically or ethically required, control or elimination of unacceptable variation. Nothing is more important to manufacturing than advance assurance that a machine or process will be able to hold the tolerances. Capability studies offer an approach to measuring and summarizing the inherent variability in machines and processes (Natural Process Limits) and are often the best tool available for qualification and validation activities. Broadly speaking, there are two types of capability studies: The *machine capability* study with its indices and the *process capability* study with its indices.¹⁻³ A capability index is a ratio statistic which relates the equipment or process center and variation to the applicable tolerance - *Table A*.

The *machine capability* study varies from

the *process capability* study not in the statistical approach or models employed, but only in its complexity. It is an evaluation of the equipment's "natural process limits" and exploration of its ability to meet predefined tolerances. It is often conducted for Factory Acceptance Testing (FAT) or periodically to test the functionality of the equipment and forms the foundation for a capable process.¹ If *short-term* it may be viewed as a best-case scenario.³ The *process capability* study considers all process variables which may have an impact upon the product's quality attribute under study. This scope difference makes it a far more formidable task than the machine capability study. Also, because quantity producible over time, re-tooling, and maintenance will always be of production and hence management concerns, the further distinction between *short-term* and *long-term* capabilities is relevant.

As can be seen from a review of the statistics (Table A), this quality tool provides only a means of summarizing the relationship between the "natural" limit of the machine or process -- given the then current state of control --- to the acceptable tolerance limits. Additional qualification work must define and document the state of control as well as relate the indices (C_m , C_{mk} and C_p , C_{pk})* to an acceptable rate and/or quantity of production. Although it may be used to support a validated process and set up Statistical Process Control (SPC) it is not a stand alone tool for the elimination of systematic process variation, or reduction of cycle time except for the clear reduction of in-process sampling.

* Although no information is gained by viewing the inverse of these ratios they are also employed in describing capability.

With an understanding of the statistic and its limitations, it is now possible to review the application with a better understanding. In the case problem presented, a syringe filling opera-

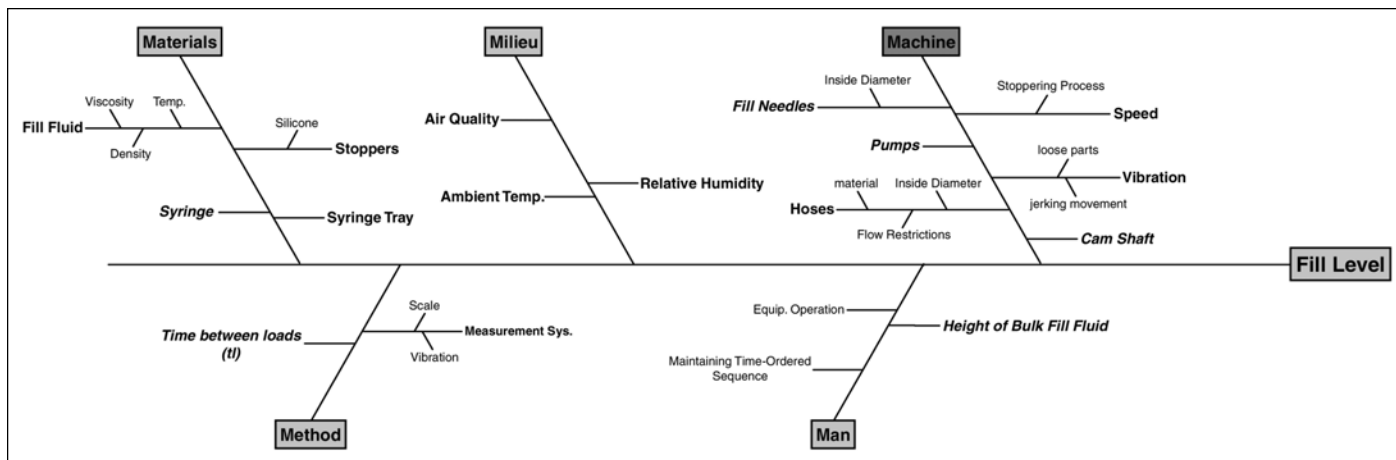


Figure 1. Partial fishbone.

tion, the cost of failure was categorized as potentially catastrophic from both an economic and ethical perspective; furthermore, the specified tolerance for this new piece of equipment --- awaiting delivery and installation --- was 0.2ml +/- 5%. A "best-case" FAT application involving the machine's natural process limits thus presented itself. Additionally, since there was a pre-defined tolerance, quantifiable with a quality attribute measurable on a ratio scale, it would be possible to relate this tolerance to the NPL in both a C_m and eventually a C_{mk} index. Hence, the application of a straight-forward *short-term machine capability* study was indicated.¹

Pre-Site Preparation and the Test Protocol
The Fishbone: Organizing the Variables

In the preparation for any qualification or validation effort, all sources of variation must be considered; however, it is critical that assignable causes of variation be evaluated in light of both costs and impact upon meeting actual operating specification and not solely from an engineering or statistical perspective. Otherwise, costs will outweigh benefits if resources do not run out first. Several approaches may be used finding these variables for the test protocol(s). Typically in our industry, this is addressed by the validation team and those on the review list. This approach functions very much like an expert panel. Whatever approach is used, it is best to organize these variables in some fashion prior to designing the actual test protocol.

Generally, the capability study will be one of several parts in a test protocol set, therefore, organizing the known and suspected sources of variation early on will be of use throughout the project and the equipment life-cycle. The objective of this exercise is to first list then organize the process variables so that they might be addressed and not to establish cause-and-effect relationships. The Fishbone (Cause-Effect) Diagrams utilizes the five basic categories into which all variables might be thrown Materials, Man, Method, Machine, and Milieu.⁴ Other suitable frameworks also may be applied.⁵⁻⁶ It is advisable to avoid lengthy theoretical discussions as to which category a variable might better fall into. For example: specific placement of ancillary equipment such as racks. Man or Method? If there is no SOP available, perhaps place in the Man category; if there is an SOP available, than place in the Method category.

Depending upon your organization, it may become necessary to further identify those variables/factors which are economically addressable, assignable, controllable, non-con-

trollable, random, non-random, etc. for cost analysis and priority setting. Again, avoid unproductive theoretical discussions with respect to cost calculations (engineering vs. cost models vs. cost-of-poor quality models).

In any machine capability study, the focus is necessarily upon the machine. This study was considered a best case scenario especially since the equipment manufacturer was available to assist. Keep in mind, it is not necessary to have all sources of variation (whether random or nonrandom) under control prior to beginning a capability study. Some sources of variation may be explored in the study itself, others may not be economically addressable, and yet others may have no impact upon meeting the operating specification and hence receive no priority from management. It is necessary to have resources, personnel, materials, and suitable test equipment to conduct the planned study. It is also necessary to have the major factors known or suspected to have an impact upon the target (fill) under control. In the case presented, several variables were required to be in control prior to start: the pumps, the syringes, the fill fluid, the fill needles, and the level of both the machine and trays - *Figure 1*.

The Design Concept and Sampling Plan

Our first encouragement came when a review of the Purchase and Sales Agreement revealed that the intended use would accept a variation much larger than the vendor reported (approximately 3 1/3 times larger).

Tolerances reported by Vendor in Purchase and Sales Agreement:	Tolerances set by Manufacturing/Owner:	
Fill Volume S_{rel}		
From 0.2 till 0.6 ml ± 1.5%	0.2ml ± 5%	0.2ml ± 0.01ml
From 0.6 till 1 ml ± 1.0%	1.0ml ± 5%	1.0ml ± 0.05ml
$C = S_{rel} = (S/\bar{x}) (100\%)$		

To use the sample size calculation formula, $n = \frac{z^2 \sigma^2}{h^2}$, we need only an estimate for σ^2 , the population variance. Two approaches to obtaining this estimate are available. First, use the vendor-reported worst-case scenario and second, perform a pilot study. Upon inquiries the need for a pilot study, based primarily upon a good vendor relationship, was ruled out.

Under the selected approach each fill range and associated

Juran, J.M. and Frank M. Gryna Jr.⁵

No distinction between machine and process capability studies

- to predict the extent to which the process will be able to hold tolerances
- to choose from among competing processes that is most appropriate for the tolerances to be met
- to plan the interrelation of sequential processes. For example, one process may distort the precision achieved by a predecessor process, as in hardening of gear teeth. Quantifying the respective process capabilities often points the way to a solution.
- to provide a quantified basis for establishing a schedule of periodic process control checks and readjustments
- to assign machines to classes of work for which they are best suited
- to test theories of cause of defects during quality improvement programs
- to serve as a basis for specifying the quality requirements for purchased machines

It is not necessary to remove all assignable causes of variation prior to start of study and generation of C_p index.

Ott, Ellis R., and Edward G. Schilling²

No distinction between machine and process capability studies. Short-run capability study termed a "Process-performance Check" Study:

- investigation of process through Control Charts
- elimination of nonrandom behavior when justified economically or quality

It is necessary to remove all (economic) assignable causes of variation prior to start of study and generation of C_p index. Process capability can only be measured when the process itself is in control.

Wheeler, Donald J., and David S. Chambers³

Distinguishes between:

- Short Term Capability
- Hypothetical Process Capability
- Capability

Blank, Hans-Peter et al.¹

MFU (Machine Capability)

- the examination of a machine's actual capability to meet pre-defined production tolerances
 - the basis for factory acceptance of a new machine
- Short-term planning.

PFU (Process Capability)

- the testing of process parameters
- the elimination of all systematic process variation
- the minimization of testing and failure costs
- the reduction of cycle time

Long-term planning.

(translated from the original German by Peter A. Hugunin)

$$C_{mk} = \frac{\text{Min}|UTL - \mu \text{ and } \mu - LTL|}{3\sigma} \quad C_m = \frac{UTL - LTL}{6\sigma}$$

This author finds the distinction between *machine* and *process* capability studies to be useful for theoretical, organizational, and practical reasons. Additionally, because quantity producible over time, re-tooling, and maintenance will always be of production and hence management concerns the distinction between *short* and *long-term* will always be necessary. The calculation of a *hypothetical* capability³ also shows some utility. It may be shown, for example, that in the case problem presented, C_{mk} is equivalent to the *hypothetical process capability*.

Although capability statistics are a useful stand-alone quality tool they are best used in conjunction with other quality tools such as Design Of Experiment (DOE); process re-engineering and flow-diagramming; Statistical Process Control (SPC); and, Failure Mode Effect Analysis (FMEA).

RSD would be reviewed to yield the worst-case estimate of σ^2 . This was found to be at the vendor reported RSD of 1.5% and 0.6mL fill volume. In simple terms, this may be viewed as (0.6mL) (0.015) = 0.009mL. Alternately, it may be viewed as

$$1.5 = \frac{s}{0.6} 100. \text{ Solving for } S, \text{ the standard deviation, we again}$$

obtain 0.009mL. Our estimate therefore for σ^2 is (0.009)².

The allowable half-width, h , in the error of measurement was set at 0.01mL/2 or 0.005mL. And, the selected confidence coefficient of 99% [$cc = 99\% (1 - \alpha/2)$] yields a z-value of 2.576, i.e. $z(0.995) = 2.576$. Finally, this resulted in the sample size calculation below:

$$n = \frac{(2.576)^2 (0.009)^2}{(0.005)^2} = 22, \text{ hence, for reasons which will}$$

become clear in Part 2 of this article, a sample size of 24 was selected.

The basic design would call for production at maximum speed for at least 12,000 units while 5 subsamples each of size 24 would be drawn. This would permit some process control during the study; the building of a 99% confidence interval (C.I.) on the population mean for each of the planned five subgroups; and, would be sufficient to form the foundations of our capability study as well as build control charts for production purposes. Note, that a sample size of 24 is not alone sufficient to determine machine capability. Sampling was planned for several hours of production from which a systematic sample in time-ordered sequence was to be taken and analyzed. This model necessarily assumes that target and variation between samples is constant. The test fluid was selected by the owner/manufacturer to substantially match the viscosity and density of an actual product.

Additional General Considerations

It can not be overemphasized that the central issue is one of prediction limits (a confidence band on the population distribution) and not confidence limits on a summary statistic such as the population mean. In a capability study, the interest lies in calculating from process data the limits which will contain all future observations (production units) and not with defining an interval within which a population statistic, such as the mean, lies. This is not peculiar to the pharmaceutical industry, but rather characteristic of all machine and process capability studies whether for parenterals, nuts and bolts, or cardboard boxes. Only the measures and the tolerances vary from one project/industry to the next.

It is not possible to have perfect knowledge of the machine's operating characteristics prior to starting first time qualification testing so plan accordingly: over plan. Collect, time permitting, more data than necessary. It may be a long way to the vendor or customer site (in our case Schabish Hall, Germany) so plan accordingly. You may have only one chance at collecting the information and data. Investigate additional factors or parameters only if time permits. The trip to Schwabish Hall, Germany, was planned well in advance and included a schedule for data collection for the capability study. It was further arranged that the vendor would assist by assigning one technician full time and others ad-hoc to our studies and the owner/manufacturer provided an electrician thus making an execution team of size three.

Capability may be calculated in various ways:

1. using a frequency distribution and histogram
2. using probability paper
3. using control charts
4. using other methods ... graphic analysis, DOE, or ANOVA

Table A. The tool and its applications.

Abbreviation	Term's Meaning
C_m	Machine Capability: $C_m = \frac{UTL - LTL}{6\sigma}$
C_{mk}	One sided machine capability: $C_{mk} = \frac{Min UTL - \mu \text{ and } \mu - LTL }{3\sigma}$. This analysis recognizes that the machine will not operate precisely at the set-point.
C_p	Process Capability: Statistically the same as C_{mk} but the analysis is for the process and not just the machine.
C_{pk}	One sided process capability.
$C(S_{rel}, RSD)$	The Relative Standard Deviation: $RSD = S_{rel} = C = 100 \frac{(s)}{\bar{x}}$
d_2	This is an adjustment factor taken from a statistical table. See Ott, Ellis R., and Edward G. Schilling ² (p. 213 and Table A.11).
FAT	Factory Acceptance Test(ing). Any testing done prior to the Sit Acceptance Testing (SAT).
h	Desired Half-width of the confidence interval (CI). How close must the estimate (sample mean) be to the population mean for it to be meaningful to the application?
k	The k factor is a function of the confidence coefficient, the percent of the population to be included within the tolerance limits, and the sample size. See Juran, J.M. and Frank M. Gryna Jr. ⁷ (p. 299 and Appendix Table K).
n_g	The subgroup sample size from which range, x_{par} , x_{max} and x_{min} values are calculated. This, in our analysis, is the number of columns, i.e. 4. It represents the smallest number of filled syringes analyzed as one group.
NPL	Natural Process Limit. The limits within which virtually all individual observations/values will fall for any system which displays a reasonable degree of statistical control. In Part 2 of this paper this will be examined under two approaches: $NPL = \bar{x} \pm 3 \frac{\bar{R}}{d_2}$ and $NPL = \bar{x} \pm kS_m$.
OEM	Original Equipment Manufacturer.
R	The mean range. $\bar{R}_{si} = \frac{\sum_{i=1}^{n_{si}} R_{ri}}{n_{si}}$ \bar{R}_{si} is the range of the i^{th} Sample Group (S1, S2, S3, S4, or S5). n_{si} is the Sample size with respect to individual range calculation, R_{si} . This is three for Sample Group S1, and is five for all others. R_{si} is the Range of the r^{th} row in the i^{th} Sample Group. This will become clear in Part 2 of this article where samples are actually drawn, organized, analyzed and turned into productive information.
RSD (C, S_{rel})	Relative Standard Deviation.
s (S_m)	Sample Standard Deviation. s represents the filling variation as calculated from OEM provided information in the purchase and sales agreement. S_m simply indicates those calculated in our studies. $S_m = \sqrt{\frac{\sum_{i=1}^n (x_i - \bar{x})^2}{n-1}} \quad \bar{x} = \frac{\sum_{i=1}^n x_i}{n}$
UTL and LTL	Upper Tolerance Level and Lower Tolerance Level. This is also known as USL and USL, Upper and Lower Specification Limit. Not to be confused with Upper Control Limit and with Lower Control Limit which will be set up in Part 2 of this article for Statistical Process Control (SPC) purposes.
z	The distance, in standardized deviations, a point (X) is from the mean under a normal standard distribution curve, i.e. a distribution with a mean of 0 and a standard deviation of 1. Note: The standard normal distribution may be denoted by $N(0/1)$ and our actual distribution may be denoted by $N(\phi/\sigma^2)$. Any $N(\phi/\sigma^2)$ may be normalized. $Z = \frac{(X - \mu)}{\sigma} \quad \text{or, for the sample distribution:} \quad Z = \frac{(\bar{x} - E\{\bar{x}\})}{\sigma_{(\bar{x})}} = \frac{\bar{x} - \mu}{\sigma/\sqrt{n}}$
ANOVA	ANalysis Of VAriance
cc	Confidence Coefficient (1 - α). The degree of confidence with which the estimate falls within the given interval.
C.I.	Confidence Interval. The interval within which the estimate will fall.
DOE	Design of Experiment.
\bar{R}	Mean of the Ranges.
$\bar{\bar{x}}$	Grand mean or average of the averages.
x_i	An individual observation (of syringe fill weight or empty syringe weight).
μ	Population mean - in practical terms this is the set-point. Estimates for this include \bar{x} and $\bar{\bar{x}}$.

Table B. Index of abbreviations and terms used in Part I.

Sometimes a simple plot of individual units against tolerance limits, with no statistical analysis, is sufficient to draw conclusions⁷ — as will be seen in Part 2 of this article. The final approach and solutions to our particular case are outlined in the protocol below.

OQ- Machine Capability Study (C_m and C_{mk})

Objectives and Acceptance Criteria

1. The machine is operator adjustable to a target of 0.2ml.
2. Once set, the machine is capable of filling at least 12,000 syringes, without intervention, which meet the required specification, i.e. 0.2ml +/- 0.01ml.
3. $C_{mk} \geq 1.33$

Procedure

1. General

- 1.1 Collected data are to be entered into the table format provided.
- 1.2 Test instrument accuracy and precision is to be at least 4 times better than +/- 0.01ml (+/- 0.01g) , i.e. +/- 0.0025ml (+/- 0.0025g).
- 1.3 WFI water cooled to ambient is to be used as the test fluid.
- 1.4 Confidence interval about μ is to be at least 99%.
- 1.5 Data are to be entered into an electronic format suitable for electronic spreadsheet analysis, e.g. Excel.
- 1.6 After start of data collection, there are to be no machine adjustments.
- 1.7 Record the ambient temperature, relative humidity, and test fluid temperature.

2. Data Evaluation

- 2.1 The sample data sequence is to be maintained in the table and the charts.
- 2.2 Construct an \bar{x} and x_{min}/x_{max} chart.
- 2.3 The population is tested for fit to normal distribution.
- 2.4 Construct an $\bar{\bar{x}}$ and x_{min}/x_{max} charts.
- 2.5 Calculate the natural process limits of this machine.
 $\bar{\bar{x}} \pm 3 \bar{R}/d_2 \quad n_g = 4 \therefore d_2 = 2,059$

References

Doc. ID	Document Description or Title
205-A-001-00	Sales and Purchase Agreement
DIN 55350-33	German Industrial Norm specifying acceptance limits and interpretation of the capability index.
MIL-STD 4566A (1988)	Calibration System Requirements

Note


MIL-STD 4566A (1988) was used rather than DIN ISO 10012 Part 1 (Quality assurance required for measuring equipment Part 1: Meteorological confirmation system for measuring equipment) because under DIN ISO 10012 Teil 1 Section 4.3 Guidance error attributable to the calibration may be up to 33% whereas under MIL-STD 4566A (1988) section 5.2 this attributable error may be a maximum of 25%. It was felt the extra 8% would reduce both the alpha and beta risks in decision making. It also was available at no additional costs.

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This article will discuss construction of hot water sanitizable CEDI modules and systems, as well as sanitization procedures. Data will be presented showing the effect of the hot water sanitization on CEDI module performance, including product water conductivity and TOC.

Hot Water Sanitization of Continuous Electrodeionization Systems

by Jonathan Wood, Junya Hirayama, and Shigeaki Satoh

Introduction

The process of continuous electrodeionization (CEDI) uses ion exchange membranes, ion exchange resins, and a DC electrical potential to remove ionizable materials from water. This process has been in use for more than 10 years in the production of USP Purified Water, as an alternative to mixed-bed deionization. One of the main advantages of the process is that it does not require chemicals to regenerate the ion exchange resins since the DC field regenerates the resins electrochemically. Another advantage is that the electric field helps minimize bacteria growth in the resin bed. CEDI is usually installed downstream of a Reverse Osmosis (RO) system to remove contaminants that have not been (or can not be) removed by the RO.

In most cases, it is desirable to be able to periodically sanitize the RO system as well as the CEDI system. Until recently, construction of RO and CEDI devices has required that disinfection be performed chemically, using non-oxidizing biocides. There are a number of potential advantages to sanitizing with hot water (65-80°C), including avoidance of chemical handling and disposal; better penetration and inactivation of biofilm; faster rinseup and easier validation. RO membranes and systems capable of hot water sanitization have been available for a few years, but only recently have hot-water sanitizable CEDI modules become available.

Water Quality Specifications

The U.S. Pharmacopeia (USP) dictates the purity of water used for the manufacture of pharmaceuticals. The compendial grades of water must meet a specification for conductivity and total organic carbon (TOC).¹ In order to meet these specifications it is often necessary to use a membrane process such as RO or UltraFiltration (UF) in combination with an ion exchange process such as CEDI or service deionization (SDI). Using membrane processes alone may not be sufficient because even double-pass

RO does not effectively remove dissolved gases such as carbon dioxide (CO₂) or ammonia (NH₃).² Adjustment of the RO inlet pH can ionize one of these gases so that it can be removed by the RO. Unfortunately, the optimum pH is much different for these two contaminants. This problem is becoming more widespread as more municipal water supplies are treated with chloramines to limit the formation of disinfection byproducts, which increases the likelihood that ammonia will be present in the RO feed water. The ion exchange processes mentioned above are capable of simultaneously removing both CO₂ and NH₃ to very low levels, and when combined with RO provide a high level of assurance that the TOC and conductivity specifications will be met.

While there is no USP specification for bacteria, the recommended "action level" is 100 colony-forming-units per milliliter (cfu/mL) for Purified Water and 10 cfu/100 mL for Water For Injection,³ and many companies have set lower action levels. In practice, the large majority of systems are maintained at bacteria counts well below the USP action levels. In order to maintain the microbial levels below these recommended maxima, it is usually necessary to periodically sanitize the water purification system.

In most cases, it is practical to meet the Purified Water action level with a properly designed RO/CEDI system and periodic chemical sanitization. However, the use of chemical disinfectants has a number of disadvantages, including the handling and disposal of hazardous chemicals, and validating that all traces of the sanitant have been removed before the system is returned to service. If the chemical solution is not properly prepared and applied, it is possible to permanently damage the expensive RO membranes or CEDI cells. Therefore an alternative to chemical sanitization is desirable. Hot water has already been successfully applied for sanitization of ion exchange resin beds⁴ and reverse osmosis membranes^{5,6} and is therefore an excellent candidate for CEDI systems.

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Operation in the laboratory...has shown that it is possible to construct a CEDI device that can be repeatedly sanitized with hot water at 65°C.

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CEDI Module Construction

The CEDI process uses ion-selective membranes and a DC electrical potential to remove salts from solutions by transferring ions from the product stream to a concentrate, or reject stream. CEDI uses a conductive filler, such as ion exchange resin, in some or all of the flow compartments, allowing the production of ultrapure water.

The most common CEDI devices are plate and frame devices consisting of alternating anion and cation ion-exchange membranes. The ion exchange membranes are not permeable to water (counterions diffuse through water that is trapped in the matrix of the ion exchange material). The spaces between the membranes are configured to create liquid flow compartments with inlets and outlets. These compartments are hydraulically in parallel and electrically in series. A transverse DC electrical field is imposed by an external power source using electrodes at the ends of the membranes and compartments, attracting ions in the liquid to their respective oppositely charged electrodes.

The result is that the ions transfer from the product compartments (bounded by the anion membrane facing the anode and the cation membrane facing the cathode) into the reject, or concentrate compartments (bounded by the anion membrane

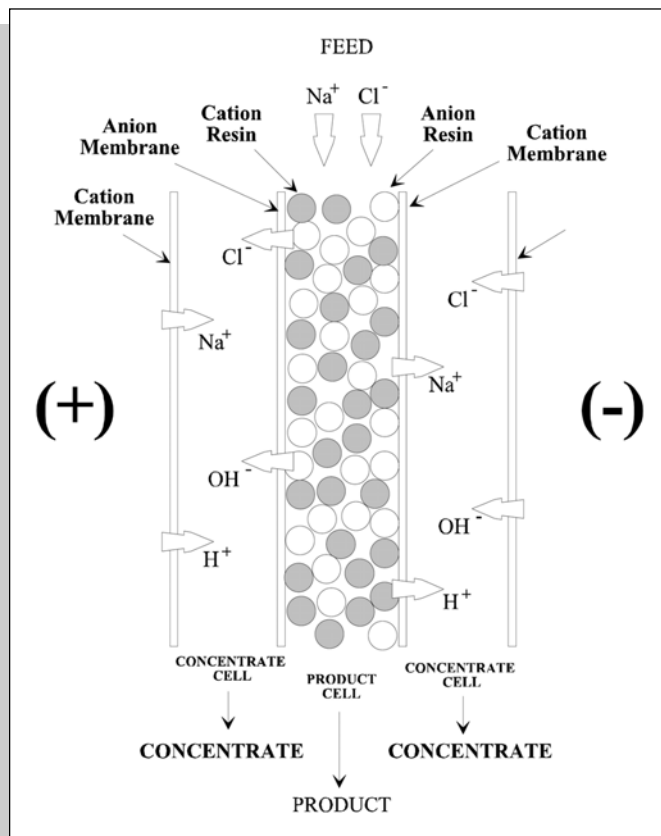


Figure 1. CEDI device - concentrate screens.

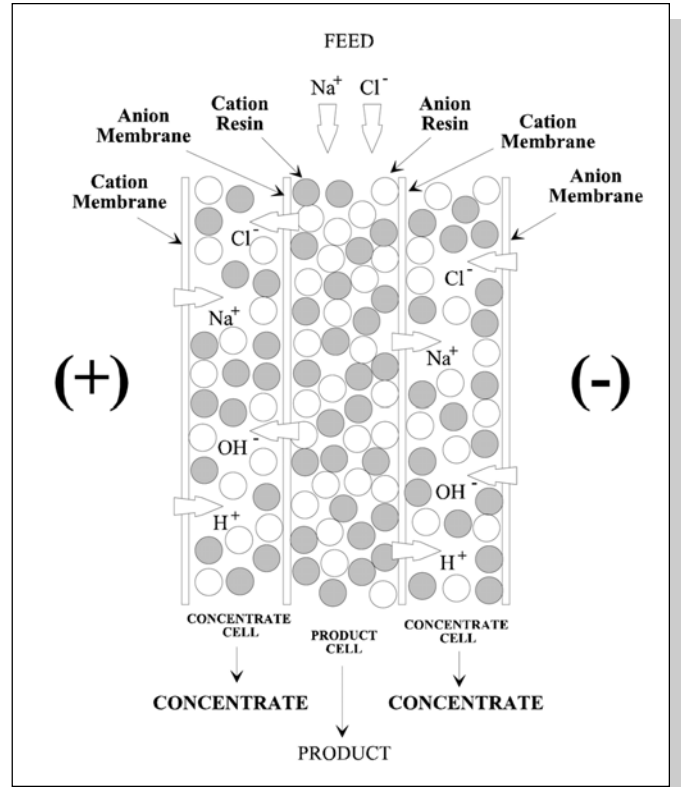


Figure 2. CEDI Device - all filled spacers.

facing the cathode and cation membrane facing the anode). About 80-95% of the water fed to the device becomes purified product water, while the other 5-20% becomes a concentrate, or reject stream.

The majority of CEDI devices have been constructed with electrically active media in the product compartments, but using a non-conductive gasketed screen for the reject compartments, as shown in Figure 1. The ion-exchange media enhances the transport of ions and can also participate as a substrate for controlled electrochemical reactions. Many different media configurations are possible, such as mixed bed, layered bed or single (separate) bed. The performance is strongly dependent upon the type of ion exchange filler.⁷

For CEDI devices that are fed low conductivity RO permeate, the electrical resistance of the concentrate compartments may limit the passage of current and therefore the removal of salt. One of the most recent advances in CEDI has been to incorporate a conductive filler in the concentrate as well as the product compartments. This type of CEDI module construction is shown in Figure 2.

The wetted components of a CEDI module include the ion exchange resins, ion exchange membranes, the resin “compartment,” the electrodes and the manifold blocks used for the piping connections to direct solutions to and from the device. In all cases the materials must be selected for compatibility with hot water. In addition, the module must be designed to allow for any thermal expansion that might occur during the heat sanitization.

This paper will describe results obtained for two different CEDI systems, one which was a laboratory test unit, and another that is a commercial system which has now operated successfully for about 24 months.



Testing indicates that with weekly sanitizations it is reasonable to expect at least a three-year module life for a CEDI module...



Laboratory Testing

Tests on hot water sanitization of a CEDI module have been performed in Atsugi, Japan over the past few years, at the Central Research Laboratory of Kurita Water Industries. The CEDI device used in this testing was a 10-compartment CDI® module, which is rated for a nominal product flow rate of 3.3 gpm (12.5 l/min) and a maximum flow of 4.4 gpm (16.7 l/min). This was a “thin-cell” device, with inter-membrane spacing of about 0.1 inch (3 mm). The relationship between intermembrane spacing and CEDI performance is described elsewhere.⁷ The module contained 10 product compartments and 10 reject compartments, all of which contained a true mixed-bed resin filler. The compartments are heat-sealed together, virtually eliminating the need for gaskets and the possibility of external leaking. Heat sealing of the ion exchange membranes to the resin compartment “spacers” requires that the components be constructed of similar materials. In this case the ion exchange membranes were heterogeneous type, consisting of a polyethylene binder and an ion exchange resin powder (either cation resin or anion resin powder, depending on the type of membrane). Therefore the resin compartment “spacers” were also made of polyethylene. All the wetted materials in the test module comply with FDA requirements for food contact surfaces.

The CEDI module was subjected to 150 hot water sanitization cycles, equivalent to sanitization once a week for three years. Each cycle consisted of a heat up period (~40 minute from 25 to 65°C), a hold time (60 minutes at 65°C) and a cool down period (~40 minute from 65 to 25°C). The sanitization was performed using deionized water at low pressure, typically 4-7 psig (0.3-0.5 kg/cm²), which gave a flow rate of about 0.4-0.5 gpm (1.5-2.0 l/min). The inlet and outlet temperature, flow and pressure were monitored during each of the cycles. The DC voltage was turned off during the hot water sanitization.

During the first three cycles the total organic carbon (TOC) of the feed and product water was measured. After 10, 50, 100 and 150 cycles the CEDI module was operated on RO permeate

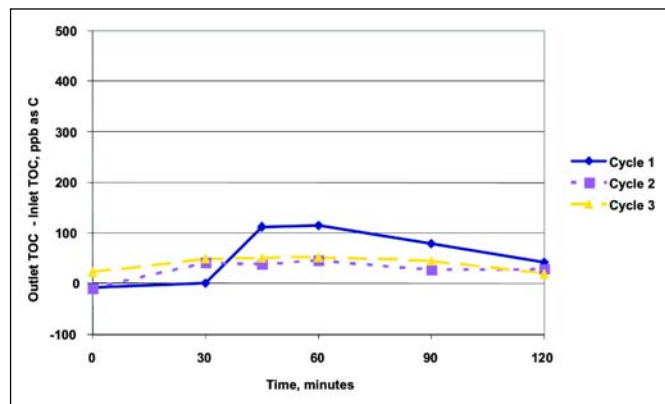


Figure 3. Lab Test - TOC during sanitization.

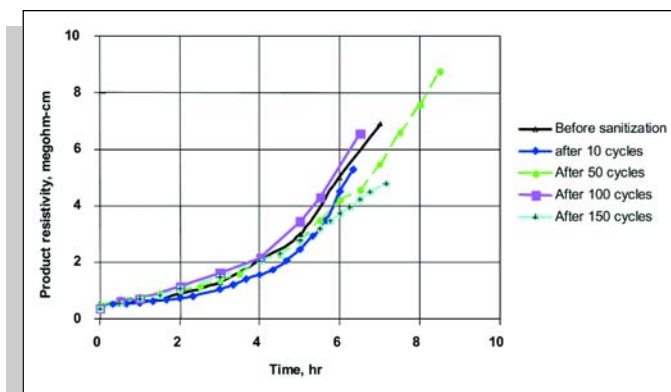


Figure 4. Lab Test - rinseup after hot water sanitization.

(conductivity 2.3-12.0 $\mu\text{S}/\text{cm}$) for several hours with DC power on (1.7-2.0 VDC/cell) and the product water resistivity recorded at least once each hour. A final test included sampling for bacteria both before and after a hot water sanitization of the entire system.

Laboratory Results

A graph of the TOC data obtained during the first three sanitization cycles is given in Figure 3. The difference between the outlet and inlet TOC is plotted as a function of time. The data indicate that during the high temperature portion of the cycle the effluent TOC is higher than the feed, but that the magnitude of the difference decreases significantly after the first cycle. This increase in TOC of the effluent is believed to be due to leaching of extractables from the new ion exchange resins. While it also could be due to degradation of the resins, this is not believed to be the case because of the results obtained in the “resistivity rinse-up” test.

The “resistivity rinse-up” test results are graphed in Figure 4, which gives the product water resistivity as a function of time for 5 different runs. The results show very little difference in product water quality before and after the 150 sanitization cycles. This suggests that there is no significant damage to the functionality of the ion exchange resins and ion exchange membranes.

The purpose of the 150 sanitization cycles at 65°C was simply to confirm that the module construction was compatible with repeated exposures to the high temperature. Once this had been demonstrated, a brief test was performed to determine the effectiveness of the hot water sanitization at reducing bacteria counts. The CEDI module was operated on water that had been pretreated by activated carbon, microfiltration, and reverse osmosis. The entire system was run for several months without sanitization, and a set of bacteria samples taken before hot water sanitization. Then the water system was sanitized, the pretreatment and RO system at 80°C, and the CEDI module at 65°C. After the hot water sanitization the entire system was run continuously for over a week, with periodic samples taken for measurement of bacteria in the CEDI inlet and outlet. Bacteria were collected by passing 100 mL of sample through a sterile 0.45 micron filter (37 mm diameter), which was cultured in m-TGE media for 72 hours at 30°C. Colonies were counted using an optical microscope. Results are shown in Table A.

Prior to the sanitization the bacteria counts in the CEDI product were slightly higher than the feed. This may be due to colonization of the piping, since the bacteriostatic effect of the

TIME	CEDI IN	CEDI OUT
Before Sanitization	75	300
After Sanitization	0.00	0.77
Day 1 (18.5 hours)	0.00	0.06
Day 3 (64.5 hours)	0.00	0.11
Day 6 (144 hours)	0.02	0.00
Day 9 (208 hours)	0.01	0.05

Table A. Standard plate counts, cfu/mL

electric field applies only to the resin bed inside the CEDI module. The subsequent data indicate that the 65°C hot water sanitization of the CEDI module was effective at reducing the number of viable bacteria in the CEDI product water. In addition, there was essentially no increase in the bacteria counts after 9 days of continuous operation.

Commercial System

A hot water sanitizable CEDI system was sold to a pharmaceutical company in Japan in 1998. The system included pretreatment, reverse osmosis, and two 30-cell CDI® modules. These were constructed with the same type of cell packs as those in the 10-cell modules used for the laboratory test described earlier. The 30-cell units are rated for a nominal product flow rate of 10 gpm (37.9 lpm) each. CEDI modules A and B were commissioned during May and June 1998. Since that time both modules have been sanitized once each week with 65°C water. The feed water to the CEDI modules has a conductivity of about 4 µS/cm, and also contains 3 ppm of CO₂ and 0.5 ppm of SiO₂. Both modules operate at about 50 VDC.

Figures 5, 6 and 7 indicate that the performance of both CEDI modules stayed extremely stable over the first six months of system operation. Figure 5 shows that the CEDI product water resistivity (temperature compensated to 25°C) remained between 13.2 and 16.1 megohm-cm (0.076 to 0.062 µS/cm). This easily meets the USP 24 stage 1 conductivity specification of ≤ 1.3 µS/cm at 25°C (≥ 0.77 megohm-cm).

Figure 6 shows both the product flow rate and pressure drop for the two modules. The stable pressure drop is an indication that the repeated hot water sanitizations have not caused any degradation to the structural integrity of the ion exchange resin, since one of the symptoms of such damage is swelling of the resins and an increase in pressure drop.

Plots of the modules' electrical resistance (the applied DC voltage divided by the resulting DC amperage) and temperature are given in Figure 7. It is important to view these parameters together because the temperature directly affects the electrical (ohmic) resistance of the module. The stability of the electrical resistance is further evidence that the CEDI modules can tolerate the repeated high temperature sanitizations.

This CEDI system has now been operating more than 24 months, with module performance remaining stable.

Discussion

The use of hot water provides several advantages over chemical sanitization. Foremost is the fact that it is considered to be more effective than the non-oxidizing biocides that are compatible with the resins and membranes of CEDI systems (oxidizing biocides such as chlorine, hydrogen peroxide and

ozone are not compatible and can not be used). This is especially true in cases where biofilm has formed, since it can be difficult for chemicals to penetrate and kill organisms inside of biofilms. Since low bacterial growth is usually associated with low endotoxin levels, hot water sanitization may also give more effective pyrogen control.

Other obvious benefits of hot water are the elimination of chemical rinseout concerns and avoiding the handling and disposal of corrosive or hazardous chemicals. For pharmaceutical manufacturers the process would be easier to validate, because it is less difficult to demonstrate the complete distribution of heat and simpler to monitor heat than chemical concentrations. Likewise, after sanitization it is easier to demonstrate the removal of heat than the complete flushout of the sanitization chemicals. Hot water sanitization may also be more straightforward to automate than a chemical disinfection process.

While construction of a hot water sanitizable CEDI module is challenging, design of the system is straightforward and can utilize most of the same materials as conventional CEDI systems, such as 316L stainless steel and polypropylene. The major design concerns are proper temperature and pressure control, to avoid exceeding the desired sanitization conditions. If a supply of hot water is not available, then the capital investment may be higher for hot water than chemical sanitization.

The use of hot water for sanitization will not necessarily eliminate the need for occasional chemical cleaning. Such cleaning may be required if an upset in the operation of the pretreatment equipment has led to scaling or fouling of the CEDI module. An interesting subject for future investigation would be the potential synergistic effect of heating the chemical cleaning solutions, and whether this would be compatible with the CEDI module construction.

The typical life of a CEDI device with monthly chemical sanitization is five years or more. Some CDI® modules remain in service after more than 12 years of continuous operation. The laboratory testing described in this paper included 150 hot water sanitization cycles because this was felt to be the minimum number that the device must be able to withstand in order for the process to gain market acceptance. The results suggest that the module would have tolerated additional sanitizations without ill effect.

Some preliminary sanitization cycle testing at 80°C also has been performed in the laboratory on a 30-cell, "all-filled" CEDI module. Initial results are very promising.

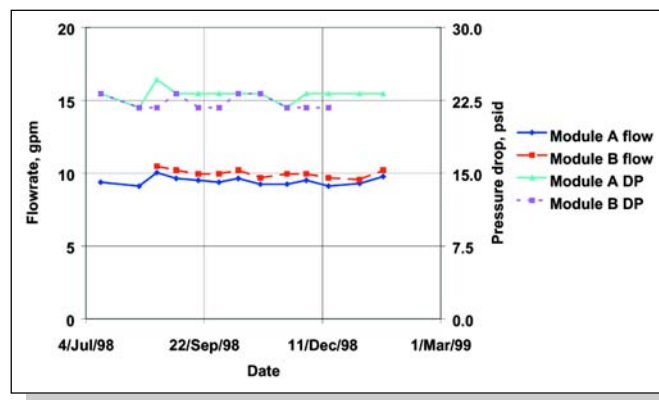


Figure 6. Commercial System - CDI product flow, DP- with weekly sanitizations at 65°C.

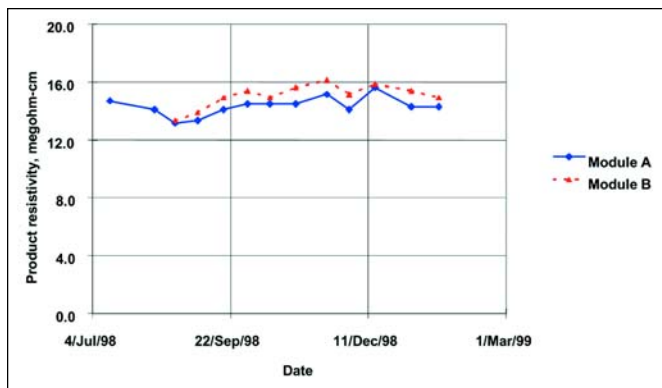


Figure 5. Commercial System - CDI resistivity-with weekly sanitizations at 65°C.

Conclusions

Operation in the laboratory and at an actual commercial installation has shown that it is possible to construct a CEDI device that can be repeatedly sanitized with hot water at 65°C. Testing indicates that with weekly sanitizations it is reasonable to expect at least a three-year module life for a CEDI module with resin filled product and concentrate spacers, and heat-welded (gasketless) module construction. The hot water sanitization process is believed to be more effective, safer, faster, and easier to validate than conventional chemical sanitization.

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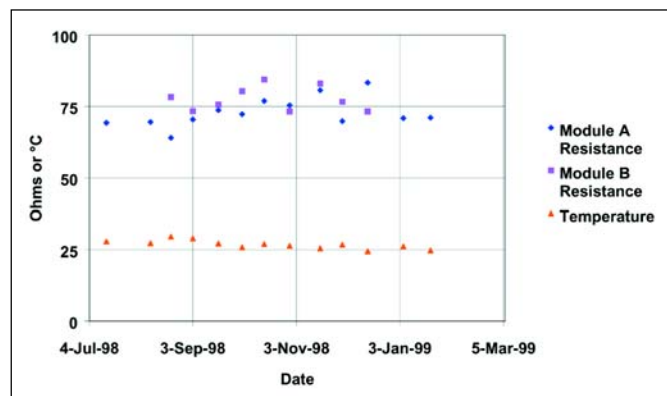


Figure 7. Commercial System - CDI ohmic resistance- with weekly sanitizations at 65°C.