This article offers a practical approach to commissioning and a method of synergy with qualification. Practical applications are explored, as well as the use of Enhanced Commissioning Documentation to minimize the qualification effort.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

A Practical Approach to Commissioning and Qualification - A Symbiotic Relationship

by Timothy D. Blackburn, PE

An initial response to the recommendation to perform commissioning is that it is just an additional step – another roadblock to engineering success and something repeated during qualification. However, effective commissioning supports engineering *and* qualification success. This article addresses efficient commissioning techniques and synergizing with qualification. Examples presented are not all definitive, and documentation may exceed or not include certain elements – commissioning (and qualification) must be structured for the project.

Commissioning Streamlines Qualification

Effective commissioning results in a focused and first-time-success validation effort. There are many ways commissioning can benefit qualification – reduce costs (but don't overstate), a less rigorous documentation regimen (except for enhanced commissioning requirements), tests are closer to the source (suppliers, contractors, etc.) and therefore are often more meaningful, debugging/trouble shooting is minimized during qualification, faster qualification, catch problems qualification might miss,

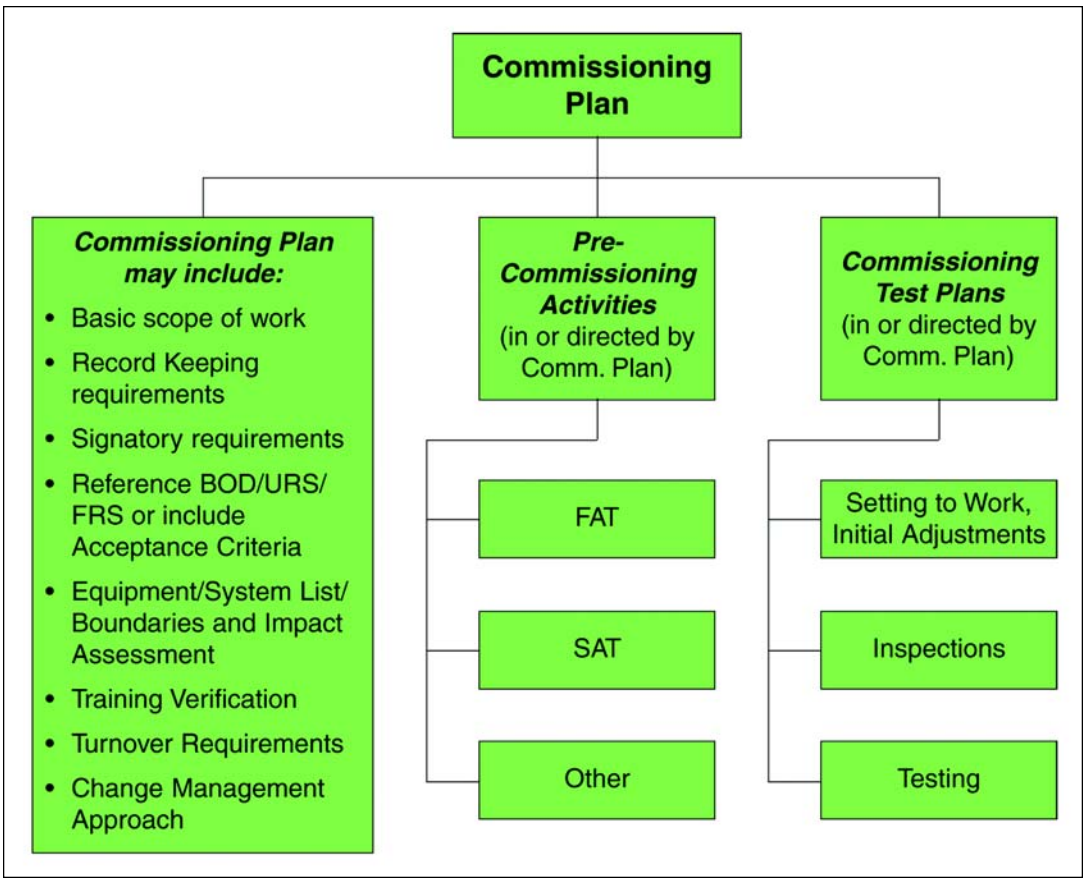

Figure 1. A commissioning documentation hierarchy.

better schedule attainment, and better project quality attainment, better customer satisfaction (when they finally realize the value of commissioning).

There are good reasons formal commissioning is needed, many of which are directly related to more efficient qualification. The following are a few examples:

1. Ratcheting Validation Costs - each project has the tendency to "one up" the previous one and qualification success may be graded by the weight of the paper generated.

2. Validation, a Debugging Exercise - due to a lack of proper commissioning, problems may be discovered during qualification that add cost, schedule duration, and undo stress. Validation should be a *one-shot* exercise and successfully completed as much as possible on the first try.

3. Overly Extensive Validation, Undue Lifecycle Burden - there is a tendency to over-qualify due to a lack of confidence in the installation (actually due to a lack of adequate commissioning), which not only adds initial cost, but unnecessary lifecycle maintenance of a validated state. This over-qualification may extend to areas not associated with product quality, and is not necessary when effective commissioning is applied.

4. Repeating Informal Commissioning Activities - Most projects include some level of Commissioning, which are often repeated during qualification.

Validation/Commissioning: The Distinctions

It is important to understand the definitions of Validation, Qualification, and Commissioning to determine the distinction and how they can effectively work together. First, validation is defined as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."[1] Qualification is a subset of validation which includes IQ/OQ/PQ, and is defined as "The documented verification that all aspects of a facility, utility, or equipment that can affect product quality... adhere to approved specifications" (Installation Qualification or IQ) ... operate as intended throughout all anticipated ranges (Operational Qualification or OQ) ... perform as intended meeting predetermined acceptance criteria"[2] (i.e., over time Performance Qualification or PQ)."

Commissioning is defined as "a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations."[3] In other words, commissioning verifies what was specified was installed, that it functions properly, and it was successfully turned over to the user, *and* reasonably ensures qualification success (avoid qualification becoming a troubleshooting exercise). For cGMP, formal commissioning provides necessary documentation to verify and record commissioning was done and supports qualification documentation.

Note the distinction between the two definitions. The validation/qualification definition emphasizes *product*; the commissioning definition emphasizes *equipment*. Validation/qualification is primarily concerned with and verifying aspects that could affect product quality. Commissioning is concerned with Good Engineering Practice (GEP) and qualification success, and is an equipment/system/facility focus. When commissioning is properly implemented, qualification can focus on what is important – aspects that could affect product quality. Defining qualification and commissioning early in a project also allows commissioning to emphasize direct impact elements to ensure qualification success.

The "W" Model

Commissioning supports qualification relationally; for example, inspection activities support and are similar to IQ, and testing activities support and are related to OQ/PQ. Factory Acceptance Tests (FATs) and Site Acceptance Tests (SATs) support and are similar to the overall qualification effort. Figure 2, a "W" Model, illustrates the relationship between design, commissioning, and qualification. This is similar to the familiar "V" model, except a center portion is added to illustrate the commissioning relationship. The primary User Requirement Specification (URS) or similar document defines the high level, low detail fundamental requirements of the project. Certain Commissioning Functionality Tests should verify the URS was complied with, which leads to PQ. Commissioning testing activities also should sufficiently verify the installation complies with the Functional Requirement Specification (a somewhat more detailed document than the URS), which leads to OQ. Commissioning inspection activities should sufficiently address the detailed spec, which leads to IQ. FAT/SAT documents may include most commissioning testing/inspection elements for some projects, and therefore be relational to all the design documents and lead in to related qualification.

InVEST Wisely in Commissioning

When establishing commissioning requirements, it is important to remain focused on common sense objectives to make the effort meaningful and cost effective. The acrostic "InVEST" is helpful in establishing the focus:

- Integrate: integrate commissioning with qualification. Don't automatically do things twice.
- Verify: does the commissioning activity adequately verify the equipment or system is what was specified and works as it should?
- Ensure Qualification Success: does the commissioning effort sufficiently ensure qualification will be successful – first time?
- Sensible: do enough, but don't over do it.
- Traceable: document it. Remember the saying, "if you don't document it, you didn't do it."

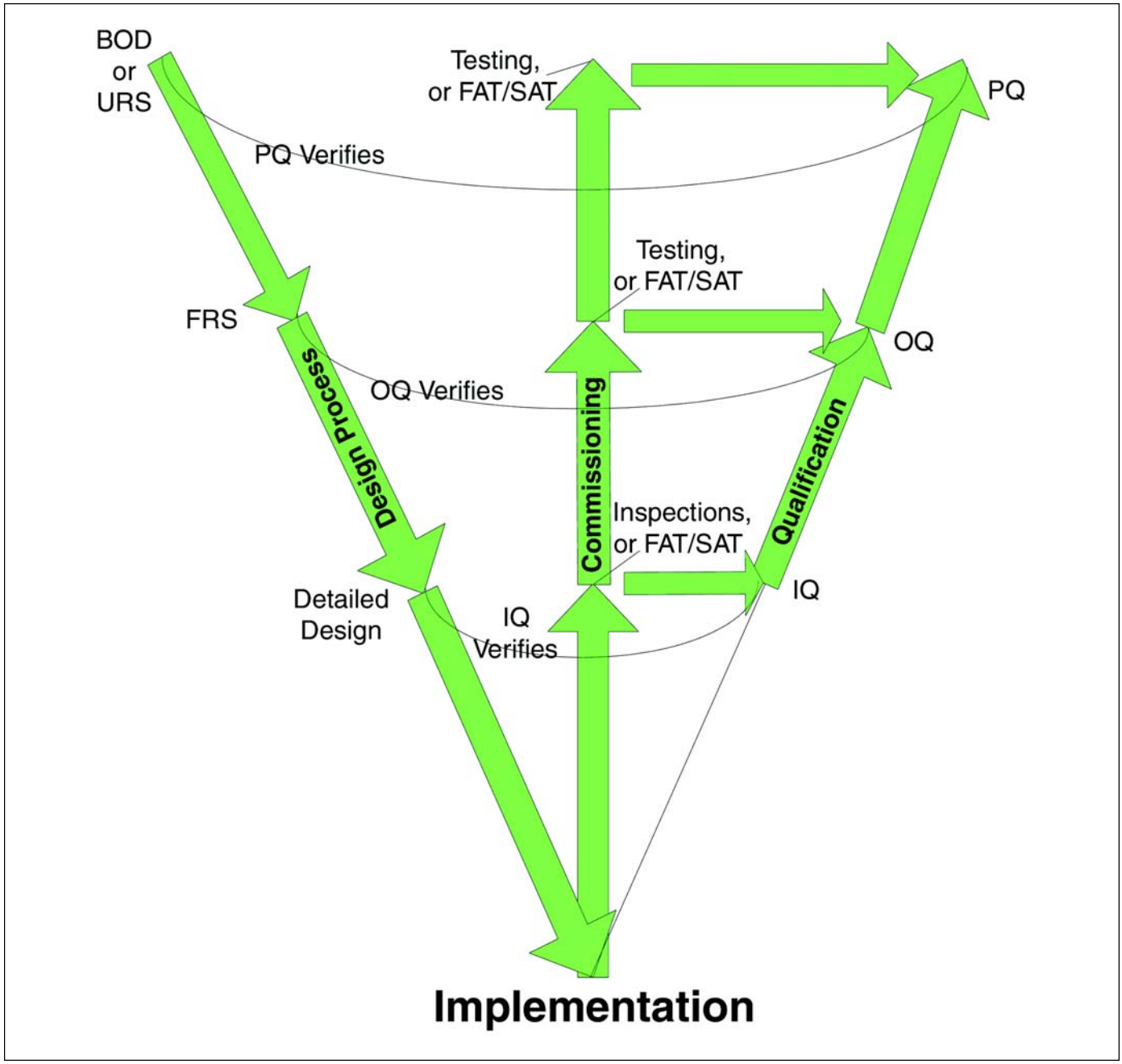

Figure 2. The "W" model.

Establishing Commissioning and Documentation Requirements

Before developing commissioning documentation, establish the extent of commissioning needed, and design efficient and effective commissioning around the needs of the project (hopefully as expressed in a well-written URS/FRS.) Effective commissioning documentation defines the commissioning process (with signatory approval when needed), defines setting to work verifications, inspections, and tests; may confirm training completion (the project is not complete until users know how to use it); and may confirm documentation turnover (the project is not complete until drawings, specs, and O&M manuals are turned over to record/as-built condition and enable users to operate/maintain).

Typical Commissioning Documents may include the following, depending on project complexity - *Figure 1*.

- Overall Commissioning Plan - for large and more complex projects - this is a master plan for commissioning when the approach needs preplanning and structure. On smaller projects/single equipment, consider relying on Standard Operating Procedure (SOP) requirements rather than a separate overall Plan.

- Pre-Commissioning: includes Factory Acceptance Test (FAT), Site Acceptance Test (SAT), and possibly other early inspection/test activities. These are usually structured for individual systems, and can be included in or

required by the commissioning plan. These could be stand alone for individual equipment/systems, and/or include essential elements of the commissioning test/inspection plans.

- Commissioning Test and Inspection Plans: these could be stand alone for individual equipment/systems. These also may supplement areas not covered by FATs/SATs. Further, self-contained commissioning checklists can be used for simple/small work. Don't create unnecessary volumes of documentation.

Enhanced Commissioning

Certain commissioning activities need not be repeated during qualification. It is possible to do commissioning activities that satisfy elements of qualification. This is called "Enhanced Commissioning." Documentation created by enhanced commissioning is considered sufficient for a related qualification aspect and not repeated during qualification. Enhanced documentation may require more extensive and/or a more rigorous test/inspection regimen, as well as additional signatures. Essentially, enhanced documentation must satisfy all the requirements of qualification documentation.

Note that commissioning never replaces qualification for direct impact systems. The commissioning process can cover only elements of qualification, and is not a substitute. Qualification should link back to properly documented enhanced elements. Consider the impact of change control (formal or project) that could affect decisions as to when to use enhanced commissioning.

Factory Acceptance Tests (FATs) and Site Acceptance Tests (SATs) may include enhanced elements. However, be careful when using FAT especially for enhanced because changes may be made at the factory in an uncontrolled setting that affects other outcomes.

FAT/SAT Considerations

For many projects (especially single equipment), the SAT may constitute the majority of the commissioning activities. When FATs (usually a business decision) are provided, SATs can have a reduced regimen; however, this must be carefully thought out when enhanced elements are included.

Typical FAT/SAT considerations may include the following, many of which are good candidates for enhanced classification. (Note: prime potential candidates to include enhanced documentation are noted by (E)).

- functionality - operate equipment/system during testing (E)
- alarms and safeties
- PLC/control thorough checkout/challenge (E)
- utilities (E)
- maintenance needs
- calibration (E)
- labeling
- training and turnover (E)

Commissioning Test Plans

Commissioning test plans may be needed to supplement SATs and to commission in an integrated setting, many elements of which may be good candidates for enhanced designation. This is not to be confused with a commissioning plan, which is the umbrella or overall document. First, the following are *Inspection* (Supporting IQ) questions that must be answered as applicable and included in a commissioning test plan:

- Was specified equipment/systems installed? (E)
- Installed correctly?
- Proper utilities? (E)
- Appropriate human interface?
- Safety/environmental/ergonomics?
- Documentation (user manuals) and other closeout needs completed? (E)
- Training of user personnel completed? (E)

The commissioning test plan also includes *Testing* Considerations that support OQ, which may answer the following questions as applicable:

- Does the equipment or system perform as specified? (E)
- Does it deliver URS/FRS or Basis of Design (BOD) requirements (or other acceptance criteria)? (E)
- Does it operate safely and produce safe results? (E)
- Does it properly function in an integrated setting? (E)
- Calibration (E)

Self-contained commissioning checklists are useful for small projects where commissioning plans and test plans are not warranted. These are useful for small work where the complete commissioning exercise can be accomplished on a succinct document. Again, *InVEST* wisely – don't do more than is needed. These checklists can be enhanced, and may include the following:

- verify item specified was installed (E)
- utility connection (E)
- functionality checkout (E)
- verify calibration completed (E)
- verify closeout documentation completed (E)
- verify training or orientation completed (E)
- CMMS entry (E)
- other internal requirements (E)

Impact Assessments

Before drafting the commissioning or final qualification documentation, it is essential to perform an impact assessment. This process is well defined in ISPE materials. An impact assessment is crucial because it enables qualification and commissioning to focus on what is important. This focus also allows commissioning to minimize qualification while supporting its success. Qualification is minimized both by breadth of coverage, and benefits from commissioning enhanced documentation. Only cGMP direct impact equipment/systems re-

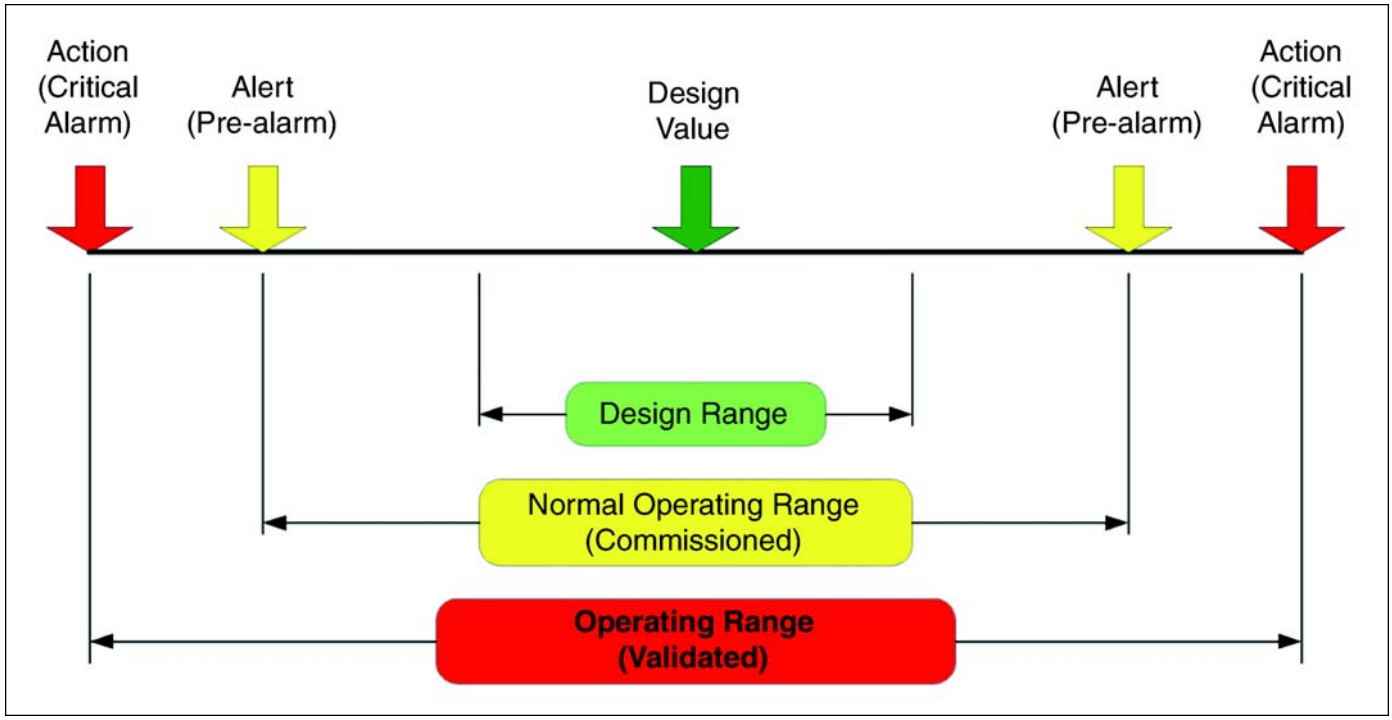

Figure 3. Design conditions chart.

quire validation, and other aspects (indirect impact and no impact) can be commissioned in accordance to Good Engineering Practice in lieu of an overstated qualification protocol.

SMART Commissioning and Qualification Acceptance Criteria/Ranges

Also important in synergizing Commissioning and Qualification and increasing the likelihood of success in both is to assign *SMART* acceptance criteria. The acrostic *SMART* is as follows:

- Sensible: be practical in assigning validated ranges. Is the range really needed to ensure product quality? What does the product really require? Can the equipment deliver this range consistently? Do the ranges also meet business/payback objectives?
- Maintainable: will the range be maintained over time?
- Accurate: is the range measurable? Are realistic tolerances considered? Can equipment consistently meet this target?
- Range: is a reasonable range assigned? Rarely can point values be maintained. Design values must be well within validated ranges to minimize nuisance alarms and quality intervention.
- Traceable: has/can the attainment of the range be verified and documented? Can it be verified later?

ISPE Baseline® Guides present design, normal operating, and operating ranges. (See Figure 3 for a graphical illustration.) *Design* is the value to which the equipment or system is designed. Normal operating is the range, wider than design, at which a pre-alert could occur for maintenance notification – this could be the commissioned range. Even wider is the operating or validated acceptance range. It is crucial to have a less stringent validated (operating) range than the commissioned (normal operating) range, both of which should be less stringent than the design range or value. For example, if the desired validated (operating) range of a filler may be 300 vials or bottles per minute, the commissioned (normal operating range) might be 320, and the design range 340. If the operating range was set at the design value or range, occasional failures would likely occur. (For this example, don't forget to also check at the lower speed during commissioning – some equipment may not operate properly at slow speeds.) Buffers should be provided. Remember, once operating or validated ranges are assigned, there could be a quality intervention required when there are excursions – obviously, this should be avoided. Ideally, acceptance criteria should be determined early, and be a part of the FRS against which final commissioning and qualification documents are drafted.

Specific Examples

Thus far, this article has argued the need for commissioning, the need to *InVEST* wisely and set *SMART* acceptance criteria, and use enhanced commissioning documentation in the qualification effort. The remainder of the article will cover examples of typical commissioning considerations and approaches for GMP technology and GMP utility systems. Obviously, any application could differ, requiring more or less of the listed considerations.

Technology systems include computer/control systems, packaging/fill, and process/manufacturing. Typical cGMP

direct impact utilities could include HVAC, purified (or WFI) water, compressed air, and others (site/product specific). As before, prime potential candidates for enhanced elements are marked with (E). URS/FRS (or acceptance criteria) elements of commissioning verification are indicated, as well as possible commissioning vehicles, i.e., documents. Given the complexity of the various systems or with some combinations of systems, overall commissioning plans also should be considered where needed.

Computer/Controls

- URS/FRS elements or acceptance criteria commissioning verification
  - hardware/software verification and testing (E)
  - security (E)
  - Part 11 issues (E)
  - functionality/challenge (E)
  - alarms (E)
  - trends (E)
  - data verification and integrity (E)
  - human interface/graphics (E)
  - backup (E)
  - input/output verification (E)
- include verification of items being controlled - somewhere (E)
- commissioning vehicle: most commissioning activities (inspections/tests) can be captured in FAT/SAT (E)

Packaging/Fill

- URS/FRS elements or acceptance criteria commissioning verification
  - verify specified equipment installed (E)
  - utility connections (E)
  - instrumentation/calibration (E)
  - controls interface (E)
  - proper installation/alignment (E)
  - materials of fabrication (E)
  - safeties/ergonomics
  - additional for sterile (E)
  - run product
    - ~ line speeds (E)
    - ~ labeling (E)
    - ~ tolerances (E)
    - ~ proper product encapsulation (E)
    - ~ finish form acceptance criteria (E)
    - ~ cartoning
- commissioning vehicle
  - most commissioning activities (inspections/tests) may be captured in FAT/SAT (E)
  - supplement with commissioning test plans (E)
  - great opportunity for qualification synergy (E)

Process/Manufacturing

- URS/FRS elements or acceptance criteria commissioning verification
  - verify specified equipment installed (E)
  - utility connections (E)
  - proper installation/alignment (E)
  - materials of fabrication, passivation (E)
  - operating parameters (flow rates, mixing, heating, cooling, vacuum, reactions) (E)
  - adjustments, balancing, tests (pressure, etc.) (E)
  - instrumentation/calibration (E)
  - safeties/ergonomics
  - acceptable product (E)
- commissioning vehicle: commissioning plan, commissioning test plans, and FAT/SAT on individual major equipment when needed. If project essentially consists of a single equipment, FAT/SAT could satisfy most of (if not all) the commissioning test/inspection activities. (E)

HVAC

- BOD/URS/FRS elements or acceptance criteria commissioning verification
  - temperature (E)
  - relative humidity (E)
  - particle counts (E)
  - differential pressure (E)
  - air change rate (E)
  - laminar flow issues (E)
  - room classifications (E)
- commissioning vehicles
  - pre-commissioning activities (FAT/SAT): Airhandler (AHU) and Building Management - System (BMS) (E)
  - major equipment factory start-up (setting-to-work, etc.) (E)
  - commissioning test plan (E)
    - ~ sequence of operation challenge (E)
    - ~ standard tests and inspections (such as IO verification, calibrations, etc.) (E)
    - ~ test and balance (E)
    - ~ HEPA filter certifications (E)
    - ~ trends (E)
    - ~ viable/non-viable counts (E)
    - ~ inspection activities (E)

Purified Water

- URS/FRS elements or acceptance criteria commissioning verification
  - TOCs (E)
  - conductivity (E)
  - production rates (E)
  - micro (E)
  - other (E)
- commissioning vehicles
  - FAT/SAT of equipment (E)
  - commissioning test plan
    - ~ challenge installed system to meet acceptance criteria, alarms, safeties, automatic operation, etc. (E)
    - ~ SCADA/PLC checkout (E)
    - ~ trends (E)
    - ~ inspection activities (E)

Compressed Air

- BOD/URS/FRS elements or acceptance criteria commissioning verification
  - viable and non-viable particle counts (E)
  - moisture (dew point) (E)
  - flow rate/Pressure (E)
  - oil free? (E)
- commissioning vehicles
  - pre-commissioning: SATs of major equipment (E)
  - commissioning test plan (E)
    - ~ challenge installed system to meet acceptance criteria, alarms, safeties, automatic operation, etc.
    - ~ trends
    - ~ inspection activities

Summary

Commissioning documentation and qualification are symbiotic when properly applied. Qualification helps define what is important for commissioning to emphasize, while commissioning minimizes the validation effort and supports its success. Remember to "*InVEST*" wisely (integrate commissioning with qualification, verify, ensure qualification success, sensible, traceable/document it), and set *SMART* acceptance criteria in the beginning (sensible, maintainable, accurate, range, traceable). To get more information, see various trade organizations (ASHRAE, etc.). Tried and tested GEP approaches and documents are available, and translate easily into documented GEP commissioning and enhanced commissioning. Of course, ISPE has many publications available, including the "Commissioning and Qualification" Baseline® Guide. But mostly, learn by doing.

References

1. FDA Guidelines on General Process Validation, May 1987.
2. ISPE Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities - Volume 5: Commissioning and Qualification, Glossary.
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This article explores the potential impact of PAT, HACCP, and Six Sigma on the Life Sciences Industry.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

PAT, HACCP, and Six Sigma - Making Sense of it All

by George R. Johnson

Introduction

The FDA, pharmaceutical and life sciences industry have recently focused on a framework known as Process Analytical Technology (PAT) with the FDA's publication of the "Guidance for Industry, PAT – A framework for Innovative Pharmaceutical Manufacturing and Quality Assurance." This guidance is part of the FDA's GMPs for the 21st Century initiative. PAT focuses specifically on the growing need to "employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g. novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment)." Primarily due to significant consumer risks inherent in rapid changes and the associated innovation, the FDA and the life sciences industry have been hesitant to implement new technologies and approaches until they have been accepted as a standard practice in the industry. This "chicken and the egg" cycle imposes restrictions that have impeded the implementation of technology or process improvements in the past, even when these new technologies and improvements offer significant promise.

In the current business environment, the synergy of Hazard Analysis and Critical Control Point (HACCP) and Six Sigma with a PAT strategy offers an opportunity to mitigate risk while implementing improvements to a process. This article will explore the potential impact of these three methodologies on the life sciences industry as well as their synergistic ability to realize the promise of PAT while minimizing potential risks to the customer.

What is HACCP?

In the late 1950s, the National Aeronautics and Space Administration (NASA) recognized that special foods would need to be developed for space travel. During this effort, one criterion that was identified was the need to ensure that the food products were absolutely safe to minimize the potentially devastating impact on future astronauts. At that time, food quality and safety were assured primarily through inspection after the fact. NASA was not comfortable that this strategy provided the appropriate level of safety and asked the primary vendor (Pillsbury Company) to design a system for assuring food safety using a process control focus. As a result of this initiative, Pillsbury developed the original Hazard Analysis and Critical Control Point (HACCP) system.

In order to implement a HACCP system, the following five preliminary tasks need to be completed:

1. Identify and assemble the HACCP Team - the team membership should include representatives from the manufacturing process as well as the technical staff. This step also requires that the team (and other appropriate people) receive training from an accredited HACCP course provider.

2. Describe the product and its distribution - this includes the common name of the product, processing methods, and distribution requirements (shelf life, heat, humidity etc).

3. Describe the intended use and consumers of the products - this includes the expected application/dosage as well as consideration

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for the likely end user of the product. Identification should be made of any potential end user groups that may have unique risk factors that preclude the safe use of the product.

4. Develop a flow diagram that describes the process - the flow diagram should detail each process step under control of the company (receiving to shipping) as well as who/what group has the primary responsibility for each step.

5. Verify the accuracy of the flow diagram - this includes a physical "walk through."

Once the preliminary tasks have been completed, the following seven basic HACCP system components can be implemented:

1. Analyze hazards - potential hazards and potential measures to control those hazards are identified. Note that a clear distinction should be made between those considerations that may be quality related as opposed to those concerns that are hazards (life or health threatening).

2. Identify Critical Control Points (CCP) - these are points in a product's production process at which a potential hazard can be controlled or eliminated. If multiple control points have been implemented that are associated with the control or elimination of a specific hazard, the final assurance point in the process flow becomes the Critical Control Point for that hazard.

3. Establish preventative measures with critical limits for each CCP - critical limits can be either extreme limits (temperature no greater than 140°F) or max/min (5 +/- 1%).

4. Establish procedures to monitor the preventative measures at each CCP.

5. Establish corrective action to be taken when monitoring shows that a CCP critical limit has not been met.

6. Establish procedures to verify that the system is working properly - this often is an oversight or audit program as well as measurement systems analysis/validation.

7. Establish effective record keeping documenting the HACCP system - this would include records of hazards and control methods, the monitoring of CCP measures, and action taken to correct potential problems.

An application example for a CCP could be in the management of raw materials. Material contamination by microbiological, chemical, or physical hazards as well as the associated purity could result in significant risks to the consumer. The primary questions here are:

1. Is there a significant hazard that could be associated with the raw material?

2. Will this hazard be processed out during the manufacture of the product?

3. Is there a cross-contamination risk to the facility or to other products?

Depending on the answers to the questions above, the manner in which the material is certified, received, handled, or stored might be CCPs. The presence of these CCPs as well as the capabilities required by the appropriate prerequisite program (cGMP, etc.) protect the process from significant risks associated with vendor management and material sourcing concerns, while allowing a significant degree of flexibility.

What is Six Sigma?

Six Sigma (a federally registered trademark), is a methodology that was originally developed by Motorola during the early 1980s to drive improvement throughout their various operations. While its origins had a heavy manufacturing focus, Six Sigma implementation has since spread to a broadly diverse number of industries and has become known throughout the world as a powerful framework that can be used to optimize business processes and link the results to the bottom line. Any processes that require improvement to a highly efficient state of near-zero defects have proven to be successful Six Sigma project opportunities.

Six Sigma achieves this amazing result by the methodical identification and control of process factors known as Key Process Input Variables or KPIVs. In the terminology of Six Sigma, this is often referred to as "Y is a function of x" or Y=f(x) where Y is the Key Process Output Variable(s) or KPIV and the x factors are the KPIVs. Y=f(x) focuses on the achievement of a thorough understanding of and subsequent control of the process rather than monitoring for defects after the fact.

The most common framework for Six Sigma project activities is known as Define, Measure, Analyze, Improve, and Control (DMAIC). Each one of these steps has a clear purpose and data driven focus which synergistically unleashes the power of Six Sigma. These are simply:

Define - select process areas that are critical to the business and need to be improved.

Measure - identify process KPOVs and target improvement values. Conduct a Measurement Systems Analysis to ensure that you have an effective means to measure the KPOVs.

Analyze - map the value stream of the process and identify KPIVs.

Improve - determine the KPIV values that optimize the associated KPOVs.

Control - determine and implement the most effective means to control the KPIVs.

The power of this framework follows a very logical progression and activity flow for quality improvement activities. The Define stage ensures that the use of Six Sigma trained resources are applied to an area of the business that will yield the maximum benefit and ensures that the project is well scoped.

The Measure stage ensures that we have a metric that will be a good measure of the improvement activity and that the measurement system is valid. The purpose of the Analysis stage is to understand what issues drive the improvement opportunity. Without this understanding and the associated validation activities, improvement activities become little more than 'best guess' implementations which potentially have no improvement impact. The Improve stage uses what was learned during the analysis stage to design process improvements that have a high probability of success. The purpose of the last stage (Control) is to lock the improvements in place. Each stage neatly builds on the foundation laid by the earlier work.

Six Sigma uses a number of well defined roles and responsibilities within its framework. They are:

Master Black Belt - mentor and trainer of Black Belts and often associated with working on strategic cross functional improvement opportunities.

Black Belt - mentor and trainer of Green Belts. The Black Belt is often associated with major business improvement opportunities.

Green Belt - a part time improvement resource who often works projects to improve areas within their daily scope of work. The Green Belt is the primary driver of the shift to a Six Sigma culture.

Champion - a senior business leader who supports a Six Sigma project effort. Champions review activities and ensure appropriate resource availability as needed to ensure the project is a success.

Six Sigma easily lends itself to any number of "ad hoc" potential improvement issues within the operation. Application and focus differ widely, determined predominately by the needs of an individual business. Any area within the operation that is not optimal or is critical for long term success is a good potential Six Sigma project opportunity.

Pieces of the Puzzle - PAT, HACCP, and Six Sigma

PAT, HACCP, and Six Sigma have a powerful synergy that holds great promise for those companies that specialize in the life sciences – pharmaceuticals, medical devices, and nutraceuticals. The following discussion will demonstrate how the various pieces can be structured to achieve this promise.

PAT offers the vision that cutting edge technology, tools, and approaches as well as a process based focus is the path to high operational efficiency and high quality products. While long on vision, PAT as a stand alone lacks the detail necessary to show how this can be achieved in a dynamic industry where frequent change often raises the specter of potential significant risk to the customer.

HACCP offers a proven risk mitigation strategy and approach that is specifically focused on ensuring that the customer is protected from any hazards created by variability or changes in the process or incoming materials. It focuses on the few CCPs necessary to achieve this objective. Its weakness as a stand alone is its heavy reliance on research of known hazards (biological, chemical, or physical) during the hazard analysis. This presents a significant potential problem in those processes which are "one of a kind" in the risks presented (formulation and/or unique customer application).

Six Sigma offers a detailed and time proven structure for improvement which has been demonstrated to be applicable to a broad range of industries and applications. Its weakness is that while Six Sigma has a very capable tool set and structure, it needs to be clearly linked to the needs of the business to be effective. Without this focus, program benefits tend to be local in nature and as such miss much of the opportunity that the program offers.

Making Sense of it All

So how does this all work? First, it's worth noting that all three structures (PAT, HACCP, and Six Sigma) start with an assumption that the fundamental processes are consistent with the application of current Good Manufacturing Practices (cGMPs). This foundation is critical to ensuring that the fundamental safeguards and associated documentation are in place to demonstrate that production practices are as free from error as possible and produce a product that is effective, high quality, and absolutely safe for the consumer. Once this foundation has been established, the process is assumed to be well managed and stable. At some point, changes in technol-

ogy or capability will create pressure to change the original process. It is at this point that all three structures (PAT, HACCP, and Six Sigma) can be utilized to minimize the adverse impact of the change to the business while assuring an absolutely safe product for the consumer.

PAT takes a philosophical center stage during this effort. All changes must be done with a full understanding of the risks and potential factor interactions introduced by the proposed changes. Six Sigma helps during this effort through its focus on real time control of output characteristics (KPOVs) by real time (ideally) control of process and input characteristics (KPIVs). Risk is significantly mitigated by the establishment and control of HACCP Critical Control Points in the process. These control points act as stage gates, ensuring that any process changes that occur prior to the CCP do not impact the product in a way that would create a hazard if passed on to the consumer.

Utilizing all three structures has the potential of enabling process capability updates to be implemented relatively quickly and without significant risk to the customer.

None of these methodologies have been recommended nor adopted by the FDA as of this date. These methodologies can adhere to the PAT guidelines when instituted using the proper metrics, measurements, and critical analysis.

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This article was adapted from a presentation at the 2003 ISPE UK Affiliate Annual Seminar, Manchester. It demonstrates how the pharmaceutical industry is capable of improved manufacturing performance.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

From Good Manufacturing Practice to Good Manufacturing Performance

by Professor Roger S. Benson, FREng and Jim D.J. McCabe

Introduction

The pharmaceutical industry has a continuous record of growth, innovation, and profitability. Operations are controlled through the principles of Good Manufacturing Practice (GMP) and regulated by the US Food and Drug Administration (FDA) and national regulatory bodies such as the Medicines and Healthcare Regulatory Authority (MHRA) in the UK.

However, the industry is faced with the following pressure to change:[1]

- stock market demanding continuation of historic growth and profitability
- reduced numbers of new chemical entities compared to increasing research and development costs
- pressures from healthcare providers to reduce the cost of life-saving medicines
- drive to increase access to life-saving medicines in developing countries
- growth of generic competition

One factor arising from these pressures is a requirement to improve manufacturing performance. The FDA in particular recognizes these pressures and has publicly stated its willingness to support the challenge of improving competitiveness in the pharmaceutical industry.[2] This combination of competitive pressure and supportive regulatory environment creates the necessary conditions for change to take place. Is the pharmaceutical industry ready to step up to the plate?

This article will argue that in many ways it is. Good manufacturing performance is sustained by good manufacturing practices. Companies that meet GMP requirements have an excellent foundation to develop and adopt innovative solutions to maintain product quality and improve manufacturing performance.

Benchmarking

Benchmarking is a process where your performance is judged against the best in the world. That is not to say that your factory or even the pharmaceutical industry has to be the best in the world, but it is important to know what the best is and to have made a conscious decision to operate at a different level of performance. In many ways, good manufacturing performance is like the decathlon in the Olympics. You don't have to win every event to win the decathlon, but you need to win some events and be above average in the other events.

> "Benchmarking is the process of continuously measuring and comparing one's business performance against comparable

Table A. Typical benchmark data.

Measure	Pharmaceutical Industry	A Winning Pharmaceutical Factory	A World Class Factory
Stock turn	3 to 5	14	50
OTIF	60% to 80%	97.4%	99.6%
RFT	85% to 95%	96.0%	99.4%
CpK	1 to 2	3.5	3.2
OEE	30.0%	74.0%	92.0%
Cycle time (hrs)	720	48	8
Safety/100,000 hrs	0.100	0.050	0.001

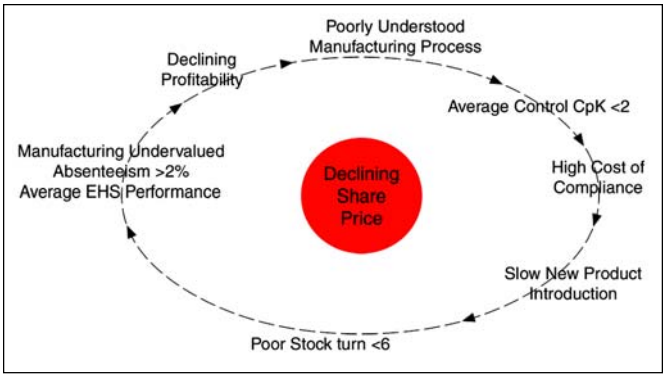

Figure 1. Destructive cycle.

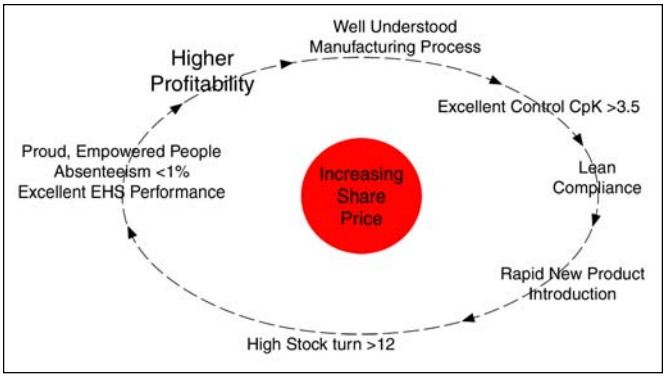

Figure 2. Virtuous cycle.

processes in leading organizations to obtain information that will help the organization identify and implement improvements."[3]

It is important to note that benchmarking must be a structured process to ensure consistency of definitions and validity of benchmarks. The process must look beyond the performance measures. It is not sufficient to know that a world-class stock turn is 50 – the process must identify what world-class companies do differently to achieve that level of performance. An external focus is essential to learn from other industries. Why can the semiconductor industry achieve Overall Equipment Effectiveness (OEE) measures in excess of 85% when the pharmaceutical industry typically operates below 50% OEE? It is not enough to benchmark within your own industry – learn from the best, whatever their industry. Finally, benchmarking is not a competition. Use it to find out where to improve and how to improve. How far and how fast you can improve your own performance is much more important than your overall position.

This is illustrated by some real benchmarks from companies that are FDA regulated. Consider the following definitions:

Stockturn - This is the total turnover of the site at manufacturing price divided by all the stock on the site on the same basis. The stock includes finished goods, work in progress, and purchased raw materials.

OTIF - On Time In Full delivery. This is the percentage of orders that are satisfied On Time In Full with zero defects. Note: if there is one defect in an order, the OTIF is zero percent.

RFT - Right First Time. This is a percentage of the products at the point of manufacture that are delivered right first time with no defects. Any recycling, blending, rework of documentation, or laboratory testing or other adjustments are excluded from the Right First Time figure.

CPK - Is a statistical process control measure of the variability of the product. A six-sigma figure corresponds to only four defects per million products, while a two-sigma figure corresponds to 308,000 defects per million products. It is measured on a logarithmic scale.

OEE - Overall Equipment Effectiveness. This measures how effectively the manufacturing equipment is used. It is a product of the product rate multiplied by the quality rate multiplied by the plant availability. A figure of 100% implies that the plant is running flat out every hour of the day making perfect product. A figure of 10% implies that the plant could achieve ten times the output that it currently achieves.

Cycle Time Hours - This is the total time from commencing manufacture to delivering products to the customer which in many cases is the factory warehouse.

Safety per 100,000 Hours - This is the number of reportable accidents, greater or equal to three days absence per hundred thousand working hours.

Table A presents the figures for three typical operations. This first column is for figures for the pharmaceutical industry in the UK that have been established and developed over several years from benchmarking discussions with a wide range of manufacturers.[4]

The second column is an award-winning pharmaceutical manufacturer that manufactures over the counter drugs, prescription drugs, and injectables. Last year, it was a winner in the UK Awards for Manufacturing.

The world-class plant is in fact a food plant supplying supermarkets and grocery stores. It may be argued that food is different than pharmaceuticals. However, food manufacture also is regulated under the principles of GMP. Consumer protection and product safety is no less a concern for a food manufacturer than it is for a pharmaceutical company. You will note from the figures that there is a significant difference.

Consider, for example, the stockturn where the pharmaceutical industry average is between three and five, but already there is a pharmaceutical manufacturer achieving 14. World-class is 50. If all of the world pharmaceutical industry (estimated annual turnover $290 billion) was to move from its current average to that of the award-winning factory, the cash released would be in the order of **$76 billion**

and if it were to move to the world class condition, it would release a further **$15 billion!** While these are one-off releases of cash, they are extremely significant, and would have dramatic effects on both the short-term and long-term profitability of the companies.

Stock turn is a powerful measure of manufacturing performance. High stocks allow operations a buffer to insulate them against poor performance. Only excellence in manufacturing will deliver a high stock turn. It is not something the accountants can adjust.

Comparison of the OEE measures would suggest that between the industry average of 30% of the equipment being used to its full potential and a world class figure of 92%, the **industry could increase the output of the present assets by more than a factor of three with minimum capital investment**.

It may be argued that since the capital has been invested, this does not represent a saving, but there is either the potential to rationalize the asset base or to use already invested capital to rapidly introduce new products to the market.

Safety is an excellent measure of manufacturing performance. Experience from other industries indicates there is a direct correlation between excellent manufacturing and excellence in safety.[3]

The other measures speak for themselves. Given the nature of the industry, one would expect a high OTIF, the Right First Time to be good, and the CPK to be running in the area of 4 - 6, not in the area of 2 - 3. Similarly, for many formulation and packaging operations, one could expect the cycle time to be measured in less than 24 hours rather than several days.

Creating Good Manufacturing Performance - the Virtuous Cycle

The evidence would suggest that in terms of manufacturing, sections of the pharmaceutical industry are in what we would call a destructive cycle - *Figure 1.*

Many pharmaceutical processes are complex and incompletely understood. Processing parameter ranges are often established empirically based on what has worked in the laboratory and confirmed during process validation. It is difficult to predict how the process will respond to variability in raw materials or control variables. This lack of predictive control can result in low CpK. Out of Specification (OOS) investigations may be triggered by deviations outside the allowed parameter ranges when such deviations have no impact on product quality, increasing the cost of compliance.

Without good process understanding, new product introductions can be delayed due to incomplete technology transfer between development and manufacturing. If the process is understood, resources can be directed at the critical control points, those parameters that have a demonstrated direct impact on product quality, in order to introduce a more robust and capable manufacturing process.

If the manufacturing process cannot be relied upon to produce product when it is needed, high levels of safety stocks are required to meet customer commitments. This results in low stock turns.

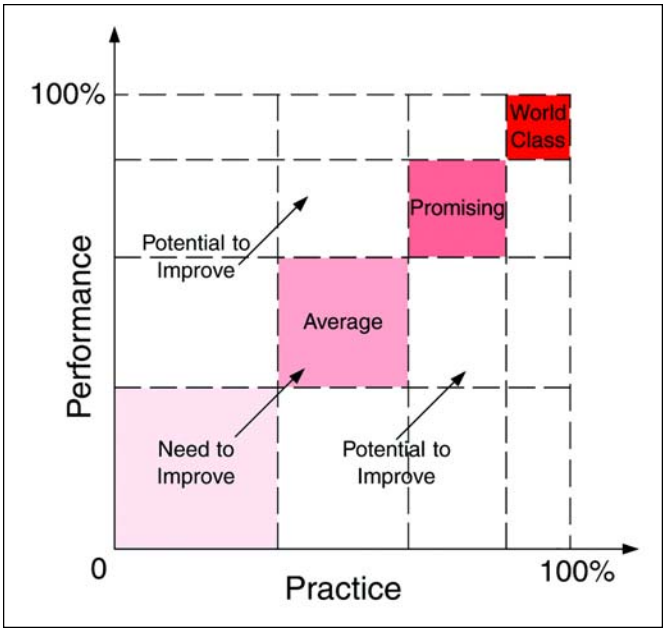

Figure 3. Practices drive performance.

Such facilities are often characterized by high levels of firefighting with manufacturing seen as a problem rather than a driver for competitive advantage. Absenteeism (measured by percentage working days lost through absenteeism) or high levels of staff turnover are indicators of low morale and high levels of workplace stress. A culture of firefighting and pressure to meet production targets is often accompanied by reductions in EHS performance.

Few companies will find themselves locked fully into the destructive cycle, but certain of these observations may be present to some extent in many pharmaceutical operations.

The priority is to move to the virtuous cycle - *Figure 2*. Note: this takes time and continuous focus over a number of years.

In the virtuous cycle, good manufacturing performance delivers higher profitability from lower stocks with quicker speed to market and equipment which is more highly used.

Practices Drive Performance

Good manufacturing performance is driven by good manufacturing practices - *Figure 3.*

Experience from benchmarking both the practices and the performance of process plants worldwide demonstrates that a direct correlation between the two has always been demonstrated.[3,5]

Sigma	ppm Defects	Yield	Cost of Quality
2σ	308,537	69.2%	25 - 35%
3σ	66,807	93.3%	20 - 25%
4σ	6,210	99.4%	12 - 18%
5σ	233	99.98%	4 - 8%
6σ	3.4	99.99966%	1 - 3%

Table B. Defects and sigma level.

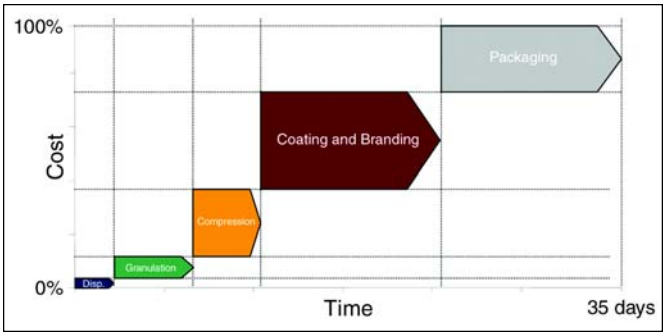

Figure 4. Cost and cycle time from dispensing to finishing.

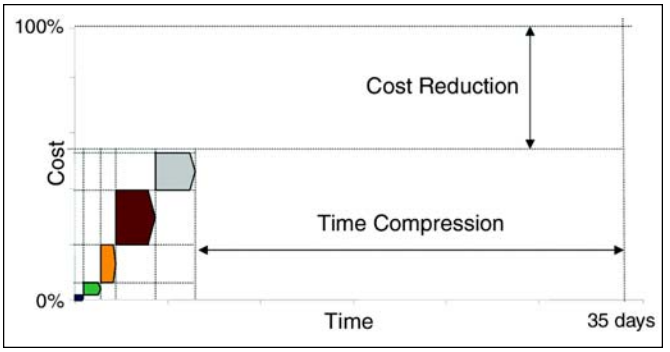

Figure 5. Effects of time compression.

The good news in the pharmaceutical industry is that it does have good manufacturing practices. These are well documented, with well-trained employees in a good environment. However, the requirements of GMP are often used as an argument against change because of a perception that it is costly and time consuming, particularly the need for revalidation. A similar argument applies for safety in the chemical industry. Again, in some plants, the argument has been used that they cannot change the manufacturing performance because it would have an impact on safety. Time and again this has been proved not to be the case, and by consciously managing the change process, within the environments of good manufacturing practice and safety, the performance has been improved quite dramatically.

In looking at what the leaders are doing, it is possible to identify a number of factors that come together that drive the process. These are summarized below:

What practices are the leaders improving?

1. Focus on manufacturing/supply chain
2. Targeting process to be "Really Right First Time"
3. Continuously aiming to increase OEE
4. Automation and on-line quality control
5. Reducing non value-added activities
6. Measurement and display for productivity
7. Reducing stock levels and never replacing
8. Focus on continuously improving quality

Really Right First Time

Really Right First Time focuses on quality. Quality is a measure of the percentage of the products that are perfect first time. You will hear in some industries the drive for six-sigma. The well-known examples are GE and Motorola though increasingly the approach (sometimes combined with lean manufacturing in an approach known as lean sigma) is becoming much more common in the pharmaceutical industry. Table B summarizes the features of sigma in terms of defects.[5] Notice that it is a logarithmic scale and that if a

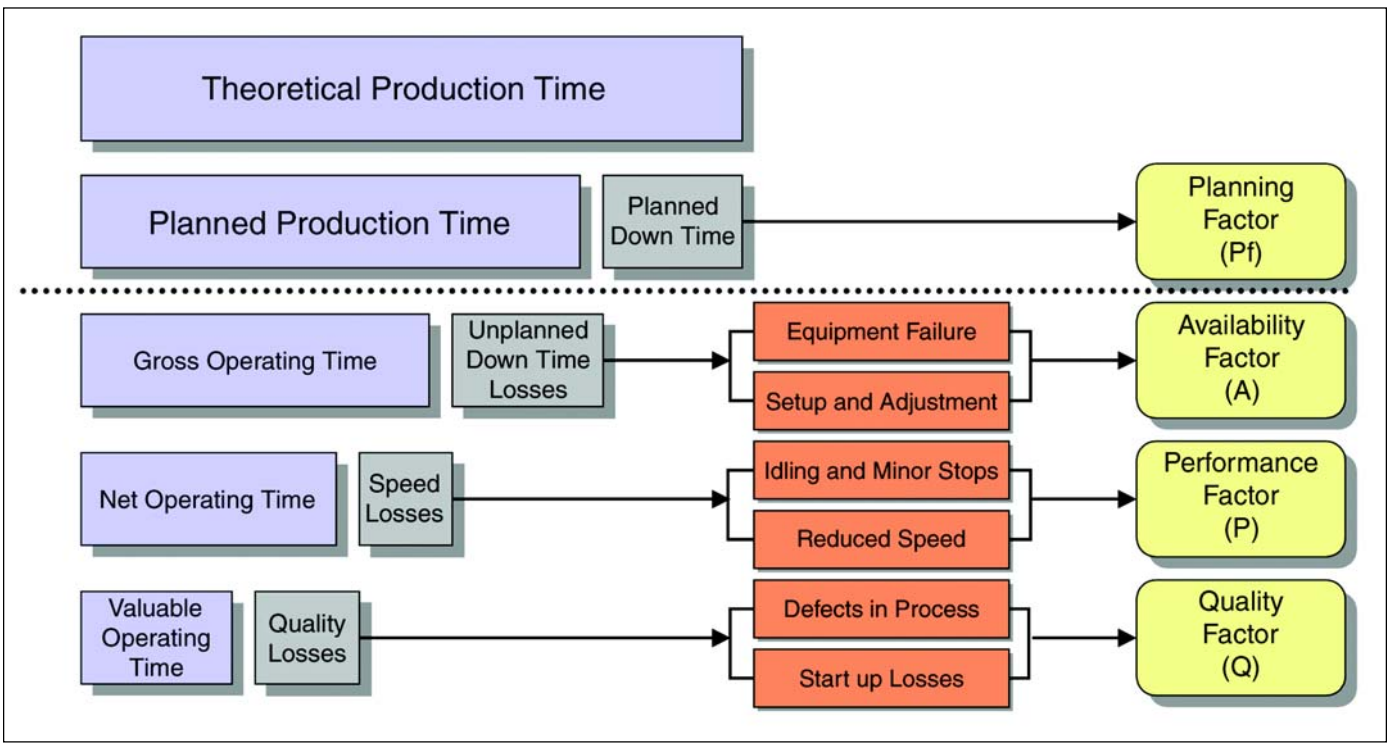

Figure 6. Elements of Overall Equipment Effectiveness (OEE).

company is operating in the 2-3 sigma range then its defects are in the order of 200,000 per million. Put that way it sounds, and is, very large. The means of delivering improved quality are measurement, process understanding and control, removal of root causes, and a period of continuous improvement.

Reduce Cycle Time

The cycle time is the time from starting manufacture to delivery (often to the warehouse). The whole process is one of compression as illustrated in Figures 4 and 5.[6]

The very act of measuring the cycle time highlights some very "quick" wins which can make a significant reduction in time without costing a great deal of money. Often the laboratory itself is one of the major delays in the whole of the cycle time and is one of the drivers in many industries for the move to Process Analytic Technology (PAT), and on line analysis.

In the example below, it is seen that focusing on value adding activities, i.e., time when the product is actually being worked on rather than waiting, e.g., for documentation, QC results, can result in significant time compression and lower manufacturing costs. Figure 4 describes a process with a cycle time of 35 days and an actual processing time of three days. It is not uncommon for actual processing time, i.e., excluding delays, QC testing, transport times, documentation, to be less than 10% of the total.[8] Figure 5 describes the case where cycle time reduction techniques (on-line analysis, flow path analysis)[9] have been used to increase the time that the product is being processed from 10% of the total cycle time to 50%. The total cycle time in this case is now six days.

Overall Equipment Effectiveness (OEE)

The third area is the OEE. Again, Figure 6 illustrates well how productive time is easily lost in the manufacturing process and it is not unusual for only 10% of the available time being used for added value activities. Of the 168 hours available in a 24/7 operation, there may be planned downtime, unpredicted loss of production time, production delays and poor planning, low speed running, scrap and rework all contributing to low OEE - *Figure 6.*

The route to improving the OEE is through loss accounting where one first measures the losses in time as they occur. Displaying these in order of priority and attacking them one at a time results in significant benefits. The impacts can be spectacular and it is not uncommon to improve the OEE by 10% per year, year-on-year.

Case History

An international biologicals supplier needed to double vial filling production capacity using existing equipment without significant capital investment. In addition to poor line utilization, product wastage was high as a result of long cycle times. The root causes of inefficiency were not well understood and were the cause of much argument.

An OEE improvement program was established and production losses were monitored with a loss accounting system to track all machine losses (availability, speed, quality). Real machine data was collected and analyzed to provide a non-subjective picture of causes of downtime. Making this data available to the production operators increased their productivity improvement awareness.

A reliability improvement team was established and met regularly to analyze the OEE data and plan and prioritize improvement actions. Real data meant that this team was able to focus efforts on areas that would have the greatest impact. The improvement team applied continuous improvement techniques: Root Cause Analysis, Cause and Effect diagrams (CEDAC), and Single Minute Exchange of Die (SMED) to these areas to identify and eliminate the root causes of the production problems.

Within two years average production speed had more than doubled and mean time between line breakdowns had increased by a factor of ten.

The Way Forward

The important message about delivering good manufacturing performance is that all the tools and techniques are well known, available, and successfully operating in many other industries and in general the pharmaceutical industry will be able to **"pinch with pride"** the ideas, tools, and techniques, and successfully implement them in their process. Some of the available technologies and tools are summarized below:

- empowered operations staff skilled in continuous improvement methodologies (including six sigma, Total Productive Maintenance [TPM], lean manufacturing, Reliability Centred Maintenance [RCM])
- loss accounting and loss management
- improved process understanding
- continuous or one-pot processing
- design for manufacture - stronger links between manufacturing and development to ensure that newly introduced processes are robust and capable
- Process Analytic Technology (PAT) - raw material and product characterization for processing predictability and in-process control
- activity based costing to identify and focus on value adding activities
- predictive, model-based process control
- agile automation of each processing step
- information technology - Integrated information collection, management, and interpretation, and its use in controlling and managing the process

- enterprise Manufacturing Execution System with Electronic Batch Record (EBR) capability

It is beyond the scope of this article to describe these tools in detail. The author welcomes any correspondence from readers who desire a more in-depth review of available technologies. It is sufficient to note that the technology is in place; continuous improvement, cycle time reduction, automation, on-line analysis and control are established techniques in other industries. The regulatory environment is supportive of improving competitiveness in the pharmaceutical industry. So why, we may ask, does pharmaceutical production underperform against almost all established manufacturing performance benchmarks?

It is a question of necessity and desire. There is no doubt that if one has to look for examples of good manufacturing performance, the best place to look is in manufacturers who have a very demanding customer. The automotive industry has been improving for 30 years and still manages to improve productivity by 3% per year, year on year.[7] For the pharmaceutical industry, those demanding customers are here today, in the shape of public and private healthcare providers, empowered consumers and retailers, and shareholders grown used to high returns on their healthcare stocks. Manufacturing will play its part in meeting those customer demands, delivering flexibly and cost-effectively in support of business goals.

Benchmarking against other industries in order to learn and improve will be a key element of this transition. It does not follow that pharmaceutical manufacturing has to be world class, but the opportunity to move from the position today toward world class is enormous and the impacts will be significant. Some pharmaceutical manufacturers are already well underway on this journey – can you afford not to join them?

Conclusions

Good Manufacturing Practice is the necessary, but not sufficient, condition for good manufacturing performance. Delivering good manufacturing performance is a journey, which starts with measurement, and recognition that the opportunity exists. It is a process of continuous improvement; the tools and techniques exist already and can be adopted with speed. The ensuing transition from the destructive to the virtuous manufacturing cycle will have a dramatic effect on the success individual pharmaceutical companies.

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This article presents cleanroom classifications as defined in ISO 14644 and FED STD 209E and their application for designing aseptic processing pharmaceutical/biotechnology facilities as defined in both USA cGMPs and European Community GMPs.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

USA/EC/ISO Regulatory Considerations for Designing Aseptic Processing Facilities

by Manuel A. del Valle, PE

Introduction

There is a large diversity of medical products and devices manufactured in pharmaceutical/biopharmaceutical facilities. Some of these include topicals (applied on skin or eyes), oral (taken by mouth, swallowed), and parenterals (intravenous or intramuscular drugs). The means by which the product is administered greatly affects how it is manufactured and sterilized (if required). When a medicine is swallowed, the human body has some natural defense mechanisms to help reduce or eliminate living organisms that may be harmful. Example of these defense mechanisms are the saliva in the mouth and acid in the stomach. Parenteral drugs by-pass some of these defense mechanisms and therefore, require sterilization. The purpose of sterilization is to reduce the number of live organisms in a parenteral product to an acceptable (aseptic) level rather than to a sterile (no live organism present at all). Sterility is practically impossible to obtain for parenteral products because they are typically affected by heat or radiation. Parenteral drugs therefore need to be manufactured under stricter and cleaner conditions. This article discusses where some of these regulations and guidelines are found in the USA, the European Community (EC), and the international standards for the design of aseptic processing facilities such as biopharmaceutical facilities. Biopharmaceutical facilities are those in which biological molecules that are destined to become diagnostics and therapeutics (among other products) are prepared and modified. Updates and drafts to these guides also will be discussed.

Clean Space Classifications

Clean space classifications are defined in terms of maximum number of particles per unit volume of air. Typical particle sizes used are 0.1 micron through 5 microns. A micron is equivalent to 1 millionth of a meter or 1/25000 of an inch.

In the USA, definitions for cleanroom classes used can be found in Federal Standard #209.[1] The latest revision of this standard was Fed-Std-209E dated 11 September 1992. Table A (based on Fed. Std. 209E Table 1) "Airborne Particulate Cleanliness Classes" lists in both metric and English units, the class numbers typically used in Pharmaceutical/Biopharmaceutical Facilities. These are classes 100 through 100,000 (class M3.5 through M6.5 in metric units). USA Pharmaceutical/Biopharmaceutical industry utilizes Class 100 through 100,000 clean areas based on 0.5 micron or

Table A. Excerpts from Fed Std. 209E Table 1 – Airborne Particulate Cleanliness Classes.

Class Name		Class Limits			
		0.5 Micron		5 Micron	
		Volume Units		Volume Units	
S1	English	(M^3)	(ft^3)	(M^3)	(ft^3)
M 3.5	100	3,530	100	-	-
M 4.5	1,000	35,300	1,000	247	7.00
M 5.5	10,000	353,000	10,000	2,470	7.00
M 6.5	100,000	3,530,000	100,000	24,700	700

ISO 14644 Part No.	Title	Status
14644-1	Classification of Air Cleanliness	Published
14644-2	Specification for Testing & Monitoring to Prove Continued Compliance with ISO 14644-1	Published
14644-3	Metrology & Test Methods	
14644-4	Design, Construction and Start-Up	Published
14644-5	Cleanroom Operations	
14644-6	Terms, Definitions & Units	
14644-7	Separative Enclosures (Clean Air Hoods, Glove Boxes, Isolators and Mini-Environments)	
14644-8	Molecular Contamination	

Table B. List of ISO 14644 parts.

larger size particles per cubic foot and for "in-operation" conditions. For example, for a space to meet a classification of Class 100, it can contain no more than 100 particles per cubic foot (3,500 particles per m^3).

On 29 November 2001, the GSA-FSS issued a notice of cancellation of Fed. Std. 209E and stated it had been superseded by the International Organization for Standardization (ISO) standard "Cleanrooms, and Associated Controlled Environments," ISO 14644-1 "Classification of Air Cleanliness," and ISO 14644-2 "Specifications for Testing and Monitoring to Prove continuous compliance with ISO 14644-1."[2]

ISO 14644 consists of eight parts - *Table B.* Of these, parts 1, 2, and 4 are official published standards, the others are in their development and/or review stages. The procedure that has been followed in the European Community is that an ISO Regulation becomes a Standard six months after being officially issued.

ISO 14644-1 "Classification of Air Borne Cleanliness:" defines clean spaces in terms of class numbers from 1 through 9 based on acceptable number of particles per cubic meter. Table C (based on ISO 14644-1, Table 1) tabulates classes typically used in Pharmaceutical/Biopharmaceutical facilities. To define a class, three items must be specified: Class number (1 through. 9), occupancy state (as-built, at rest, or in operation), and particle size (0.1 through 5 micron) including count (number of particles).

Definitions of occupancy states:

ISO Classification Number (N)	Maximum number of particles/CU. Mtr. Equal to or larger for sizes shown below	
	0.5	5 Micron
ISO Class 5	3,520	29
ISO Class 6	35,200	293
ISO Class 7	352,000	2,930
ISO Class 8	3,520,000	29,300
ISO Class 9	35,200,000	293,000

Table C. Excerpts from ISO 14644-1, Table I Airborne Particulate Cleanliness Classes for Cleanroom and Clean Zones.

As-Built: installation is complete with all services connected and functioning, but with no production equipment, materials, or personnel present.

At-Rest: installation is complete with production equipment installed and in operational condition, but not in use and with no personnel present. The ventilation (HVAC) system is in operation to maintain cleanliness and pressurization.

In-Operation: installation is functioning in the specified manner with the specified number of personnel present and the specified production equipment in operation.

It should be noted that the phrase "operating, but with no operating personnel present" should normally be taken to mean that ventilation systems are operating and other equipment is present in an operational condition, but not in use.[3]

An example of an ISO cleanroom classification may be: ISO Class 5; operational state; 0.5 micron particles (3,520 particles/m^3).

USA Regulations/Guidelines Related to Pharmaceutical/Biopharmaceutical Aseptic Processing Facilities

In the USA, all medical products and devices fall under the Food, Drug, and Cosmetic Act. Section 501 of the Act states that a drug, device, diagnostic, or bulk pharmaceutical chemical is considered to be adulterated if it is not manufactured in accordance with current Good Manufacturing Practices (cGMPs). Minimum standards of the cGMPs are found in parts 210, 211, 606 to 680, and 820 of Chapter 1, Title 21 of the Code of Federal Regulations (CFR). Sections that greatly affect HVAC are found in part 211, subpart C-Buildings and Facilities, Sections 211.42 (Design and Construction Features), and 211.46 (Ventilation, Air Filtration, Air Heating and Cooling).

Examining these sections emphasizes the point that these regulations were written in vague terms to allow for engineering to develop creative ways of meeting the GMPs. Examples of the vagueness include terms such as: suitable, to facilitate, to prevent, as appropriate, adequate. One item that is specifically mentioned is the use of High Efficiency Particulate Air (HEPA) filters. Section 211.42, (10) - Aseptic Processing, states under sub-section (iii) "An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar." The author has been asked if HEPAs are required for cleanrooms classified as Class 100,000 in the USA.

Terminal Sterilization vs. Aseptic Processing

To ensure product sterility, the US FDA requires that sterile drug products be terminally sterilized. The FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing"[4] defines terminal sterilization and aseptic processing. Terminal sterilization involves filling and closing product containers under conditions of a high quality environment; the

product, container, and closure are usually of high microbial quality, but not sterile. The product in its final container is then subjected to a sterilization process (usually by means of heat or radiation). Unfortunately, most biopharmaceutical products cannot be terminally sterilized without detriment to the product. The FDA allows an alternative means of sterilization: aseptic processing.

In aseptic processing, the product, container, and closure are subjected to the sterilization process separately and then brought together in the fill line. Some examples of sterilization methods involve using dry heat for glass containers, moist steam for rubber closures, and 0.2 micron filtration for liquid dosage forms.

Guideline on Sterile Drug Products Produced by Aseptic Processing

Complying with the clean space classifications defined in ISO 14644-1 helps minimize the number of foreign particles that end up in medicines during preparation and filling operations. Unfortunately, these classifications do not address live organisms that can reproduce themselves forming a Colony Forming Unit (CFU), which may be harmful to a person or deadly in an extreme situation.

A USA FDA guideline that defines cleanroom requirements and CFU limits in the pharmaceutical industry for a sterile drug product is the FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing" mentioned above. Section III - "Buildings and Facilities" of that guide refers to sections 211.42 and 211.46 of the GMPs (see above) and defines two product exposure areas that are particularly important to drug product quality: critical areas and controlled areas.

Critical Areas are those in which the sterilized dosage forms, containers, and closures are exposed to the environment. Requirements for these areas include:

- Class 100 (maximum of 100 particles size 0.5 micron and larger per cubic foot), when measured not more than one foot away from the worksite, and upstream of the airflow during filling/closing operations.
- Air supplied at the point of use as HEPA filtered laminar flow air (currently referred to as "unidirectional" flow).
- An airflow rate of 90 feet per minute (FPM) ± 20%. This velocity is typically measured 6 to 12 inches below ceiling terminal HEPAs. Since the purpose of this velocity is to sweep away particulate matter from the filling/closing area, this author recommends measuring air velocity at the same location where particle counts are to be measured, that is, no more than a foot away from the work site, and upstream of the airflow during filling/closing operations.
- Maximum of one Colony-Forming Unit (CFU) per 10 cubic feet of air.
- The fill room static air pressure with all doors closed should be as least 0.05 inches water gage (12.5 pascals) positive to adjacent less cleanrooms.

Controlled Areas are defined as those in which unsterilized products, in-process materials, and containers/closures are prepared. Requirements for these areas include:

- Class 100,000 (maximum of 100,000 per particles 0.5 micron and larger per cubic foot) in the vicinity of exposed particles during periods of activity.
- Minimum airflow rate of 20 air changes per hour (ac/hr).
- Maximum of 25 CFU per 10 cubic feet.
- Room static air pressure with all doors closed should be at least 0.05 inches WG positive to adjacent less cleanrooms. When doors are open, outward airflow should be sufficient to minimize ingress of contamination.

Other room classifications such as Class 10,000 are typically used at some controlled areas, especially to meet European Community and International Standards. One question that is frequently asked is what airflow rate should be used for Class 10,000 areas. An airflow rate this author has used for many years with satisfactory results is 60 ac/hr. Some designers have obtained satisfactory results (proven by validation on specific cases) with lower airflow rates. The airflow rate should be sufficient to sweep particulate matter away from exposed product. Therefore, one would use a larger flow rate for rooms where the product is in powder form and exposed to the ambient for a long period of time than for a liquid product which is enclosed in vessels and in piping.

Another topic that is often raised as far as air distribution in clean areas is the location of the HEPA filters and the return/exhaust grilles/registers. A register is a grille with a balancing damper attached. For cleanrooms Class 10,000 and cleaner, the FDA expects ceiling terminal HEPAs and low wall returns in order to reduce drafts and to remove particles at floor level where they are mostly collected or generated. For Class 100,000 areas the FDA still prefers ceiling terminal HEPAs and low wall returns, but accept HEPAs in the Air Handling Units (AHUs) as well as ceiling returns.

This author prefers to use ceiling terminal HEPAs and low wall returns in most Class 100,000 rooms for the following reasons:

- It is a cleaner operation since the HEPA is at the point of use (the ceiling of the room). When HEPAs are located in the AHU or in the supply duct main, any dust in the ductwork (oxidation dust from galvanized ductwork, or dust entering duct when duct access doors are opened) ends up in the room.

	At rest		In operation	
Grade	Maximum permitted number of particles m/^{3} equal to or above			
	0.5μm	5μm	0.5μm	5μm
A	3,500	0	3,500	0
B	3,500	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

Table D. Excerpts from EC GMP Guide, Annex 1 - Table on Airborne Particulate Classification Grades.

- It is easier to upgrade a Class 100,000 room to a cleaner Class (Class 10,000) since the supply air duct is already sized for the gauge (thickness) required by the HEPAs higher static pressure loss, and low wall returns are already in place. Only additional terminal HEPAs and low wall returns are needed. The existing air distribution can be re-used. A Class 10,000 room requires about three times the airflow rate of a Class 100,000 room (about 10.5 cfm/sq. ft. vs 3.5 cfm/sq.ft. for a space with a 9 foot ceiling).

- HEPAs remain cleaner (after in place testing and certification) with terminal HEPAs than HEPAs in AHUs since each terminal HEPA may be challenged (with DOP sample or other aerosol) individually instead of as a group in AHUs. This means that the terminal HEPAs do not have to filter as much DOP since they are exposed to it for a shorter period of time.

An application where ceiling return/exhaust may be recommended is in some areas of washrooms in order to remove water vapor where it is generated. Another application where HEPAs in AHUs and ceiling returns may be practical for Class 100,000 spaces may be perimeter corridors which often surround clean areas, when these corridors require Class 100,000 classification.

European Community Regulations and Guidelines Related to Pharmaceutical/ Biopharmaceutical Aseptic Processing Facilities

In the European Community, cleanroom classification also is based on ISO 14644-1 and ISO 14644-2.

The EC GMP Guideline that defines cleanroom classes and CFU limits for aseptic processing is the "Guide to Good Manufacturing Practice for Medicinal Products," Annex 1 – Manufacture of Sterile Medicinal Products. This guide is found in the Medicines Control Agency (British Equivalent to USA FDA) "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" 2002. This publication also is known as "the Orange Guide" because of the color its cover.[5]

	Recommended limits for microbial contamination (a)			
Grade	Air Sample Cfu/m^3	Settles Plate (dia. 90mm), cfm/4 hours (b)	ContactPlates (dia. 55 mm), cfu/plate	Glove Print 5 fingers, cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Table E. Excerpts from EC GMP Guide, Annex I - Table on Limits for Microbial Contamination.

This guideline defines four cleanroom classifications (Grade A, B, C, D) for two occupancy states: "at rest" and "in operation." It tabulates particle counts for its classifications in both occupancy states for two particle sizes: 0.5 micron and 5 micron - *Table D.*

Limits of microbiological counts are shown in a second table (Table E) for cleanroom Grades A through D, in operation. Four methods of collecting microbiological counts are shown on that table.

The guideline states that components after washing should be handled in at least a Grade D environment. It also states that preparation of solutions, which are to be sterile filtered during the process, should be done in a Grade C environment. Finally, it mentions that "Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a Grade A environment with Grade B background or in sealed transfer trays in a Grade B environment."

As far as air filtration and airflow rates, the guideline says that Grade A zones shall be provided with laminar airflow at an air speed of 0.45 m/s (90fpm) ± 20% at the working position. For Grades B, C, and D, all it requires is that HEPA filters be used, and that the air change rate be related to the size of the room and the equipment and personnel present in the room.

In terms of air pressurization between rooms, the guide requires an air pressure differential of 10-15 pascals (0.04 to 0.05 IN wg) between adjacent rooms of different grades.

In regard to changing rooms, the guide states they should be designed as airlocks and that "the final stage of the changing room should in the at rest state be the same grade as the area into which it leads."

Comparison Table - ISO/USA/EC

Table F compares USA/EC/ISO guidelines. It uses, as a common base for comparison, a particle size of 0.5 micron. Note that the left hand section of the table called "Airborne Particulate Cleanliness Classes" only defines cleanroom classes in terms of allowable number of particles per cubic volume of air.

The right hand section of the table called "Sterile Drugs Environmental Requirements" shows recommendations by USA and EC GMPs for applying the cleanliness classes and limiting the number of live organisms.

It should be remembered that USA regulations and guidelines are concerned with particle counts in size 0.5 micron during "in operation" conditions while to satisfy European Community regulations both "in-operation" and "at-rest" conditions must be met for two particle size counts, typically 0.5 and 5 micron.

In reference to Barrier Isolation, the USA cGMPs, expect the isolator to be located in a Class 100,000 room environment while the European community expects it to be in a Grade D room environment.

Update to USA Aseptic Processing Guide

The US FDA is scheduled to publish a draft of an update to its 1987 Aseptic Processing Guide. The draft title is "Sterile Drug Products Produced by Aseptic Processing Draft 2002." The following are some excerpts from that draft which revise areas previously covered or add new ones:

1. Addition: "...sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible."

2. Addition: an Air Classification Table (Table 1) covering Classes 100 through 100,000 areas based on size 0.5 micron particles per cubic foot for both: particles in general and microbiological counts. The table is based on "in-operation" conditions.

3. Revised Controlled (Class 100,000) rooms nomenclature and calls it now "Supporting Clean Areas." It states that these supporting clean areas should be Class 10,000 in the area immediately adjacent to the aseptic processing line. It also states that manufacturers can classify this area as Class 1,000 or maintain the entire aseptic filling room at Class 100. It mentions that for a Class 10,000 room at least 20 air changes per hour is typically acceptable, but adds no recommendations for other less clean areas such as Class 10,000.

4. Addition: Poly-Alpha-Oleofin (PAO) as an alternative aerol for DOP for integrity testing of HEPA filters and states that filter scanning should be conducted at a position about one to two inches from the face of the filter.

5. Addition: airflow velocities are measured six inches from the filter face or at a defined distance proximal to the work surface for each HEPA filter.

6. Addition: "lyophilization processes include transfer of aseptically fixed products in partially-sealed containers…assure that the area between the filling line and the lyophilizer, and the transport and loading procedures, provide Class 100 protection."

7. Addition: airlocks should be installed between the aseptic processing area entrance and the adjoining uncontrolled area and those other interfaces such as personnel entries also are appropriate locations for airlocks.

8. Addition: drains are not considered appropriate for rooms in classified area of the aseptic processing facility.

9. Addition: microbiological environmental monitoring should include both alert and action limits.

Environmental Requirements for Sterile Medicinal Products

Airborne Particulate Cleanliness Classes				**Sterile Drugs Environmental Requirements**						
International Standard ISO 14644-1 Classification of Air Cleanliness (1999); ISO 14644-2 Specs. For Testing & Monitoring (2000)		USA Federal Standard 209E Cleanroom and Workstation Requirements, Controlled Environment, 1992 (Note 2)		USA FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987			European Commission 1997 GMP Guide, Annex 1 Manufacture of Sterile Medicinal Products			
	State (Note 1)		In Operation		In Operation			At Rest	In Operation	
Descriptive	Max. Number particles 0.5 micron and larger per m^3	Descriptive	Max. Number particles 0.5 micron and larger per ft^3	Descriptive	Max. Number particles 0.5 micron and larger per ft^3 ($per\ m^3$)	Max. Number of viable microorganisms (CFU) per ft^3 ($per\ m^3$)	Descriptive	Max. Number particles 0.5 micron and larger per m^3 ($per\ ft^3$)	Max. Number particles 0.5 micron and larger per m^3 ($per\ ft^3$)	Max. Number of viable microorganisms (CFU) per m^3 ($per\ ft^3$)
ISO Class 5	3,520	Class 100	100	Critical Areas Class 100	100 (3,546)	0.1 (3.5)	Grade A	3,500 (99)	3,500 (99)	Less than one (0.03)
ISO Class 6	35,200	Class 1,000	1,000							
ISO Class 7	352,000	Class 10,000	10,000				Grade B	3,500 (99)	350,000 (9,912)	10 (028)
ISO Class 8	3,520,000	Class 100,000	100,000	Controlled Areas Class 100,000	100,000 (3,546,100)	2.5 (88.7)	Grade C	350,000 (9,912)	3,500,000 (99,129)	100 2.8
ISO Class 9	35,200,000						Grade D	3,500,000 (99,129)	Not Defined	200 5.7

Notes:
1. Define state: as built, at rest, or in operation.
2. On 29 Nov. 2001 Fed. Std. 209E was cancelled and superseded by ISO 14644-1 and ISO 14644-2.

Table F. Environmental Requirements for Sterile Medicinal Products.

Volume	Title	Status
1	Bulk Pharmaceutical Chemicals	Published Jun 1996
2	Oral Solid Dosage Forms	Published Feb 1998
3	Sterile Manufacturing Facilities	Published Jan 1999
4	Water and Steam Systems	Published Jan 2001
5	Commissioning and Qualification	Published Mar 2001
6	Biopharmaceutical Manufacturing Facilities	Published Jun 2004
	Packaging, Labeling and Warehousing Operations	In draft stage
	Maintenance	In draft stage
	Laboratories	In draft stage
	Oral Liquids and Aerosols	Proposed for future

Table G. List of ISPE Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities.

10. Addition: Appendix 1: "Aseptic Processing Isolators" and states that they should not be located in an unclassified room and recommends location inside Class 100,000 or 10,000 rooms. It states that the interior of the isolator should, at minimum, meet Class 100 standards and that its interior air pressure be between 0.07" to 0.2" water gage above its surrounding environment.

11. Addition: Appendix 2: "Blow-Fill-Seal-Technology" and states that they should be located in a Class 10,000 environment, but that using isolation technology can justify an alternate classification. Also mentions that air in the critical zone should meet Class 100 particulate and microbiological standards.

12. Addition: Appendix 3: "processing prior to filling/sealing operations" and states that procedures that expose the product to the environment, such as aseptic connections should be performed under unidirectional airflow in a Class 100 environment, in a Class 10,000, or better room. It furthers states that microbiological and particulate monitoring should be performed during operations.

Updated to EC Aseptic Processing Guide

The previous EC Guide to Good Manufacturing Practice dated 1997 was found in Chapter 4 - EU Guidance on Manufacture of "The Orange Guide," the British Medicine Control Agency publication titled "Rules and Guidance for Pharmaceutical Manufacturers and Distributors." Its Guide to Aseptic Processing was found at the end of Chapter 4, under Annex 1 - Manufacture of Sterile Medicinal Products.

This most recent edition of "The Orange Guide" is dated 2002. Almost nothing changed in Annex 1 between these two issues. The Guide still defines clean areas in terms for Grades A through. D and the classification tables still list both at-rest and in-operation conditions for two particle sizes: 0.5 and 5 micron.

The following are excerpts from the 2002 issue of Annex 1 that shows additions or omissions.

1. Omission: under the "General" section, item #5 the 1997 issue included microbiological monitoring. The 2002 issue deleted this requirement. In this author's opinion, microbial monitoring is a "must" in validating an aseptic process.

2. Addition: the 2002 issue adds under the "Processing" section, Item #42 that "Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift..." It further adds that "normally process simulation tests should be repeated twice a year per shift and process."

3. Omission: in both the 1997 and 2002 issues, Annex 1 defines the "at-rest" condition occupancy state as "the condition where the installation is complete and operating…but with no operating personnel present." This statement gives the misconception that the "process" equipment is in operation. The last paragraphs of Annex 1, 1997 issue included "Notes and References" that clarified that the phrase "operating, but with no operating personnel present" should normally be taken to mean that ventilation systems are operating and other equipment is present and in an operational condition, but not in use." In other words, the air conditioning system is working to maintain cleanliness and pressurization, but the rest of the equipment in the room is not. This very important clarification was omitted from the 2002 issue. This author sent an e-mail to the editor of "The Orange Guide" who answered, "…it was felt that it was not appropriate to include advice from the UK Medicines Inspectorate in an official EU Guide Annex. However, we note your comments and we shall consider reinstalling a modified version in the next edition." Let's hope they do because next to personnel, the process equipment is the major contributor to particles in a cleanroom and the "at-rest" particle count limits may not be met if the process equipment is allowed to be in operation during the "at-rest" condition.

ISPE Baseline® Pharmaceutical Engineering Guides[6]

As mentioned previously, GMPs are written in a vague language. This leads some designers of pharmaceutical/biopharmaceutical facilities to overdesign and others to underdesign. An international association that is helping in this respect is the International Society for Pharmaceutical Engineering (ISPE) with its "Baseline® Pharmaceutical Engineering Guides." This is a series of 10 guides that are being developed in the USA in cooperation with FDA to provide minimum design criteria for designing systems that would meet FDA requirements. Table G lists the proposed guides and indicates which ones have already been published.

Conclusion

This article pointed out some of the regulations, guidelines, and standards that must be followed to design an aseptic processing facility, and also tried to point out the interrelationship among them. An important item to remember is that the old Fed. Std. 209E and the current ISO 14644-1 that replaces it, only defined cleanrooms in terms of particles per unit volume. Where to use these cleanrooms and the maximum allowed CFUs for each class are only found in the EC and USA guidelines for aseptic processing facilities.

One last comment this author wants to make is that it is about time that both the 2002 EC Guide and the 2002 USA Aseptic Processing draft come together and use ISO 14644-1 (that both agencies have approved) as the common base to classify cleanrooms. To avoid confusion, the "Grades" used by the EC and the "Classes" used by the USA should be deleted and all classification based on ISO-14644-1.

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6. ISPE Baseline® Pharmaceutical Engineering Guides, ISPE, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, FL 33607, Tel: 1-813/960-2105, Fax: 1-813/264-2816, Web site: www.ispe.org.

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This article describes the importance of Validation Master Planning as it relates to the success of both project management and contractor coordination.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

Validation Outsourcing Best Practices: What Does this Mean for the Client-Contractor Relationship?

by Katie Henchir and Cynthia Ingols

Introduction

What is "Validation" to you and your organization? Does hearing the term "Validation" make you cringe? If you are a validation engineer, do you find that people seemingly avoid you? Why has validation become the "necessary evil" of the pharmaceutical industry? Let's look to the FDA.

In 1976, the FDA revised the Good Manufacturing Practices (GMPs), placing significant emphasis on quality controls to be implemented in manufacturing, packaging, storing, and distributing of products, and then in the validation of this quality. After three years of public hearings, the FDA declared the GMPs a substantive regulation and received the right to prosecute an organization for failing to comply. To further reinforce their commitment to quality and the shift toward validation, the FDA published in 1987, *"General Principles of Process Validation."* Now the term *validation* is widely referred to as establishing documented evidence that a system or equipment consistently produces a result meeting a predetermined specification. How has validation, an important and yet apparently straightforward process, come to be seen as a "necessary evil?"

Concurrent with the FDA's drive toward validation standards was private industry's move to outsourcing. In the 1980s, management gurus urged executives to focus on their core competencies and to outsource non-essential functions and services. Validation processes became a prime target for outsourcing since the need for validation work is often cyclical. In addition, as more and more companies outsourced, firms and individuals who specialized in outsourcing, such as validation engineer specialists and/or contracting firms, grew. Today, outsourcing plays a significant role in validation efforts.

Outsourcing validation processes paradoxically both simplifies and complicates management's tasks. On the one hand, outsourcing makes validation easier for management since outside specialists come in for a specified time and for a specific task, do it, and leave. On the other hand, these outsiders need to learn quickly an organization's "ropes," who's who, and the specific needs for a project. People - both company insiders and outside specialists - are the key factors in developing adequate *or* high quality validation work. Management

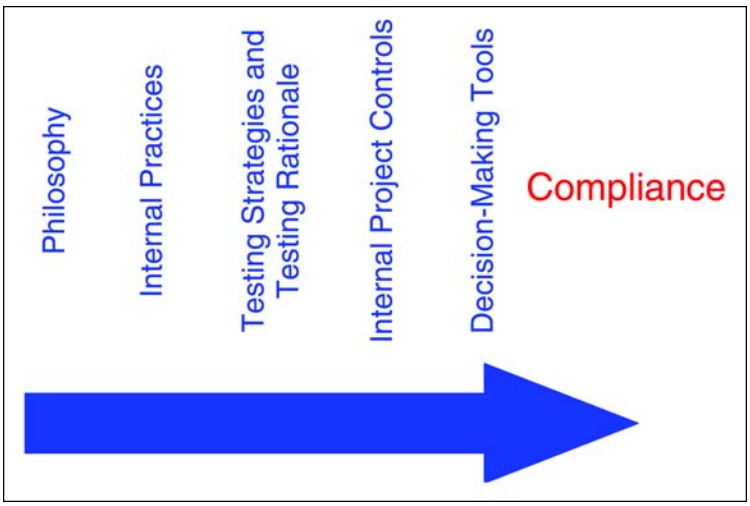

Figure 1. Five key elements to a successful VMP.

"All Validation activities should be planned. The key elements of a validation program should be clearly defined and documented in a Validation Master Plan (VMP). The VMP should be a summary document, which is brief, concise, and clear. The VMP should contain data on at least the following:

(a) validation policy
(b) organizational structure of validation activities
(c) summary of facilities, systems, equipment, and processes to be validated
(d) documentation format; the format to be used for protocols and reports
(e) planning and scheduling
(f) change control
(g) references to existing document.

In case of large projects, it may be necessary to create separate Validation Master Plans."

Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice, Validation Master Plans.

of relationships, then, is the critical people component in making projects run smoothly.

To ascertain the best practices in managing the people aspect of outsourcing the validation process, the authors interviewed validation specialists. The findings from the interviews evolved into the following best practices in the development of a Validation Master Plan (VMP) and in implementation of it, using outsourced validation specialists.

Preparing Insiders: Validation Master Planning and its Purposes

The purpose of a Validation Master Plan (VMP) is to create a central document to guide a validation effort. Although a VMP can be a powerful management tool, the document is recommended, but not required by the FDA in its *US Good Manufacturing Practices*. The European Union's (EU) *Guide to Good Manufacturing Practices* notes that "the VMP should be a summary document, which is brief, concise, and clear (note in references)." (See sidebars for recommended categories and data in EU's *Guide* and for standard sections in VMPs developed by US companies).

But the human side of developing a VMP is just as important as the categories and data placed into such a document. What are the people elements that are critical to high-quality validation work?

Requires Leadership

Selecting a strong interdisciplinary group, pulling them together, and writing a high quality VMP requires leadership. Since the potential for group discord is ever-present, a leader who connects members and engages them in strategic thinking is needed. This person should be appointed by a top-level executive with the mandate to make a "team hum" and a "VMP live."

Needs Committed Multi-Disciplinary Team

An equally important task in VMP development is identifying who should be involved. Savvy representatives from each department that will be touched by the validation process should sit around the table. Generally, representatives from manufacturing, quality control, regulatory affairs, quality assurance, and engineering should be part of the conversation. Leaving out any department is likely to weaken the thinking behind a VMP and acceptance of the document.

Once the right people are sitting around the table, there are three important tasks associated with the development of the VMP and its subsequent implementation.

Promotes Strategic Thinking

A VMP *can* push managers to consider a company's approach for "winning" at validation. If the right people are part of the conversation and if conversations are robust, then the VMP can be a document that promotes strategic thinking. There is, of course, tension between an efficient process where one pulls from files of a previously-used VMP and inserts sections into the next VMP and the more time- consuming approach of re-thinking and re-writing a VMP.

In developing documents such as VMPs, there is the human inclination to make the process routine and bureaucratic, draining it of strategic intent. The challenge is to make the process engaging and vigorous enough to draw out people's best ideas. Asking people about the implementation of the last VMP "What went well?" and "What should we improve?" are important questions to answer.

Paints a Clear Picture

There is inherent tension between giving the multi-disciplinary group enough time to talk and writing a draft of the VMP. After an initial conversation, circulate a draft of the VMP to the group and request feedback. Getting an agreed-upon VMP delivers a single message to the multi-disciplinary group and company. The VMP, with its concise milestones and project goals, signals how the validation will be implemented. For example, a detailed VMP can include testing strategy for equipment providing clear guidance during the protocol generation phase.

Ensures Compliance

Because many functional areas review the document, this developmental approach of the VMP will push the group to evaluate how each component complies or does not comply with regulations.

With the underlying force of achieving compliance, there are five key elements in developing a useful VMP - *Figure 1.*

Philosophy

Many times we resort to "that's our philosophy" when the employed validation practices are questioned. But really, what is a validation philosophy? On the project level, the philosophy governs details of a validation program; a philosophy dictates everyday practices by delivering a sound methodology for achieving compliance. When addressing the philosophy question, the intent is to develop a rationale for why things are done the way they are. For a risk-taking company, the philosophy may combine the risk-based approach with the goal of minimizing redundant testing – this philosophy

may then result in the use of commissioning documents to support qualification efforts based on the level of risk.

Internal Practices

When a validation project is initiated, there can be several external players, such as equipment vendors, a design firm, third-party representative, and contractors. Internal practices become very important to the success of the project and generating the VMP is an opportune time to evaluate how and who should be involved. Evaluating internal practices include identifying key players, strategies for managing contractors, assigning clear roles and responsibilities, and developing (or reviewing) supporting SOPs or policies that are consistent with the philosophy.

Test Strategies and Test Rationales

The VMP typically includes a list of equipment followed by a brief system description; the document can function as a tool when ramping up a validation team. Clearly identifying equipment-specific test strategies can be very helpful on the project by reducing the time spent generating protocols. It is also important to capture your testing rationale in a document – why not the VMP. The VMP is a central place to house information and can be readily available during an inspection or even a team meeting. The rationale for a testing strategy must support the philosophy.

Current industry tools to assess validation needs and facilitate development of testing strategies and testing rationales are the Impact Assessment and the GAP Analysis.

Internal Project Controls

When the VMP is prepared prior to the start of a project, the project team can assess the appropriate internal project controls. The project team can determine the frequency of meetings, time constraints, milestones, timelines, budgets, and a variety of performance measures as key indicators to ensure the project is on track.

Decision-Making Tool

Once the document has been prepared and approved, it then serves as a decision-making tool. All the pertinent project information has been captured in the central and accessible document, presenting the same message to the entire team. The team players can use this document to make compliance decisions or to include additional testing as deemed necessary. For the project team, it is a reminder of time-lines, the importance of the effort, and lastly, a tool that governs the actions as the project unfolds.

Evaluating the Impact of a Validation Master Plan

The focus of our discussion has been on the development of a VMP and how the VMP can be used to support validation efforts. The document as we have highlighted plays a significant role in planning and preparing for the project. To continue our discussion, we have evaluated current practices for managing a large-scale validation project with the focus on the client-contractor best practices and concepts that should be addressed in the VMP.

To aid in developing strategies for managing validation contractors and how to successfully develop and implement a VMP, common threads were identified from the industry validation engineers' interviews.

The findings from the interviews have been placed into the following best practice categories for managing a large-scale validation effort and implementing a successful VMP:

Preparing for Contractors

The question is: how does the operating company need to prepare for contractors? This stage involves four levels of activities: 1. diagnosing your need for a contractor; 2. gathering documentation to facilitate and minimize the time spent searching for information and getting the contractor up to speed; 3. appointing an inside manager as point person for the contractor; and communicating to key organizational players about the contractors, their work, and 4. the organization's expectations.

Laying a Foundation for Quality Work

The essential task in this stage is to build the relationship with the contractor and to make her a member of the team. Once a contractor is on site, the point-person needs to train, share information, and introduce the contractor to key players and establish clear lines of communications. With this foundation, the contractor minimizes the time searching for information and maximizes the time spent meeting your goals.

Implementing for Efficiency

Contractors can deliver a scientifically sound qualification package given the appropriate support and tools. However, the vision and tools must come from the operating company. The most powerful tools producing a vision are clear, continuous communication and guidance, and proactive project management. The operating company must be aware that the contractors will continue to need guidance, support and time; the key to success is for the operating company to ensure continuous and consistent communications and direction.

Once the decision has been made that validation support is needed for a specific reason, the client must request a proposal from a preferred contracting firm that outlines their needs and staffing requirements. This is the first and foremost important tool that is essential for establishing a sound project. The proposal creates a common understanding of roles, responsibilities, deadlines, and budget constraints. Without this document, the project has the potential for roadblocks, missed deadlines, and an increase in spending. And without this tool, an operating company cannot successfully implement the suggested best practices for validation outsourcing - *Figure 2*.

How to Use the VMP to Establish Best Practices for Managing Contractors

With the proposal in place, the project team needs to evaluate

what, when, and how to prepare for the contractors. This exercise can be performed during the VMP development and in tandem with the proposal development or award of bid to ensure the most efficient use of the contractors. The VMP will document a list of internal and external references that the contractors will need to fully understand the validation practices, policies, and project overview. Use this documentation to get the contractor started in the most efficient manner:

> *"Usually, my biggest complaint is that the operating company doesn't think about what a contractor needs to get the job done... I spend time digging up information when they don't have the materials ready for me to work when I arrive."*

This documentation typically includes corporate and departmental procedures, project plans, design specifications, and protocol templates. The benefit of compiling the information for review is to minimize the contractor's time spent tracking information down and maximizing the time for your project.

> *"...it can take me five days to learn where materials are located. It slows down the project and is very frustrating."*

As the project team identifies timelines for the VMP, consideration should be given to schedule minimal time for contractors to become knowledgeable about the owner's documents and facilities. By compiling the documentation prior to the contractor's arrival, significant time and energy will be saved and utilized more efficiently as the project unfolds. To further proactively manage the learning curve, appoint a Project Lead or point person in the Responsibilities section of the VMP. A single person within the organization familiar with the culture, practices, and end goal of the project can address concerns and begin to lead the validation contractor toward the common goal.

> *"Everyone has a learning curve. When I am first on-site, I have to learn my way around and who is who. People have to get to know my role. Otherwise, I try to schedule a meeting and people respond by saying "who's this, why do I have to go meet with him?"*

Finally, organizational expectations should be communicated with key players and how their role may impact the project. By simply sharing information internally, the overall project awareness heightens and the key players can begin to prepare as they see fit.

Laying a Foundation for Quality Work

Delivering the compiled documentation and providing adequate training should occur on the first day contractors arrive. The documentation review and training will allow time for the contractor to sense the company culture and become accustomed to the new environment. This exercise is not only creating efficiencies in contractor utilization, but it also satisfies the cGMPs:

> *21 CFR §211.25 Personnel Qualifications*
> (a)"Each person engaged in the manufacture, processing, packing, or holding of drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions..."

The initial role of the project lead is to support and facilitate the development of the contractor. The best practice is to simply have the project lead at the disposal of the contractors to address questions, provide guidance, and ensure adequate training to support the job function of the contractor has been satisfied.

> *"There was one contact person. That was my personal best experience just because I got thrown into such a mess and he was there to help me out."*

There are two best practices for meeting key players that could be spelled out in a VMP. The first is to have the project lead organize a kick-off meeting with all key players in the room at the same time. The advantage of this approach is that everyone hears the same message. The second approach is to individually introduce the contractor to key players. The latter approach often is less stressful for contractors since one-on-one meetings allow greater in-depth knowledge of one another. Once the introductions are made, it is up to the contractor to partner with the individuals to ensure the project stays on track.

Finally and most importantly, clear communication is the key ingredient to a successful validation effort. There are two components to communication. The first is active listening and the second is articulation.

Active listening is much more than jotting down notes or catching a word here and there. The word "active" is the essential component of active listening. It means to be engaged in the conversation, to observe nonverbal signals, to name emotions, and to get to the heart of a discussion. The second element of communication – articulation – provides an opportunity to clearly convey a request, need, or information. Articulation is characterized as clear expression of language that is meaningful and accurate. Articulating a point requires the ability to relate to the audience, adapt to the audience's style, and state the position.

Active listening and clear articulation are important skills for a point person and contractor. In contrast, a Validation Engineer talked about a poorly administered validation project:

> *"Communication was awful. Key people had a wealth of information, but they would never share it with the rest of the team. They would only share little pieces and they provided no explanations for their reasoning."*

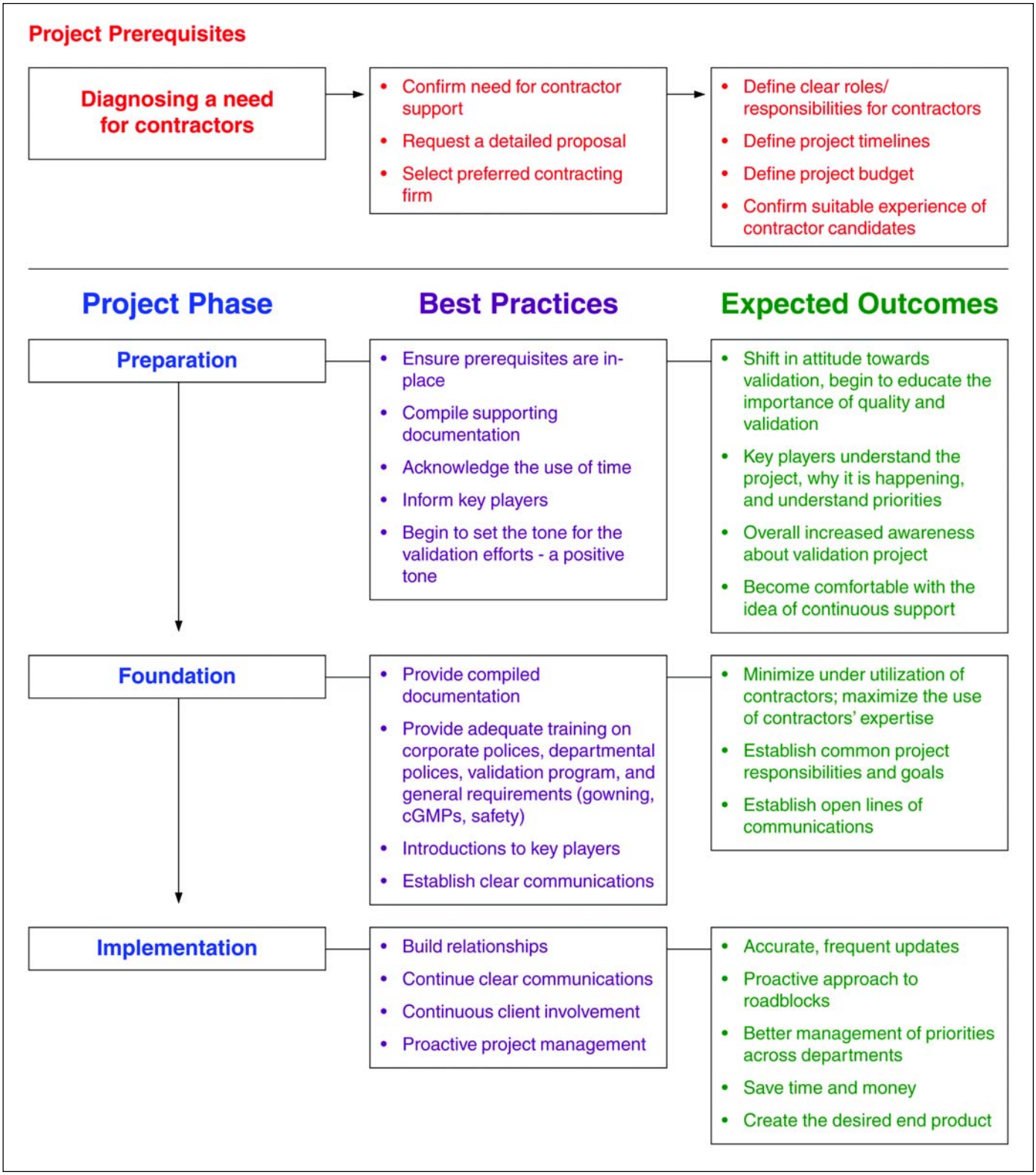

Figure 2. Validation contractor management overview for the operating company.

Coupling active listening with articulation by the point person and contractor paints a clear picture of what is happening. Such communication allows the project lead to determine the roadblocks, implement a plan of action for testing deviations, be informed of accurate updates, and establish strong relationships.

Implementing for Efficiency

It is essential for the operating company to take the lead and establish the foundation for the contractor as well as the project. The efforts thus far should have created common understandings between the contractor and key players, setting a positive tone and sense of partnership for the

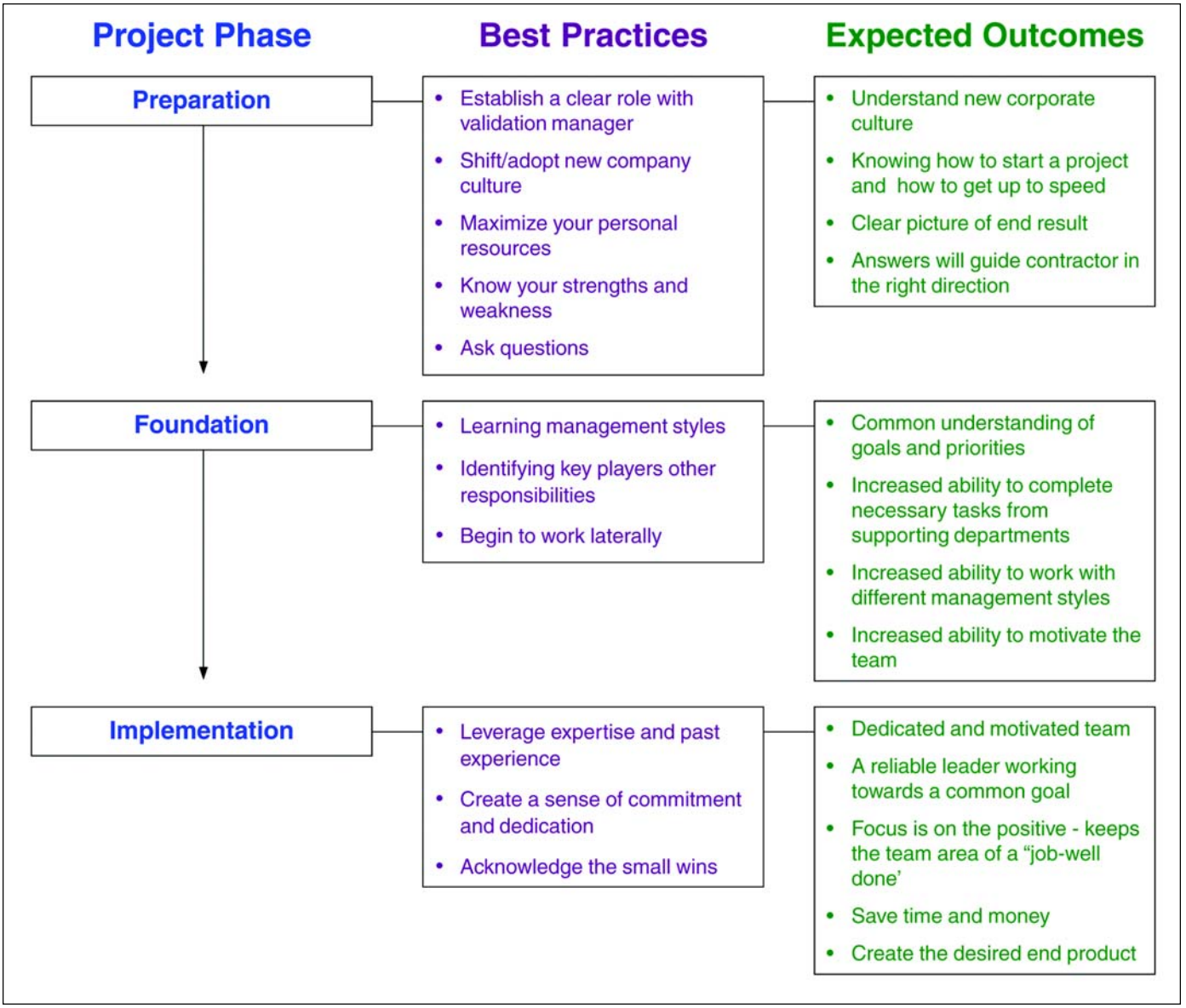

Figure 3. Validation client management overview for the contractor.

validation efforts. This foundation empowers the contractor to optimize her skills and implies continued active involvement by your company's project lead and key players.

Maintaining common goals and sense of urgency among the validation team throughout a project is imperative. At the same time, reality often intrudes into the life of a project: schedules shift, equipment breaks, unions threaten or go on strike, or other dramatic events occur. The VMP should be a living document and change as reality changes. But the question is: how are deadlines met under these new and difficult circumstances? How do you continue to share the same sense of urgency with the Validation team in a different context?

Time and time again, the answer is through relationship building. The client-contractor relationship is what drives the project. A savvy Validation Engineer explained:

> *"Any relationship in this business is my priority. In the long run and in the short run, the relationships impact the success of the project."*

Making the relationships and communication the priority is the most effective way to resolve project issues. Specifically the lead person should establish a regular process and schedule for communicating and updating contractors. For example, one point person held regular Monday morning meetings to update contractors on progress of the project and to talk about any problems in the proceeding week. If the point person does not assume these tasks, then contractors can lead the communication efforts. The savvy Validation Engineer continued:

> *"I am a firm believer in "footstones," a quick down-and-dirty e-mail about what I accomplished during the week. Especially in some projects, it is difficult to get five minutes of face time with the lead person. However, that does not stop me from communicating with him!"*

If communication is strong between client and contractor, then small problems are identified early and fixed. In such a situation larger problems are often avoided.

Finally, remember that the client-contractor relationship is primarily between the project lead and contractor(s). A strong relationship allows the client to acknowledge the validation priorities, work through problems efficiently, and exercise strong project management skills. A long-time veteran of validation projects said:

"….what it came down to was having that one contact person…that's what made the project work efficiently."

What are best practices for the contractor?

Since the client-contractor relationship is a two-way street, there are two sets of responsibilities. Some aspects of the responsibilities are the same, while others are different.

Clients may need to remember what motivates contractors. Part of the excitement of contracting is traveling and meeting new people. More importantly, however, contracting allows a Validation Engineer to broaden his knowledge by visiting companies around the world. The exposure to many sites increases the contracting Validation Engineer's experience with equipment, systems, validation philosophies, protocol formats, and approaches to validation project management. In many ways, this exposure educates the contractor about best practices.

Since contractors often have broad experience in validation engineering, what specifically do they need to do on each and every project?

Preparing for the Client Site

More often than not, a contractor is flying from one site to the next with minimal downtime. The contractor's preparation time often begins upon site arrival - *Figure 3*.

Developing a Foundation for Success

A contractor needs to take the initiative in four fundamental ways. First, the contractor needs to read and understand the clients' documents. Second, meet the point person and the key players for the project. If the company has not appointed a lead person, then explain the importance of the role. If company insiders are evasive about acknowledging key players, then ask several insiders the same question. With smart detective work, contractors can identify the key players. Third, ask questions based upon the documents and information that the contractor has been given – in other words, don't ask questions that were answered in the written materials. And fourth, establish communication channels, schedules, and what should be conveyed in the messages.

Implementing Efficiency

For a contractor, the key elements to project success include demonstrating commitment to quality, leveraging the contractor's existing skill set, and strengthening relationships - *Figure 3*.

Preparing for the Client Site

Preparation essentially begins when the contractor arrives on-site. It becomes the contractor's responsibility to quickly adapt to the operating company's style and validation goals. The first identified best practice is to meet with the Validation Manager to discuss your role and their expectations. This initial dialogue creates a common ground for the client-contractor relationship and enables the contractor to sense the management style for the Validation Group.

To gain a clear idea of your role, it is more important to ask good questions. As a contractor, there are stacks of documents to read through, understand, and act upon those documents, whether it is preparing a protocol or gowning for a cleanroom. In all cases, the contractor must learn to ask good questions that lead to direct and clear answers to move forward on the project. A successful Validation Engineer noted:

"I ask good questions to get the job done."

Developing a Foundation for Success

For the contractor, the first step in the foundation phase focuses on reviewing documents, undergoing training, and getting up to speed with the operating company's policies and project. Contractors should be careful with this document and policy review since all companies will be different. The second foundation for success for the contractor is meeting with the lead person and key players and learning to understand and manage their styles and meet their expectations. The third step that contractors must take is to ask smart questions about the documents and the players in the organization. This is not a moment to gossip, but rather to note how the company is structured, people's roles, and how people like to interact. For example, are meetings or e-mail messages the preferred means of communicating?

The fourth step for the contractor is to identify the departments and to name the people upon whom the project depends. Often several departments, such as manufacturing, quality assurance or microbiology, perform essential tasks for the Validation project. As a result; learning how to manage relationships across the departments is a significant priority during the foundation phase.

Implementing Efficiently

Once assigned to a Validation project, the client expects the contractor to take the lead and drive the project. To do this, it is imperative that the contractor demonstrates commitment and dedication to quality work and to the overall project. One practice that demonstrates commitment is to be visible in the company, to show support for the key players, and to offer to help with different tasks. A successful Validation Engineer explained his approach:

"I was real hands-on. They saw me every single day; it instilled in them that I did care about the project and that I would help in whatever way that I could."

"Validation Master Planning is not only the latest craze; it has evolved into an instrument enabling operating companies to proactively plan for large-scale validation efforts."

Contractors also are expected to be or become the expert of the equipment or system. The client anticipates the contractor will leverage their ability to learn and past experiences to deliver on time and within budget.

"You need to be the expert, especially if no one is there to guide you."

Exceptional Validation Engineers know that throughout the project it is their responsibility – as much as the insider lead person – to communicate continuously both the good and bad news. Smart, constant, and consistent communication helps to build trust and to strengthen the relationship.

What does it all mean?

Validation Master Planning is not only the latest craze; it has evolved into an instrument enabling operating companies to proactively plan for large-scale validation efforts. The document forces the project team to ask and answer difficult questions and has become a practicable management resource.

Validation Outsourcing, Validation Project Plans, what does it really mean? For operating companies, validation outsourcing coupled with a VMP is a tool to achieve and ensure compliance. For contractors, validation is a way of life. For both, it is establishing common goals, clear communications, and solid relationships.

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This article describes how a properly planned and executed commissioning strategy can eliminate downstream problems and accomplish much of the data required for qualifications and plant delivery.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

Commissioning and Time-To-Market

by Wael Allan

Introduction

Quality, risk management, and time-to-market are probably the most important aspects of a biopharmaceutical project. These elements seriously impact the viability of a drug. Missing a launch date for a product or losing a race to market may result in serious loss of revenue and/or market share.

Quality of a drug is a prerequisite for success and it must be built in at every stage during development, design, construction, manufacturing, and distribution. Quality must be established at the outset and the appropriate level of quality must be determined for all phases of a project.

As in all industries, anticipation, analysis, and management of risks are a constant challenge requiring appropriate proven methodology.

The above elements are critical to the success of a project.

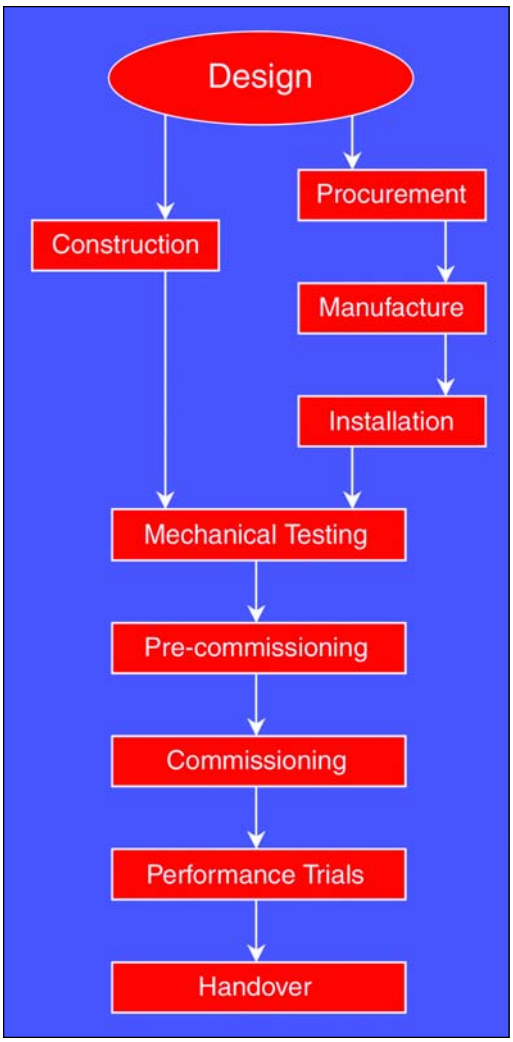

Figure 1. Typical phases of a project.

Background

The biopharmaceutical industry is one of the most regulated industries, due to the nature of the products and the regulations that govern their usability. A drug is heavily controlled from the point of molecule discovery to the point where it reaches the patient either via a prescription distributed through a pharmacy/chemist or in hospital. This has made biopharmaceutical companies cautious and conservative with regard to the scope awarded to a contractor in an Engineering, Procurement, and Construction (EPC) project. Most industries would feel comfortable awarding a project to a contractor and having them conduct construction, mechanical testing, commissioning, and performance trials ready for handover and production - *Figure 1*. In the biopharmaceutical industry, handover is normally performed at "mechanical completion." This approach has put pressure on cost, time-to-market (as integration becomes more difficult), and also has placed more pressure on clients to participate extensively throughout the whole project.

Many engineering firms have developed "integrated approaches" to EPC, but the key is achieving a reduced time-to-market and a better quality product, while managing client risks appropriately and cost effectively. The success of this is still being debated.

Construction companies have a good track record in risk management by nature of their

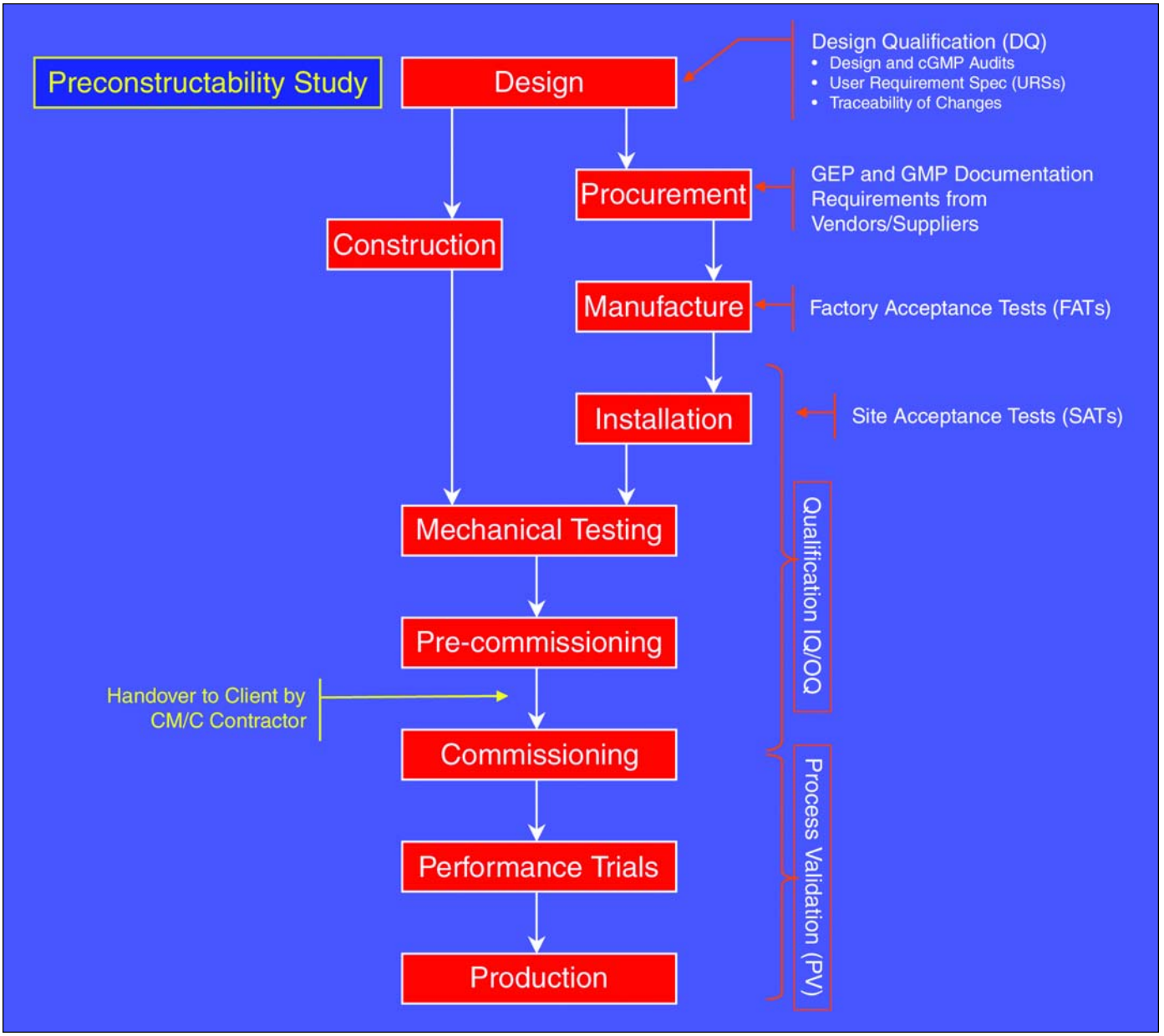

Figure 2. Typical phases of a pharmaceutical project.

work. Are such firms more suited to integrate installation, commissioning, qualification, and validation? And through this integration, can they reduce time-to-market, provide a quality facility, and manage the client's risks effectively?

For the last 15 years, the industry, led by many engineering firms, has marketed the concept of integrating engineering, procurement, construction, and validation for new pharmaceutical/biotechnology facilities. Certainly, the idea is a commendable one; however, in reality, it has no significant impact on time-to-market or cost. In many cases, the cost escalated and the schedule was extended due to the failure of integration and the lack of quality documentation by the constructor.

In the last 15 years, engineering design has come a long way in terms of Good Practice (GP) compliance through properly documented and executed GP audits. Advances have been made to the point where the work product of any major engineering firm specializing in this business can be deemed to be GP compliant.

The Mystique of Validation

Commissioning and validation have become a costly and time-consuming exercise. For large, new capital expansion projects, an owner's cost for validation, inclusive of both internal and external services, includes spent labor and materials, and is on the same order of magnitude as typical costs for engineering or construction management services. While actual validation costs will vary depending upon an owner's approach and the nature and location of the project, the range of costs are shown in Table A.

In the majority of cases, much attention has been paid to qualification/validation at the expense of commissioning.

The effectiveness of commissioning as a proven method to expedite plant delivery has been overshadowed in the phar-

maceutical industry by the emphasis on qualification/validation. Often the problems encountered in qualification are due to incomplete commissioning.

A properly planned and executed commissioning can eliminate many downstream problems and accomplish much of the data required for qualifications and plant delivery.

Construction Qualification

In light of the "Risk-Based Approach to Validation" and the increasing pressures on cost and time-to-market, a new methodology is needed to ensure the true and successful integration of construction, commissioning, and qualification.

Many API producers in Europe were not familiar with qualification/validation some 15 years ago; however, they knew that in a regulated industry they needed to ensure quality and competitiveness so they relied on GP and risk analysis as part of a methodology, namely Design Qualification (DQ).

In Europe, bulk producers regarded DQ as "qualification" for a long time before installation and operational qualifications were enforced. Typically, Design Qualification encompassed:

- Design and GP/Audits
- Risk Assessment and Criticality Analysis
- User Requirements Specifications (URSs)
- Traceability of Changes

This methodology worked well from a design perspective, but was not extended effectively to the field - *Figure 2*. Thus, providing design compliance without much impact on cost and time-to-market. Extrapolate this methodology to the field and you have Construction Qualification (CQ).

The CQ methodology is aimed at reducing cost and time-to-market through a number of critical steps as follows:

- Risk Assessment and Criticality Analysis
- Construction Audits at Approved For Design (AFD), Approved For Construction (AFC), and during field activities (based on Risk/Criticality Analysis)
- Turnover Package Organization
- GP construction forms
- Control and traceability of field charges

See Figure 3 (CQ Approach).

"CQ is a prerequisite to successful integration with Commissioning."

The activities stated above are key to expediting a project to conclusion and delivery. They impact commissioning, as many of the final construction activities (for mechanical completion) are entwined with pre-commissioning/commissioning activities.

Mechanical completion is the phase between installation and commissioning, in which components of the plant/facility are proved to be mechanically fit for their duty. It can be considered as a specialized part of the pre-commissioning activity in which each component is prepared for process commissioning. Since installation may be continuing in some areas of the plant while others are being tested and commissioned, site safety must be given detailed consideration. For example, component suppliers and sub-contractors must be carefully controlled during this phase since areas can change classification during the course of construction and commissioning.

	Engineering	Construction Management	Validation[1]
Bulk Chemical API	10 - 14%	5 - 11%	5 -7%
Bulk Bio API	14 - 18%	5 - 11%	10 - 15%
Secondary Pharmaceuticals (Solid Dosage, Liquids, and Ointments)	7 - 10%	4.5 - 8%	5 -9%

[1] Includes owner spent material and plant labor costs up through qualification costs.

Table A. Typical Engineering, CM, and Validation Costs (% of Total Installed Cost "TIC").

Generally, pre-commissioning refers to preparing the facility/plant for the introduction of process materials, and its main purpose is to eliminate any problems which might arise at later and more critical stages of facility/plant operations.

The sequence of mechanical completion is governed by the overall program, but usually starts with electrical power and utilities. The objective of mechanical completion is to prove that an installed plant component is suitable for commissioning.

Commissioning

Properly planned commissioning begins during the pre-construction phase of a project. During this time, the parameters for commissioning and qualification turnover documents are identified. Also, Factory Acceptance Test (FAT) plans and Site Acceptance Test (SAT) plans are developed for pre-purchased equipment and systems.

The goal is to have the commissioning and closeout documentation requirements identified in outline form prior to the start of construction. Specific requirements for long lead equipment and modules require definition and will be fully developed for incorporation into the bid documents.

Overall, it is the intent to utilize the project's commissioning process to enhance and reduce the time taken for qualification, hence reducing time-to-market. Properly documented commissioning can be leveraged into qualification by systems and completing the process in phases, allowing for early production and manufacturing.

Commissioning is defined as a well planned, documented, and managed approach to the start-up and turnover of systems and equipment to the end-user that results in operational, safe, and functional systems, which meets established operational requirements and end-user quality expectations.

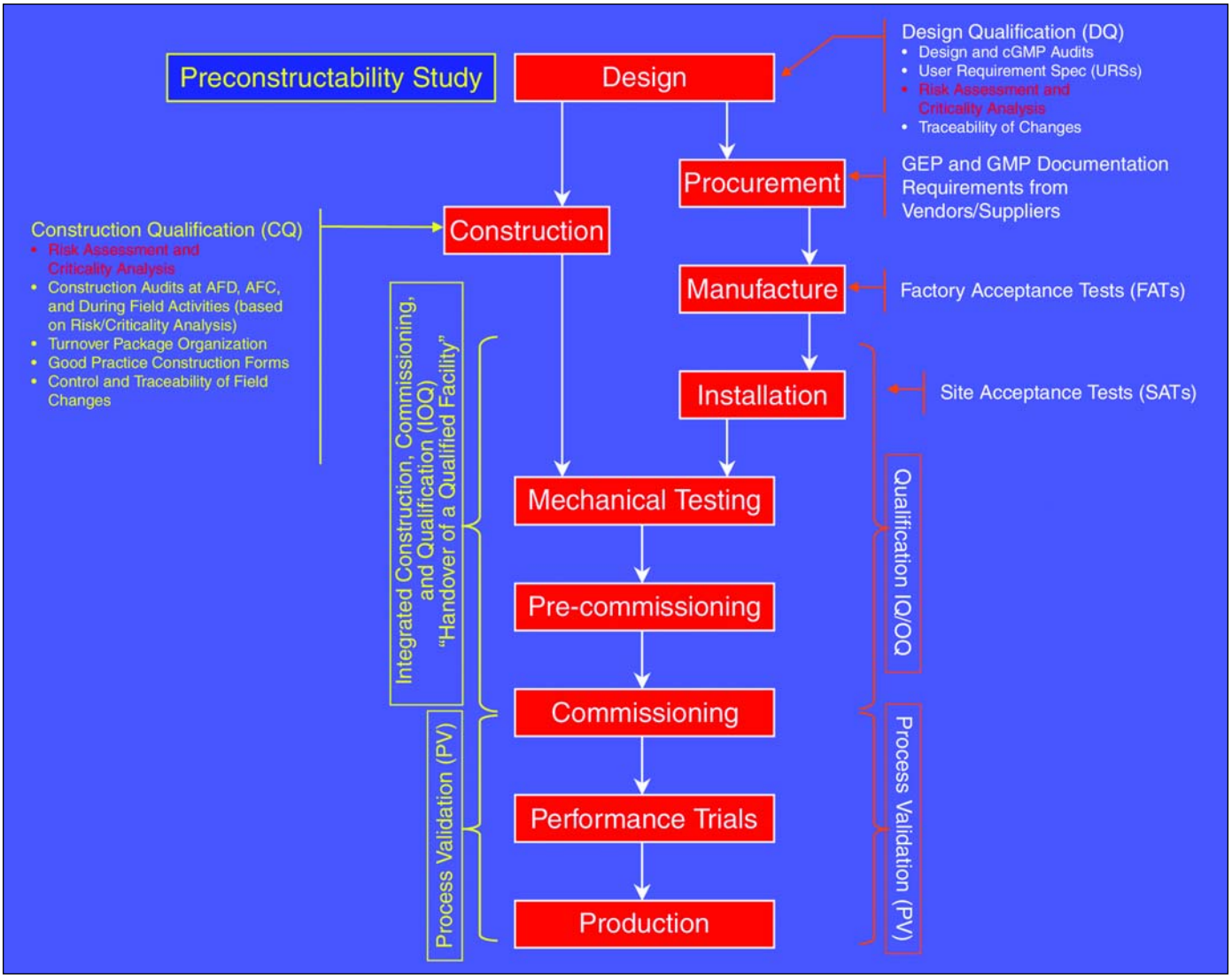

Figure 3. Construction Qualification (CQ).

Commissioning can be accomplished through different phases and methodologies. There are a number of proven methods to achieve commissioning in the biopharmaceutical industry. For purposes of illustration, it will be broken down into six phases to reflect the various tasks that will be executed through the project. These phases and tasks are summarized below and described in detail in the following sections.

1. Design Phase
   - Kick-off of Commissioning Activities
   - Focus Design Review (System Impact Assessment)
   - Documentation Requirements
   - Commissioning Protocol Writing (toward the end of detailed engineering)

2. Procurement Phase
   - Vendor selection
   - Long lead
   - Equipment Modules
   - Qualified Subcontractors

3. Construction Phase
   - Component Impact Assessment
   - Commissioning Protocol Writing and Approval
   - Construction Quality Control Activities
   - Owner Quality Assurance Activities

4. Start-Up Phase
   - Construction Quality Control Activities
   - Trade Contractor Pre-Commissioning Checks
   - Owner Quality Assurance Activities

5. Inspection, Testing, and Documentation Phase
   - Construction Quality Control Activities
   - Owner Quality Assurance Activities
   - Installation Commissioning/Verification "IC"
   - Initial Calibration
   - Operational Commissioning/Verification "OC"
   - Training

6. Handover to End-User Phase
   - Closeout Reports/Deviation Resolution

Design Phase

This is the phase of the project when the scope of commissioning is defined, the commissioning team is assembled, responsibilities are assigned, information is obtained, and protocols drafting is planned.

Kick-off of Commissioning Activities

The project manager assigns a commissioning team for the project. The project has a basis of design, a control level schedule and control estimates, and a preliminary equipment list available to assist the commissioning team in defining the commissioning activities. The commissioning team breaks the project into a series of systems, which formulates the basis for the commissioning plan.

The first draft of the commissioning plan is produced as outlined by the team. The commissioning plan is distributed for review and comment. Subsequent team meetings are held to review and resolve comments.

Focus Design Review (System Impact Assessment)

The team conducts a System Impact Assessment using the system list. The systems list covers the entire scope of the project, broken up into manageable segments. Typically, these are by equipment package, distribution or piping systems, and architectural items.

The team assesses each system with regard to its effect on product quality. In effect, the systems will be categorized into one of three categories.

- Direct Impact on Product Quality
- Indirect Impact on Product Quality
- No Impact on Product Quality

The Direct Impact Systems require further qualification after commissioning and the Indirect Impact and No Impact Systems will not require further qualification after commissioning. However, this is dependent on company policies, for example, some companies will further qualify some Indirect Impact Systems depending on the criticality of the interface with a Direct Impact System. These categories and the assessment criteria are further defined by the commissioning team and are usually documented in the System Impact Assessment Report.

Documentation Requirements

During the design phase, the User Requirement Specification (URS) and Design Specifications for Good Manufacturing Practice (GMP) critical systems and equipment should be reviewed with regard to the vendor/contractor documentation required to support commissioning and qualification as well as operations and maintenance. Where appropriate, documentation numbering, layout, formats, etc., should be specified. In most instances, the equipment/system vendor is best placed to provide the documentation required to support the commissioning and qualification effort. Therefore, this must be stated during the design phase of the project so that the documentation becomes one of the key deliverables for the vendor/contractor.

Commissioning Protocol Writing

The team will decide how to generate the commissioning protocols and who will execute them. Two approaches exist.

1. The equipment manufacturer (vendor) provides a Site Acceptance Test (SAT), which is incorporated into the commissioning protocol. The vendor also executes the SAT.

2. The commissioning team writes the commissioning protocol for engineered systems, such as utility distribution systems. Subject matter experts are consulted as required. The commissioning team also executes the protocol.

Procurement Phase

The procurement of subcontractors, vendors, and equipment design and fabrications systems could potentially have "added value" to the overall schedule and cost of a project. Without proper integration of design, prefabrication, and construction, the maximum benefit may not be obtained. In addition, without a rigorous implementation strategy, not only will inefficiencies result that erode the schedule and cost benefits, but the end product may be viewed as a compromise and fall short of expectations.

A successful approach must influence the project from the early stages of preliminary engineering. This early involvement will yield dividends for every phase of the project.

1. Objective

- Maximize the use of 'Equipment Modules" to provide the optimum combined schedule and cost benefit value while increasing the overall quality and improving the project's schedule.

2. How Implemented

- Assemble a team of individuals who possess a unique combination of pharmaceutical/biotech design and construction experience.
- A team with the design, construction, and integration of skidded process equipment.
- A team with know-how in project turnover requirements for Good Practice facilities.
- A team with experience in the start-up and commissioning of pharmaceutical/biotechnology facilities.
- Empower the team to be part of the up-front engineering

3. Engineering and Design Recommendations

- Develop module boundaries for the project.
- Lead in the development of an "Equipment Module Design, Fabrication, and Installation Standard" (EMDFIS).
- Review and critique layout and general arrangement studies in regard to module implementation.
- Develop engineering and design boundaries between process engineer/design firm and equipment module manu-

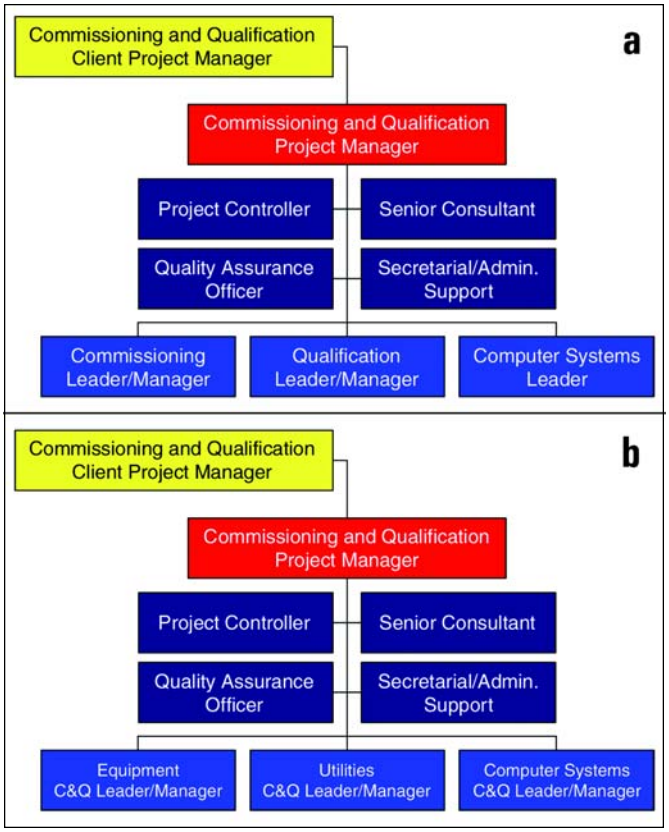

Figure 4a. Proposed organizational chart.
Figure 4b. Alternative organizational chart (C&Q = Commissioning and Qualification).

facturer to optimize design schedule and cost.
- Prepare a construction strategy that identifies field versus shop work and interface requirements as well as standards for controls, piping, electrical, etc.

4. Procurement Strategies

- Conduct pre-qualification visits to potential suppliers of equipment modules.
- Evaluate best methods of design and construction that may influence the EMDFIS.
- Evaluate integration options of module boundaries.
- Develop options for the field and module scope boundaries.
- Review overall shop capabilities in regard to projected workload, shop capacity, quality program, maximum assembly size, technical capability, turnover documents, etc.
- Develop a procurement strategy to maximize buying power and scope distribution across vendor availability.
- Evaluate major equipment, instrument, and controls procurement with drop ships to equipment module vendors versus turnkey approach.

Construction Phase

Subcontractors, vendors, operations, maintenance, and engineering develop support documentation that will be reviewed during commissioning.

Component Impact Assessment

To evaluate the impact of system's components on product quality, the team meets to review the details of each system. Similar criteria that were used for the System Impact Assessment are used to judge a component's effect on product quality. Although all systems undergo a component impact assessment, emphasis is placed on the direct impact systems. The spirit and principle of risk analysis and management plays a vital role here, and this information also is recorded in the Component Impact Assessment Report.

Commissioning Protocol Writing and Approval

It is the commissioning team's responsibility to ensure that the proper information is getting to the individuals who are writing the protocols with the operations and maintenance representatives on the team serving as the focal points of this information flow.

The data for these protocols is gathered from end-users, the construction manager, third parties, or subject matter experts as required.

The commissioning team reviews and approves all protocol submittals and then signs the protocols prior to execution according to the document approval matrix.

Note: If commissioning is to be leveraged into qualification then the involvement of the clients' Quality Assurance (QA) organization is a pre-requisite. The level of involvement is critical as this impacts the approval times and the overall schedule.

Construction Quality Control Activities

At this stage of the project, construction groups and equipment vendors review documentation and drawings for design completeness and adherence to building codes and practices. As construction progresses, the quality control activities become more physically orientated to ensure installation complies with approved design. Deviations are tracked in the project worklist/punchlist.

Owner Quality Assurance Activities

Similar to the construction control process, but with owner participation along with the construction groups and engineers who review documentation and drawings for design completeness and adherence with regulatory requirements, operational requirements, and best practices. As construction progresses, the quality control activities will become more physically orientated to ensure installation complies with approved design. Deviations are tracked in the project worklist/punchlist.

Start-Up Phase

Vendors and system representatives power-up the systems and perform necessary procedures to make the systems fully operational. This phase culminates in the handover of systems to the commissioning team.

Construction Quality Control Activities

The construction manager and the commissioning team conduct periodic reviews of the construction progress and the

quality of the installation (walk downs). Deficiencies are tracked in the project worklist/punchlist, which contains commissioning, qualification, and general items still requiring completion.

Trade Contractor Pre-Commissioning Checks

Prior to system or equipment start-up, the trade contractor is responsible for performing valve/equipment line-ups to ensure that all equipment is in the proper operating condition and no equipment or system damage will occur.

Continuity checks also are performed and documented in accordance with the specifications.

Turnover of a system from construction to commissioning is based on the acceptance of a system by the commissioning team. The following items are typically required to define construction process as being complete:

- Construction manager, contractors, vendors or system representatives, engineering, and operations sign off on the construction turnover package.
- All installation documents required to support commissioning are complete and available.
- Required utility services are available in adequate supply to properly operate the system.
- All controls signals from external sources are available or can be reliably simulated.
- Equipment/system start-ups requiring lockout/tagout for equipment or personal protection are performed using owner procedures.
- After the system has been checked, the construction manager assembles the completed forms and provides them to the commissioning leader for review. The construction manager provides copies of the completed forms to the commissioning leader and keeps the originals for inclusion in the turnover package.

Owner Quality Assurance Activities

System walkdowns, which begin when installation of a system is approximately 90 percent complete, are coordinated with the owner representative. The construction manager informs the owner representative prior to system/equipment start-up, and coordinates times when the equipment could be available for certain activities, should the owner representative need or wish to access the systems/equipment at any time.

Coordination with the owner representative is critical to ensure that start-up of the equipment does not affect areas outside of the scope of specified project.

After a successful start-up and commissioning has been completed, plant personnel including facilities engineering, operations, and safety are notified that the system is ready for them to prepare, execute, and issue plant specific readiness reviews or an Operational Readiness Report (ORR) indicating it is safe to be turned over to operations for regular use.

Start-Up

The equipment vendors and/or contractors review their own internal installation complete checklist to make certain the equipment/system has been properly installed and is ready to be safely activated.

The equipment vendors/engineers will activate the equipment, and perform all necessary activities required to make the equipment/system fully functional. This includes checking liquid/lubrication levels, checking motor rotations, tuning loops, debugging installation problems, confirming installation against as shipped drawings, setting system specific parameters, and making the equipment/system ready for testing.

Calibrations also are performed during this phase, which vendors require to finish their start-up procedures. Full loop checks are performed (field device through software to console or vice versa) and documented.

Inspection, Testing, and Documentation Phase

The commissioning team executes the commissioning protocols in this phase. The executed protocols, system closeout, and handover reports are then reviewed by the team. Execution of the commissioning protocols confirms that the installation was performed according to the approved design. The acceptance criteria are defined in the approved design documents.

Installation Commissioning/Verification

The commissioning team reviews the available documents comparing them to the requirements outlined in the Engineering Turn Over Package (ETOP). The commissioning protocol execution ensures that the required documents are complete and available.

The installation is checked against the approved drawings. This process includes such activities as P&ID verification, general arrangement drawing verification, and nameplate verification.

Initial Calibration

Proper documentation of the calibration is referenced back to a traceable standard depending on the country, e.g., USA: NIST. The initial calibration is performed as part of the vendor or system start-up activities. The documented evidence is reviewed at this stage.

Operational Commissioning/Functional Testing

The commissioning team system representatives execute the commissioning protocols to ensure proper operation of the machine as defined in the approved project documents. The commissioning team signs off the executed protocols accepting the results of the execution.

Training

The commissioning team ensures that operator and maintenance training has been addressed to the end-user's satisfac-

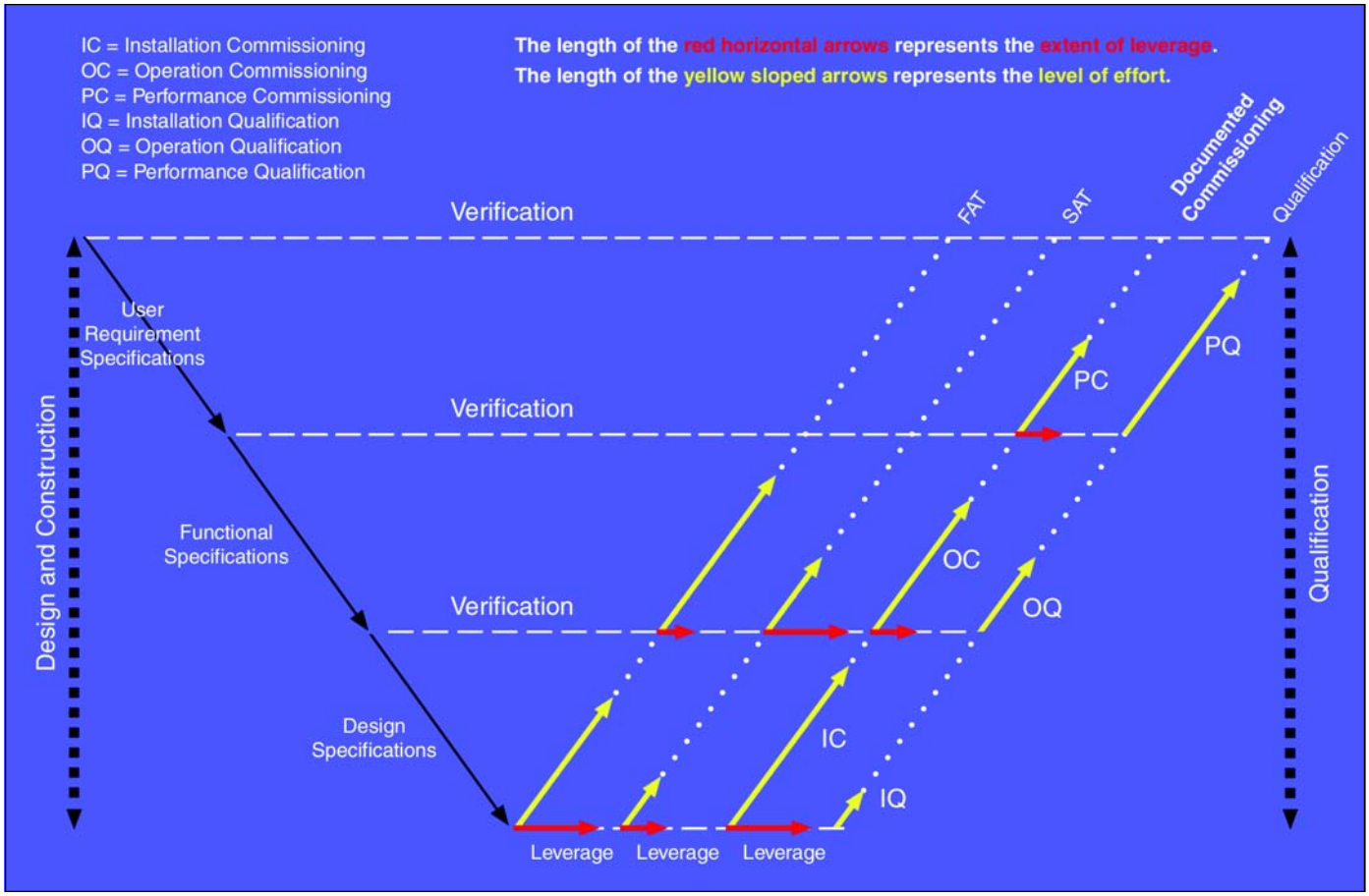

Figure 5. Leveraging commissioning into qualification.

tion. The commissioning protocol ensures that training documentation has been provided to the end-user and that training has been scheduled.

Handover to End-User Phase

Commissioning is complete; the system end-user formally accepts the systems. Plant maintenance is responsible for the preventative maintenance of systems, some of which undergo further qualification.

For true integration to take place and in order for commissioning to be leveraged into qualification, it is strongly advised to have the same team members perform qualification for the systems they commissioned.

Closeout Reports/Deviation Resolution

Closeout reports address open issues, identify corrective actions required, the responsible party, and dates for completion. Deviations, documented on the project worklist/punchlist, are reviewed to ensure that all remaining open issues are transferred to the closeout report.

Project Organization and Execution

There are many different ways to organize a commissioning team, but the most time and cost-effective is when commissioning and qualification activities are integrated.

It is not the intent of this article to offer details with respect to project organization and execution; however, the following structures are proposed as examples - *Figures 4a and 4b*.

Commissioning in Support of Qualification

Earlier in the article, reference was made to the fact that overemphasis on qualification/validation has overshadowed commissioning, resulting in problems during validation due to incomplete commissioning. Some of these problems can be detrimental to cost and time-to-market since fixing them requires a high level of backtracking and mending of installation and documentation.

Commissioning performed in new construction and existing facilities helps to ensure that systems are installed, functionally tested, and capable of being operated and maintained to perform in conformity with the design intent and the owner's needs. This ensures that a new facility begins its life cycle at optimal productivity. Commissioning also can result in restoring an existing facility to optimal operation. Furthermore, when commissioning is repeated periodically throughout the life of a facility, it improves the likelihood that the facility will maintain a higher level of performance.

Placing more emphasis on Documented Commissioning (DC) may have cost and schedule consequences. In general, qualification costs can be at least twice as much as that of commissioning. Reversing the emphasis will make the cost of documented commissioning higher. However, the cost of qualification could come down significantly as documented

commissioning can be the lion's share of the effort required for qualification. More significantly, by adopting documented commissioning as the basis of qualification, clients could significantly reduce the risk of non-compliance and serious problems affecting the delivery of a qualified facility, hence reducing time-to-market.

In order for DC to work effectively as the basis for qualification, early active participation of the client's quality unit is key to ensuring that various commissioning activities are eventually accepted for inclusion in support of the installation and operational qualification. These protocols, along with any performance qualification protocols that are required, form the basis of the qualification/validation effort. This is in accordance with the framework set forth in the ISPE Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities, Volume 5, Commissioning and Qualification. It is worth referencing the ISPE definition of commissioning as a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

DC must be treated as a unique and discrete activity in accordance with the above definition to be used as the basis of qualification/validation. In many cases, where attempts were made to mix commissioning and qualification together serious delays and shortfalls occurred - *Figure 5*.

The Future

The new order for our industry is, as always, driven by pressures on cost and constant changes to meet market demands. The new industry drivers are risks (analysis and management), cost, and time-to-market. If you agree that those stated above are the real drivers in our industry, would it make sense to expect C/CM contractors to deliver a qualified facility rather than a mechanically complete facility. Clearly, the goal is to be cost-effective, fast, as well as comprehensive. Redundancies in testing may be eliminated through the implementation of a smart and efficient approach to installation and operational qualification of systems and equipment. This logic, or "Qualification Rationale" as it is called by the ISPE Baseline® Guide, can be achieved through the integration and implementation of Construction Qualification (CQ) and Documented Commissioning (DC).

Finally, the next decade may see Documented Commissioning replacing Qualification and/or Qualification becoming the QA function for Documented Commissioning.

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This article describes the results of the electrochemical corrosion testing of the as welded, mechanically polished, and electropolished AL-6XN fusion welded to Inconel 22. Also tested was a single electropolished weld segment, which was submerged in a ferric chloride solution in accordance with the ASTM G-48 procedure to further elucidate corrosion resistance and sites of attack.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

Investigation of the Corrosion Characteristic of AL-6XN Fusion Welded to Inconel Alloy 22

by Arnie Grant and John Jermain

Introduction

A corrosion study was undertaken in support of Fluid Line Technology development efforts to investigate the corrosion characteristics of AL-6XN fusion welded (no filler) to Inconel 22. The purpose of the study was to compare and rank the corrosion characteristics of the dissimilar metallic weld in the 1. as welded condition, 2. mechanically polished (180 grit) after welding, and 3. electropolished after welding. Of interest in this work, in addition to measuring the difference in pitting potential, was to identify the sites or specific susceptibility on the weld coupons at which corrosion would initiate, e.g., Heat Affected Zone (HAZ) and the type of corrosion, e.g., intergranular. A single electropolished weld segment was tested per ASTM G-48, Pitting Corrosion by Use of Ferric Chloride to further elucidate corrosion resistance and sites of attack. All samples were tested as-received with no additional cleaning or passivation.

Table A. Specification limits for AL-6XN and Inconel 22.

Composition	AL-6XN	INCONEL 22
Carbon	0.03%	0.015%
Chromium	20.00/22.00%	20.00/22.50%
Cobalt	-----	2.50%
Copper	0.75%	-----
Iron	42.00/47.00%	2.00/6.00%
Manganese	2.00%	0.50%
Molybdenum	6.00/7.00%	12.50/14.50%
Nickel	23.50/25.50%	50.00/59.50%
Nitrogen	0.18/0.25%	——
Phosphorus	0.040%	0.02%
Silicon	1.00%	0.08%
Sulfur	0.030%	0.02 %
Tungsten	-----	2.50/3.50%
Vanadium	-----	0.35%

The specification compositional limits for the two alloys are listed in Table A. Inconel alloy 22, a nickel-chromium-molybdenum-tungsten alloy, and AL-6XN, a "super-austenitic" alloy, are utilized in corrosive environments for excellent resistance to general corrosion, pitting, crevice corrosion, and intergranular attack. Due to their exceptional corrosion resistance, these two alloys have been used in a large variety of industrial applications, and most recently in the pharmaceutical/biotech industry.

Alloy - AL-6XN

AL-6XN was initially intended to be used in a seawater environment, but extensive testing has demonstrated it to be resistant to a variety of corrosive elements. Its excellent chloride pitting resistance is attributable to its 6.50% molybdenum content, while its significant resistance to chloride stress corrosion cracking is a result of its nickel content of about 25.00%. The addition of nitrogen enhances its pitting resistance as well as mechanical strength. Nitrogen also serves to significantly reduce the formation of potentially harmful secondary phases during the manufacture of large cross-section products. The Allegheny Ludlum Corporation, which developed the AL-6XN alloy, has tested it against other stainless steel alloys and concluded that it is the most corrosion resistant iron-base austenitic stainless alloy presently available.[1]

Alloy - Inconel 22

Inconel alloy 22 is a nickel-base al-

Figure 1. PAMO meter and test cell.

loy made up of 21.5% chromium, 13.6% molybdenum, and 3% tungsten. The material is an adapted version of Inconel alloy 622, which offers superior resistance to pitting and crevice corrosion in acid chloride solutions and resistance to general corrosion in mixed and reducing acids. The alloy is used to manufacture a wide variety of chemical process equipment such as: Flue gas scrubbers, chlorination systems, acid production and pickling systems, outlet ducting and stack liners for power plants, sulfur dioxide scrubbers, pulp and paper bleach plants and for weld overlay of less corrosion resistant metals.

Test Methodology

Material - Weld Test Coupons

The weld coupons were made from AL-6XN TUBE, 1.5" OD x 0.071, Heat Number 023 BFW, and Inconel 22 Tube, 1.5" OD, Heat Number 024 BIG. Chemical analysis yielded the data in Table B, which are within their respective specification tolerances. Each E_{PIT} test coupon cylinder was 2" long x 1.5" OD with the weld at the center. No data was provided on the welding parameters.

Electrochemical Corrosion Test - Cal-Chem Passivation Monitor (PAMO Meter)

The pitting potentials (E_{PIT}) of the three AL-6XN/Inconel 22 weld coupons, 1. as-welded, 2. mechanically polished, and 3. electropolished, were measured using the electrochemical Passivation Monitor (PAMO) shown in Figure 1 with the test cell configuration. The electrolyte solution is 1.0 M KCl and the test temperature is 60°C, the counting electrode was 316L, and reference electrode was Calomel. This field portable monitor was developed by Cal-Chem in conjunction with the Materials Science Department at USC to provide data on pitting potential equivalent to ASTM G-61. This procedure tests the resistance of the sample coupon cylinder to electrochemically induced pitting. The pitting potential for these highly corrosion resistant alloys is measured after two hours at 60°C with an applied current to the test cylinder via the potentiometer. For comparison, the pitting potential for the much less corrosion resistant 316L alloy is measured in 0.1 M KCl at 15 minutes at ambient temperature. This E_{PIT} value may then be conveniently used to compare the relative corrosion resistance before and after passivation for the same alloy as well as comparison of corrosion susceptibility for the three surface finishes above. The larger the value of the E_{PIT}, the better is the resistance to pitting corrosion. The "Breakthrough Time" or time to onset of corrosion also was used as an indication of relative corrosion resistance.

Composition	AL-6XN	INCONEL 22
Carbon	0.02%	0.003%
Chromium	20.44%	20.53%
Cobalt	-----	0.10%
Copper	0.26%	-----
Iron	48.13%	3.36%
Manganese	0.35%	0.21%
Molybdenum	6.25%	14.25%
Nickel	23.93%	58.27%
Nitrogen	0.20%	-----
Phosphorus	0.020%	0.007%
Silicon	0.39%	0.05%
Sulfur	0.001%	0.001%
Tungsten	-----	3.19%
Vanadium	-----	0.02%

Table B. Chemical analysis of test alloys.

ASTM G-48, Pitting Corrosion of Ferric Chloride Solution

A single electropolished weld segment was supplied for the G-48 immersion test (Method A) in which the test coupon is submerged in a 6% solution of ferric chloride at a prescribed temperature and time to determine resistance to pitting corrosion of stainless steels. The recommended elevated temperature is 50°C and time is 72 hours. The sample is removed periodically, cleaned, examined, and weighed, and the observations are recorded to give an appraisal of corrosion susceptibility.

Photographic Documentation

Photographs were taken of the samples to document the appearance of the internal surfaces before and after the corrosion tests. Because it was noted that a very significant discoloration (oxidation) appeared on the post E_{PIT} test specimens, it was decided to cut the cylinders longitudinally and to "derouge" one half of the cylinder to see if the discoloration (oxide) was removed. These discolored and derouged photographs also are presented. After photographing the post test cylinders, they were bisected to document the areas of corrosion attack.

Experimental Results

Photographic Documentation from the Electrochemical Pitting Potential Testing

Figures 2, 3, and 4 present the photos of the as-welded, mechanically polished, and electropolished cylinders, (a) before the electrochemical pitting corrosion test looking down the cylinder, (b) after the electrochemical pitting corrosion test, and (c) before and after derouging of oxide discoloration.

On the as-welded sample (Figure 2) after E_{PIT} testing, very dark blue/purple discoloration occurred immediately adjacent to the weld bead on the Inconel 22 side at the down slope area. To a lesser degree, yellow, blue, green, and purple discoloration was very obvious on the entire Inconel 22

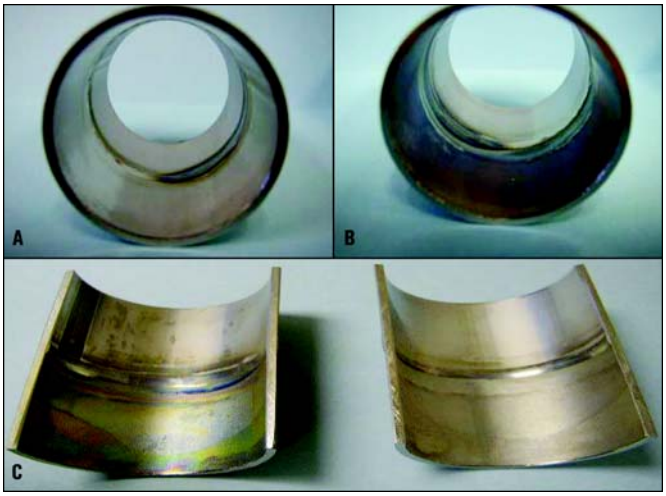

Figure 2. As welded (mill finish ID and OD).
A. Before pitting corrosion test.
B. After pitting corrosion test.
C. Surface comparison of as welded samples (left = after pitting corrosion test, right = after derouge). AL-6XN is shown above the weld and INCONEL 22 is shown below the weld.

surface. It is presumed these discolorations are indicative of oxidation of the various metals on the surface and variations in oxide thickness. There was no evidence of pitting at 10X magnification. The AL-6XN side of the cylinder did not display the bright profusion of oxide coloration. Instead, there were distinct areas (much more localized) of rust spots. These are taken as a precursor or nucleation areas of pitting. In addition, hazy areas appeared on the AL-6XN side immediately adjacent to the weld bead and in the HAZ, which appeared to be intergranular corrosion. Verification of the latter assumption would require further metallographic testing. After derouging (not passivation), the Inconel 22 discoloration was removed, but the surface appeared mottled gray following the contours of the earlier discoloration. A distinct straw color remained on the AL-6XN HAZ, but the dispersed rust areas were removed.

The mechanically polished sample (Figure 3) displayed a lesser degree of yellow, blue, and purple discoloration on the Inconel 22 side and no apparent rust spots on the AL-6XN side after the electrochemical corrosion test. Intergranular corrosion (hazing) did not appear on the AL-6XN side as it did on the as-welded cylinder. After derouging, the Inconel 22 portion was a dull gray with a mottled appearance.

The electropolished sample (Figure 4) displayed the overall yellow, green, blue, and purple discoloration on the Inconel 22 side and a relatively slight uniform yellowing on the AL-6XN side. After derouging, the Inconel 22 was very slightly mottled and the slight yellowing was removed from the AL-6XN leaving a bright metallic shine.

As can be seen in the photographs, the surface of the Inconel 22 portions of the as-welded and electropolished cylinder appear to be pebbly (orange peel) in appearance and the weld bead protrusion is very apparent. Mechanical polishing removed the pebbly surface and the weld bead protrusions - *Figures 3 and 4.* The as-welded coupon also displayed significant discoloration in the weldment area not present in

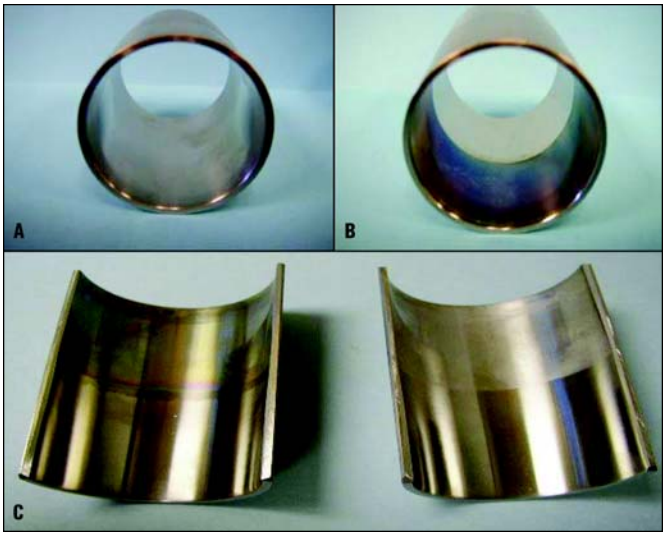

Figure 3. Mechanical polished ID - 180 grit (no electropolish) - OD is mill finish.
A. Before pitting corrosion test.
B. After pitting corrosion test.
C. Surface comparison of mechanical polished (left = after pitting corrosion test, right = after derouge). AL-6XN is shown below the weld and INCONEL 22 is shown above the weld.

the other two cylinders. Extensive surface discoloration occurred on the Inconel 22 portion of all samples after the pitting potential test; the as-welded being the worst.

Results from the Electrochemical Pitting Potential Testing

The pitting potential data and breakthrough times for the three samples are presented in Table C and shown graphically in Figures 5 through 9. With both pitting potential and breakthrough times as the criteria, the electropolished sample had the highest resistance to corrosion and the as-welded had

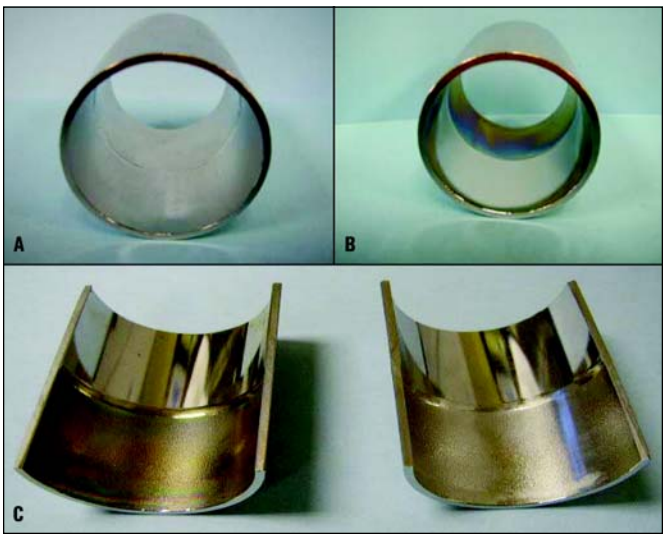

Figure 4. Electropolish ID and OD (mill finish).
A. Before pitting corrosion test.
B. After pitting corrosion test.
C. Surface comparison of electropolished (left = after pitting corrosion test, right = after derouge). AL-6XN is shown above the weld and INCONEL 22 is shown below the weld.

	Breakthrough Time	E_{PIT} Value
As-Received	57 minutes	97 mV
Mechanically Polished	67 minutes	157 mV
Electropolished	94 minutes	187 mV

Table C. Breakthrough time and E_{PIT} for the three surfaces.

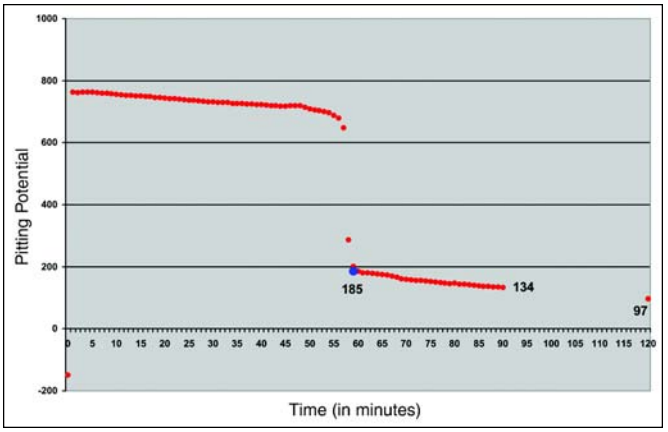

Figure 5. Pitting potential (mV) curve for as welded cylinder.

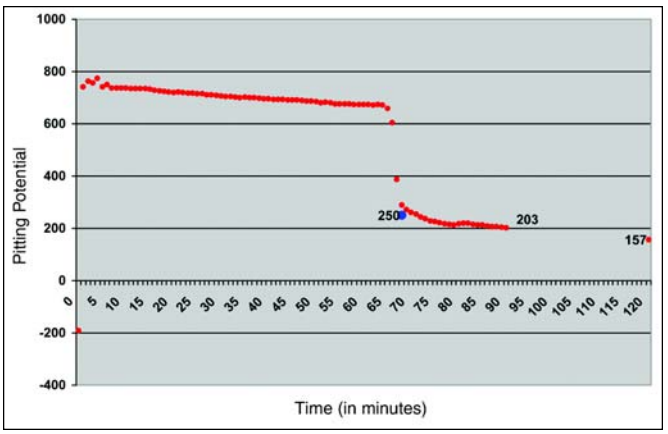

Figure 6. Pitting potential (mV) curve for mechanical polished cylinder.

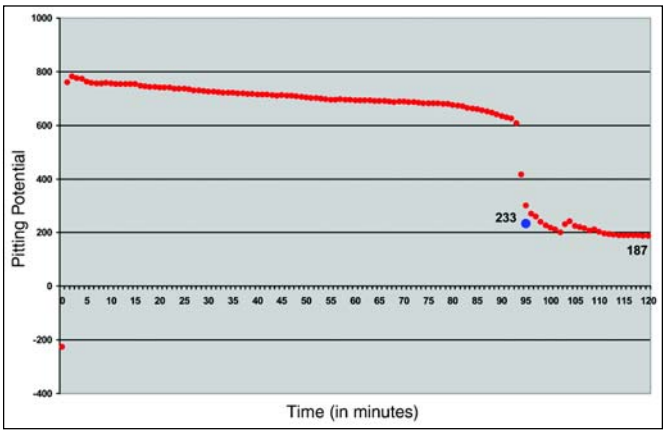

Figure 7. Pitting potential (mV) curve for electropolished cylinder.

the lowest resistance.

In the electrochemical pitting test, equilibration to the open circuit potential is achieved at temperature before the polarizing current is applied. Then the voltage is recorded as a function of time for a period of two hours at which time the E_{PIT} is established. The millivolt vs. time plots for the as-welded, mechanically polished and electropolished welded cylinders are presented in Figures 5, 6, and 7, respectively. The breakthrough time is taken as the time point at which a rapid drop in voltage occurs signifying that corrosion has begun. This data is shown in bar graph form in Figure 8. The pitting potential values of E_{PIT} are taken uniformly at 120 minutes elapsed time for comparison. The E_{PIT} values are shown in bar graph form in Figure 9.

These results are tabulated in Table C, comparing breakthrough time and E_{PIT} for the three surface finishes of the AL-6XN/Inconel 22 fusion weld. Both parameters show the as-welded sample at the lowest value, the mechanically polished sample at a midpoint value, and the electropolished at the highest, most corrosion resistant value. Taking the E_{PIT} value as the more important test parameter in the evaluation, mechanically polishing the ID of the weld improved corrosion resistance by 62% while electropolishing improved corrosion resistance by 93%.

Results from the Ferric Chloride Corrosion Test (ASTM G-48)

Table D presents the ASTM G-48 weight loss data for the electropolished segment at various times. Because no weight loss was observed after 60 hours at 50°C, the test temperature was increased to 60°C for an additional period of 12 hours. Photographs of the segment at test initiation (0 hours), and 72 hours (60 hours at 50°C + 12 hours at 60°C) are shown in Figures 10a and 10b. After 12 hours at 60°C, the sample lost 0.72% of its weight in the form of a single large pit (Figure 10b) away from the weld bead and HAZ on the AL-6XN side in the parent metal. No pitting corrosion could be seen with magnification up to 10X in the Inconel 22, weld bead or the HAZ of either metal.

From this visual data, it would appear that the electrochemical pitting potential test measures the nucleation stage while the G-48 test induced the rapid propagation stage of pitting.

Discussion

Inconel Alloy 22, a Ni-Cr-Mo alloy, demonstrates excellent corrosion resistance under a wide variety of corrosive environments including pitting by chloride and oxidation by ferric chloride. The AL-6XN, a superaustenitic alloy with high levels of nickel (25%) and molybdenum (6.5%) also demonstrates excellent corrosion resistance, especially under chloride pitting conditions.

All three of the Al-6XN/Inconel 22 cylindrical fusion weld coupons showed outstanding resistance to the two accelerated laboratory chloride corrosion tests that were employed to compare the as-welded condition to the post weld mechani-

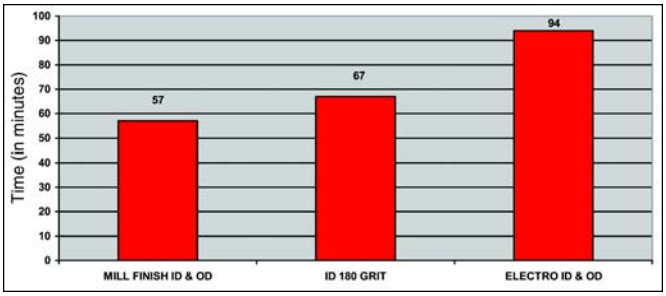

Figure 8. Pitting potential breakthrough time.

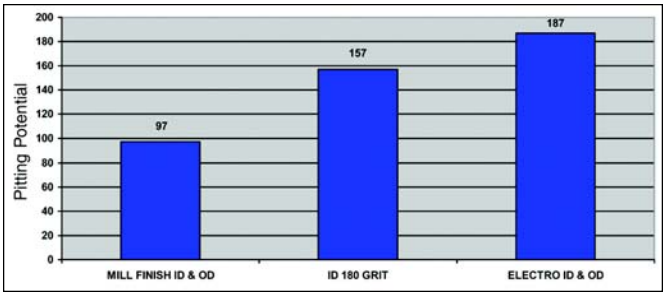

Figure 9. Pitting potential (mV).

cally polished and electropolished cylinders.

As noted above to illustrate the exceptional degree of corrosion resistance of these weld coupons compared to 316L stainless steel, the pitting potential for 316L is measured in 0.1 M KCl at ambient temperature after 15 minutes of applied potential. No corrosion could be induced on these test specimens under these test conditions. After a series of experiments, it was determined that the test parameters required were 1.0 M KCl electrolyte at 60°C for a period of two hours to obtain meaningful pitting corrosion data.

In the as-welded condition, the Inconel 22 side of the weld appears to be susceptible to oxidation discoloration immediately adjacent to the weld and in the parent metal but to a superficial depth. Corrosion susceptibility appears to be on the AL-6XN side of the weldment where possible intergranular attack occurs in the HAZ and pitting occurs in the parent metal.

By mechanically polishing the ID of the weld area, significant improvement in both breakthrough time and E_{PIT} is seen. The Inconel 22 discolored to a lesser degree and the significant attack appeared to be on the AL-6XN portion. By far, the best corrosion protection is obtained by electropolishing the ID after welding. However, oxidative discoloration is still seen on the Inconel 22, but the significant corrosive attack still occurs on the AL-6XN. It should be emphasized that this is a very limited study performed on a single sample of each surface condition. Also, the pitting potential and G-48 test parameters were under development as part of this study. We

Id Number	Weight at 0 Hours	Weight at 24 Hours at 50°C	Weight at 48 Hours at 50°C	Weight at 72 Hours*	Weight Loss after 72 Hours**	% Weight Loss after 72 Hours**
Electropolished G-48 SEGMENT INCONEL 22/AL-6XN	18.7789 grams	18.7741 grams	18.7737 grams	18.6437 grams	0.1352 grams	0.72 %
* 60 hours at 50°C and 12 hours at 60°C ** Essentially, all weight loss occurred after 12 hours at 60°C						

Table D. G-48 results.

Figure 10. Photographs of G-48 pitting corrosion segment.
A. Electropolished segment at 0 hours.
B. Electropolished segment after 72 hours.

should like to expand this study to obtain statistical validation of our conclusions.

Furthermore, since we have shown that CHELANT passivation of AL-6XN removes significant levels of iron from the alloy surface, improving Cr/Fe Ratio by 100%, it would be most prudent to explore the corrosion improvement obtained by passivation of the as-received welds.[1]

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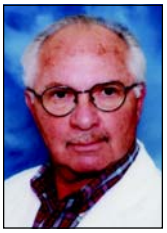
Acknowledgments

Alloy tubing was provided by Theo Wolfe at Fluid Line Technology.

Dedication

Theo Wolfe at Fluid Line Technology initiated this study and this article is dedicated to his memory.

About the Authors



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This article describes the effects of methyl jasmonate elicitation on the alkaloid production of *Catharanthus roseus* cell suspensions.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

Increasing Alkaloid Production from *Catharanthus roseus* Suspensions through Methyl Jasmonate Elicitation

by Jennifer L. Gaines

This article won the undergraduate level award at the ISPE Boston Area Chapter's Student Poster Competition in the spring of 2003, and went on to compete in the International Student Poster Competition at the ISPE Annual Meeting in November 2003.

An exceedingly large population relies on pharmaceuticals derived from plants. The *Catharanthus roseus* plant produces two anti-cancer compounds, vincristine and vinblastine, as well as the anti-hypertensive and sedative compounds, ajmalicine and serpentine. Through plant cell culture, these pharmaceuticals can be made more available to those in need. Plant cell culture offers controlled conditions for rapid cell reproduction without depleting natural resources. Methyl jasmonate elicitation was utilized to increase the production of the alkaloids in the cell suspension cultures. Two fold and five fold increases in serpentine and ajmalicine production were obtained when methyl jasmonate was introduced to cell suspensions on day 6 of growth at a concentration of 10µM and 100µM. The implementation of agar immobilization did not increase alkaloid production in conjunction with methyl jasmonate elicitation.

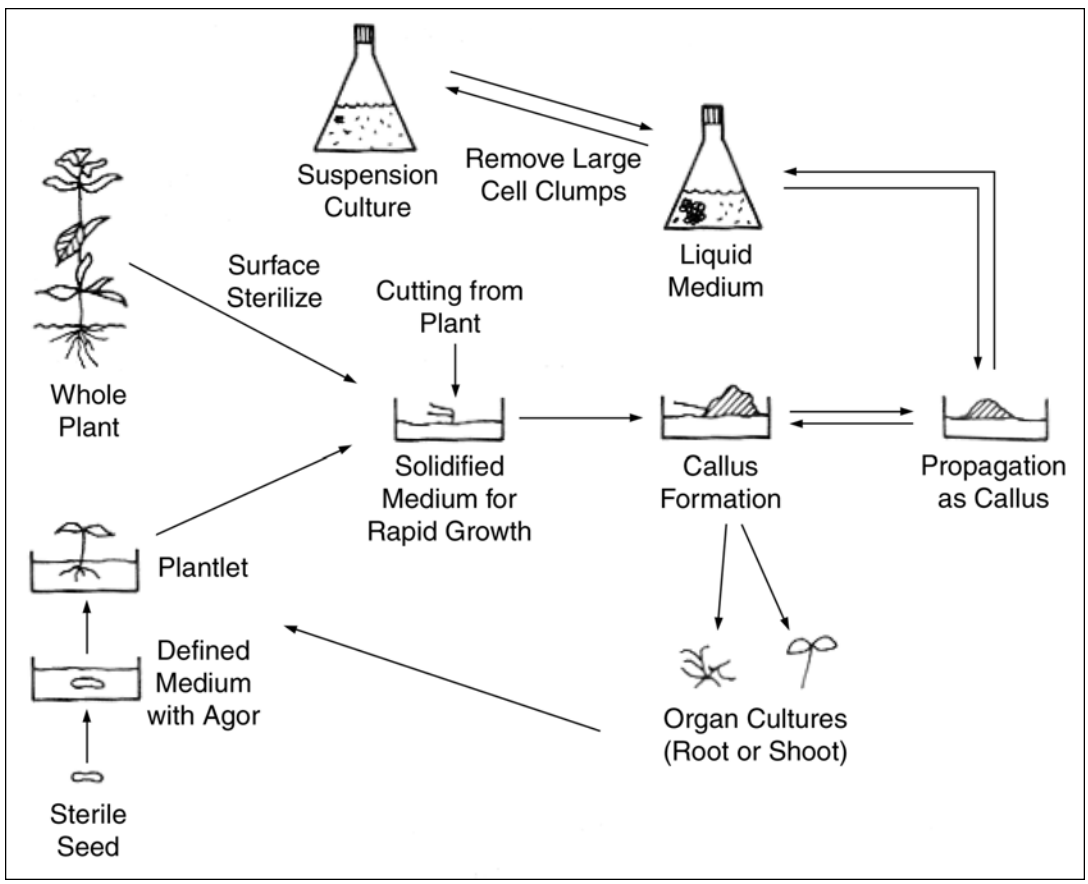

Figure 1. Establishing a plant cell culture.[1] Illustration of the steps involved in establishing a cell suspension culture.

"Through plant cell culture, pharmaceuticals can be produced on a large-scale in turn increasing the accessibility of the product."

Introduction

It is estimated that 75% of the world's population is dependant upon plant-derived pharmaceuticals. Some very common plant-derived pharmaceuticals include quinine which is an anti-malarial from the *Cinchona ledgeriana*, codeine from the *Papaver somniferum*, and paclitaxel, an anti-cancer treatment from the *Taxus brevifolia*. Affordability and availability of pharmaceuticals are the most prevalent issues facing the world today. The need for methods of increasing the production of plant-derived pharmaceuticals cost-effectively and with environmental consideration is becoming more important. Through plant cell culture, pharmaceuticals can be produced on a large-scale in turn increasing the accessibility of the product.

Of particular interest are the pharmaceutically valuable alkaloids from the *Catharanthus roseus* (Madagascar periwinkle). These include ajmalicine (anti-hypertensive), serpentine (sedative), vincristine and vinblastine (anti-cancer). The compounds range in price from $30,950 per kg ($14,068 per lb) to $36 million per kg ($16.4 million per lb). An increase in production of these pharmaceuticals through plant cell culture will result in greater accessibility and affordability of the product.

Background

Figure 1 illustrates the steps involved in developing a plant cell culture suspension. Establishing a cell culture suspension begins with a sterile seed or cutting from the plant. The sterile seed or cutting is placed on a solid media known as agar, usually in a Petri-dish. The agar contains vitamins, sugars, salts, and hormones necessary for growth. The piece of plant (either from the cutting or plant growth from the seed) is allowed to incubate on the agar until a callus has formed. The callus is an undifferentiated and aggregated mass of cells similar to a stem cell in the human body in that it is not assigned to a specific role as a plant cell. The callus is transferred into liquid medium that contains the same vitamins, sugars, salts, and hormones. Cells are sloughed off of the aggregate and a more homogeneous cell suspension is formed. The cells must be continually transferred into fresh media in order to keep the plant cells in a live and reproductive state.

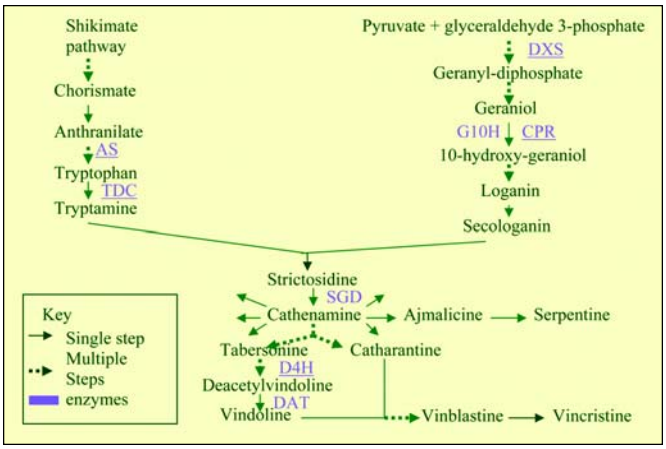

Figure 2. Biosynthetic Pathway of *Catharanthus roseus* Alkaloids.[2] Outline of the series of reactions that occur within the *C.roseus* cell.

There are numerous benefits to utilizing plant cell culture. These benefits include the ability to control the growth conditions of the culture, such as nutritional and supplemental components in the media, light, temperature, pH, and oxygen (or dissolved gasses). Preservation of natural resources also can be experienced because plant cell culture allows for the rapid reproduction of plant cells without the need for depletion of natural crops or disturbance of surrounding wildlife for product extraction. A particularly important benefit is the ability to manipulate and improve the production of desired compounds within the plant cell through experimentation with cell culture.

In order to manipulate and improve the production of a desired compound, there must be knowledge of where or how the compound is produced within the naturally occurring plant. Figure 2 illustrates the series of complex reactions that occur within the *Catharanthus roseus,* known as its biosynthetic pathway. Ajmalicine, serpentine, vincristine and vinblastine are known as secondary metabolites and are found toward the bottom of the illustrated series of reactions. Secondary metabolites are compounds within the plant that participate in reactions within the metabolic pathway, but do not contribute to the growth of the plant. With knowledge of these reactions, experimentation is conducted to manipulate the production of the pharmaceutical compounds.

Increasing the production of the pharmaceutically valuable compounds was attempted through methyl jasmonate elicitation. Methyl jasmonate is a compound that has been known to stimulate reactions within the metabolic pathway of the *Catharanthus roseus*. Given the precursory compounds necessary for reaction are present, methyl jasmonate will help that the reaction to completion. The following experiments were performed with the intent of increasing the alkaloid production of the *Catharanthus roseus* by the treatment of cell suspensions with methyl jasmonate.

Timing of Methyl Jasmonate Addition

The first of two experiments involved the timing and dosage of methyl jasmonate addition. The purpose of this experiment was to determine the optimal time and concentration of methyl jasmonate to introduce to the cell suspension culture. Effects of methyl jasmonate elicitation may be different depending on the concentration of methyl jasmonate and the state of the cell upon addition. The *Catharanthus roseus* has

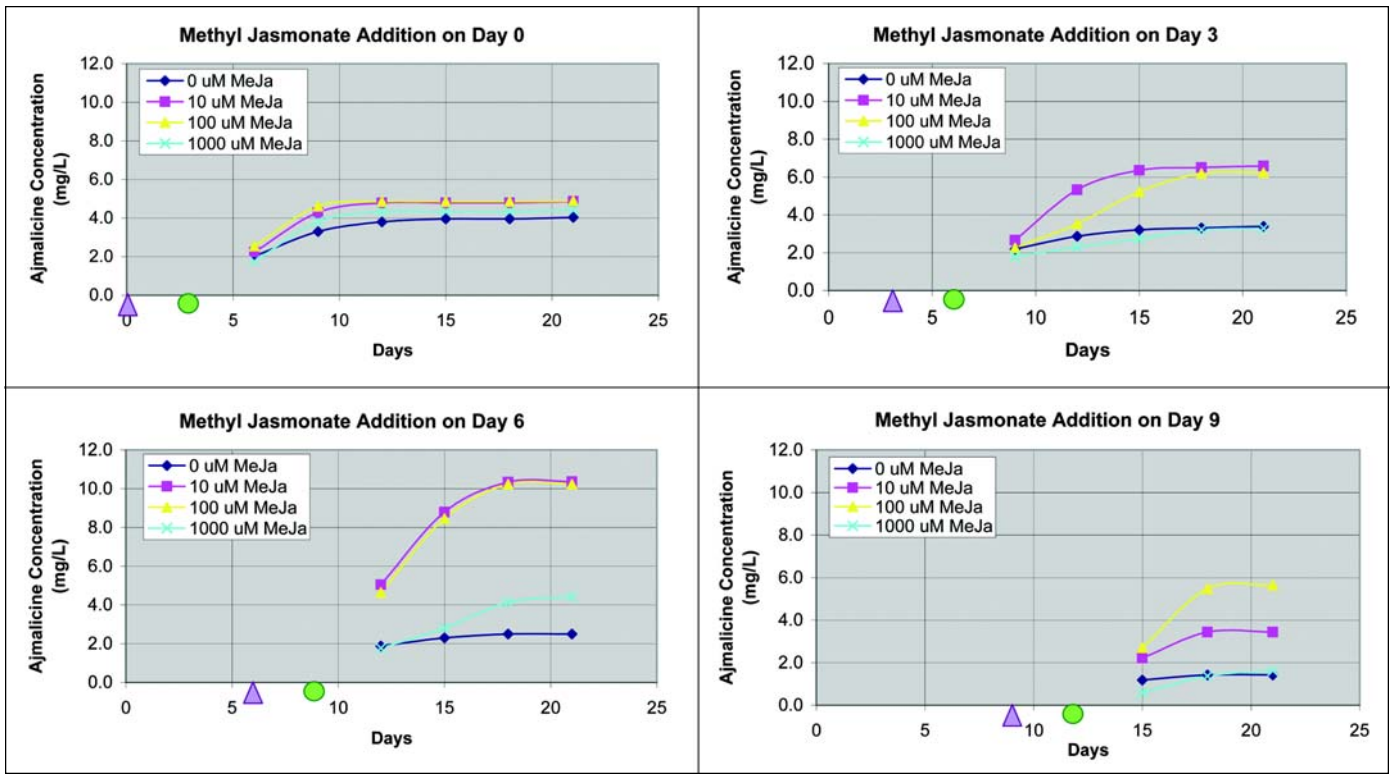

Figure 3. Effect of MeJa Timing and Dosage on Ajmalicine Concentration. Shows the cumulative ajmalicine production over the span of the experiment for methyl jasmonate addition on day 0, 3, 6, and 9 (day 12 and 15 not shown).

a 15 day growth cycle. From the day that cells are introduced into fresh media (subculture, day zero) to day three of growth, the cells are in what is known as a lag phase. During the lag phase, cell growth is slow because the cells are acclimating to the fresh media and begining the uptake of nutrients from the media. From day three to day nine is an exponential phase of growth where the cells have acclimated to their environment and are rapidly growing and reproducing. Day nine to day 15

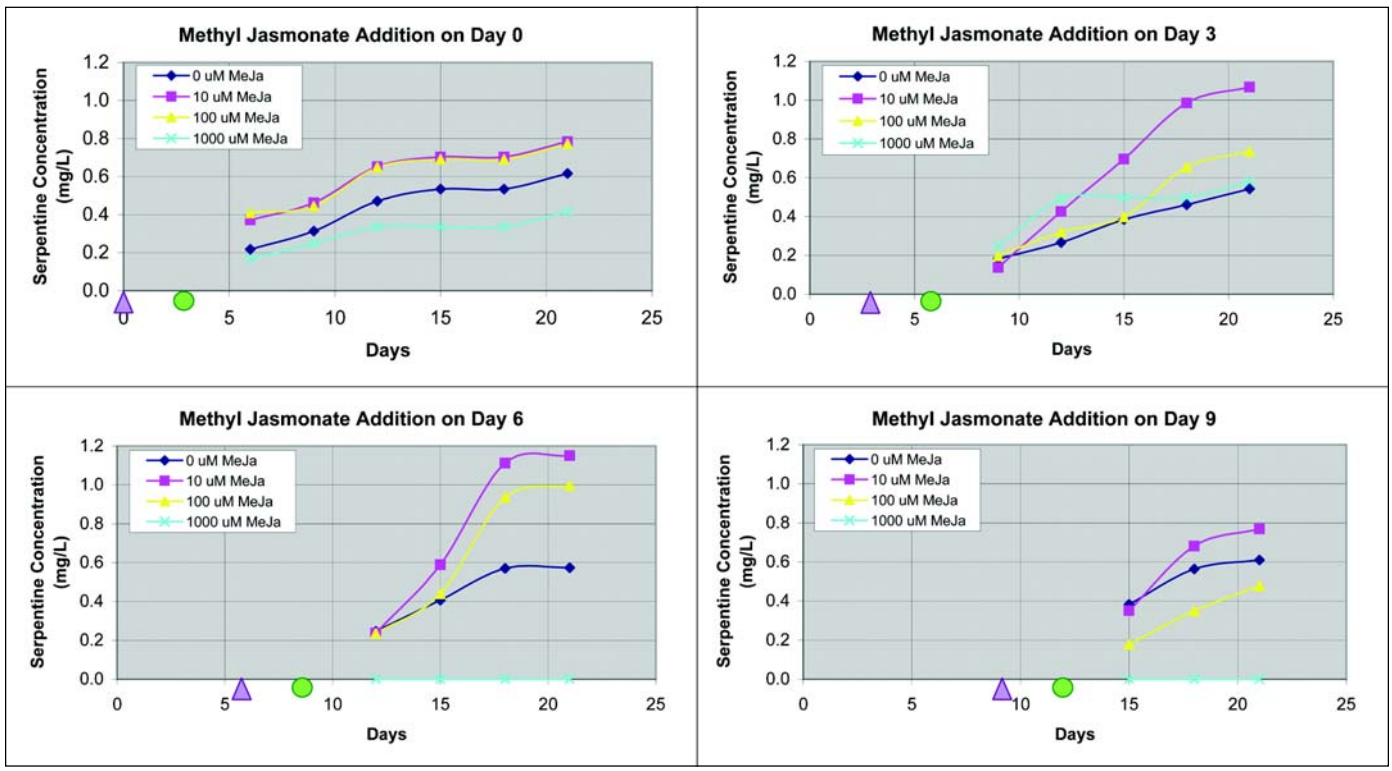

Figure 4. Effect of MeJa Timing and Dosage on Serpentine Concentration. Shows the cumulative serpentine production over the span of the experiment for methyl jasmonate addition on day 0, 3, 6, and 9 (day 12 and 15 not shown).

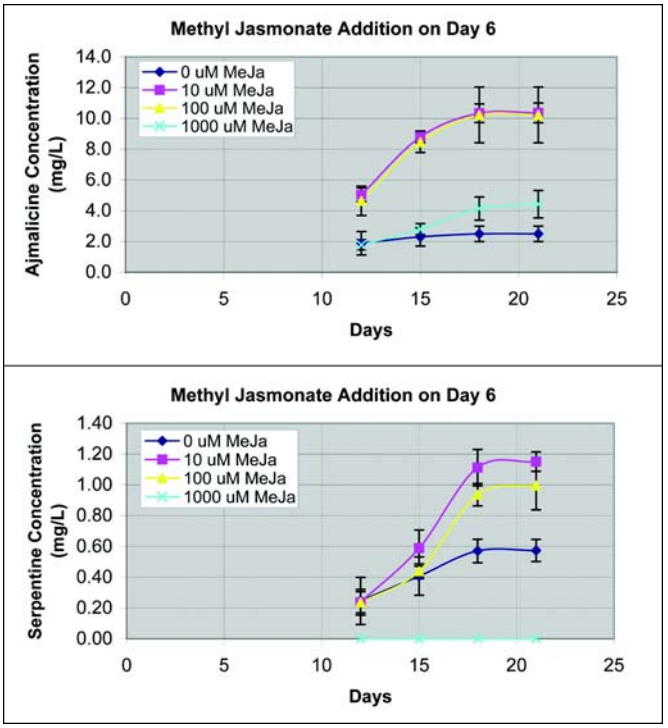

Figure 5. Highest Ajmalicine and Serpentine Productions. Focuses on the optimal time and dosage of methyl jasmonate addition.

is a deceleration phase where the cells have used most of the available nutrients and are producing some toxic by-products. Growth is slowed and transfer into fresh media is necessary for the survival of the cells. Addition of methyl jasmonate at different concentrations and during the different periods of growth resulted in a relatively comprehensive optimization study.

Method

Catharanthus roseus cell line A_{11} was obtained from the laboratory of Dr. Carolyn Lee-Parsons at Northeastern University. Methyl jasmonate addition was studied at concentrations of 0, 10, 100 and 100µM within the cell suspension. Each concentration of methyl jasmonate was added on either day 0, 3, 6, 9, 12, or 15 of growth. 1g (0.0022lb) of XAD-7 resins (Sigma) were introduced into the cell suspension three days after the methyl jasmonate addition and after which exchanged for fresh resins every three days through the termination of the experiment. The alkaloids produced from the cell suspension were adsorbed onto the resin. The alkaloids were then removed from the resin with a series of methanol washes and analyzed for content by high pressure liquid chromatography.

	Ajmalicine (mg/L)	Serpentine (mg/L)
Suspension	4.1 +/- 0.65	0.72 +/- 0.12
Heated	4.4 +/- 0.97	0.77 +/- 0.18
Agar Immobilized	1.5 +/- 0.65	0.32 +/- 0.16

Table A. Effect of Agar Immobilization on Alkaloid Production. Shows the cumulative ajmalicine and serpentine production over the span of the experiment for cell suspensions, heated cell suspensions, and agar immobilized suspensions.

Results

Results are shown in Figures 3 and 4. The charts indicate cumulative production of the alkaloids (ajmalicine or serpentine) over the span of the experiment (21 days). For clarification, the purple triangles indicate the day of methyl jasmonate addition and the green circles indicate the day of resin addition. In terms of both ajmalicine and serpentine, an increase in production is observed when methyl jasmonate is introduced on day three as opposed to day zero. A greater increase in production is observed with methyl jasmonate addition on day six as opposed to day three. A decrease in production is observed when methyl jasmonate is introduced on day nine. A further decrease in production is observed when methyl jasmonate is added on day 12 and also day 15 (both not shown). Addition of methyl jasmonate on day six of cell growth appears to lead to the greatest production of the alkaloids. As seen in Figures 3 and 4, concentrations of 10µM and 100µM of methyl jasmonate elicited the most optimal production. Figure 5 focuses on the day six addition of methyl jasmonate. There were replicates of each methyl jasmonate addition on each day in order to determine standard deviation and error within the experiment. Figure 5 includes error bars to illustrate this. The error bars overlap and indicate that the effects from adding 10µM and 100µM on day six may be equal for both ajmalicine and serpentine.

Discussion

It is possible that the greatest alkaloid production was achieved with methyl jasmonate addition on day six of growth because at that point the cells had become accustomed to their environment, as well as in a healthy state of growth with plenty of nutrients and negligible by-product accumulation. The effects of 10µM or 100µM of methyl jasmonate addition show a five fold increase in terms of ajmalicine production and a two fold increase in terms of serpentine production over a 0µM concentration. Although the methyl jasmonate elicitation was successful in increasing the production of the alkaloids, multiple tactics may be utilized to further increase productivity.

Agar Cell Immobilization

The second of two experiments studies the use of agar immobilization in conjunction with methyl jasmonate elicitation. Cell immobilization occurs when cells are trapped or encased in a material such as mesh, gel, or a polymer. The growth is restricted while at the same time allowing mass transfer of media and dissolved gasses. Agar immobilization involves the same agar that was used as a solid growth media as the immobilizing agent. Benefits to studying cell immobilization include a decrease in shear stress that the cell may experience in suspension because of a protective coating given by the immobilization material. In some instances, cells have been known to excrete the desired product into the media.

This allows for cell reuse because the cell does not need to be damaged in order to obtain the desired product that is simply within the media. Immobilization also may increase production in certain cell types. The purpose of the second experiment was to determine how restricting growth through agar immobilization in conjunction with methyl jasmonate elicitation affects alkaloid production.

Method

The A_{11} cell line was used to study agar immobilization. In order to determine the effects of restricted growth with methyl jasmonate elicitation, agar immobilized suspensions were compared to cell suspensions and heated cell suspensions. A heated cell suspension was included because the agar is heated upon mixing with the cells. Heating effects were studied in order to ensure that the resultant alkaloid production from the agar immobilization was due to restricted growth and not heat. In order to immobilize a cell suspension in agar, the plant cells are mixed with warm agar at 50°C and poured in a flask to cool. The agar which contains the necessary nutrients and hormones quickly hardens around the cells rendering them immobilized. The immobilized cells simply resemble a thin film of agar with cells trapped inside. The thin film is then placed in fresh liquid media where it incubates for the duration of the experiment. Methyl jasmonate was added to all suspensions on day zero at a concentration of 100µM. 1g (0.0022lb) of XAD-7 Resins were added three days after the methyl jasmonate addition and exchanged for fresh resins every three days until the termination of the experiment. The alkaloids were adsorbed onto the resins and then recovered with a series of methanol washings similar to the prior experiment. The alkaloid content was analyzed by HPLC.

Results

Results are shown in Table A. The table indicates cumulative production of the alkaloid (ajmalicine or serpentine) over the span of the experiment. The experiment was performed in replicate in order to determine standard deviation and error. From Table A, it is clear that there is not a great difference between the alkaloid productions of the cell suspension as compared to the heated cell suspension. The alkaloid production resultant from agar immobilization is notably lower than both the cell suspension and the heated cell suspension. Because the heated cell suspension was included in the experiment, it is determined that the decrease in alkaloid production can be attributed to restricted growth and not heat effects.

Discussion

Numerous reasons could be given as to why agar immobilization caused a decrease of alkaloid production. It is possible that the restricted growth was too much of a stress to the cell itself or in conjunction with the methyl jasmonate elicitation. It also is possible that agar may not be the optimal immobilizing material for this particular cell.

Conclusion

Methyl jasmonate elicitation has shown a definite effect on alkaloid production in the *Catharanthus roseus*. As the first of two experiments shows, optimal timing and dosage are necessary in order to obtain the largest alkaloid production. The optimal time and dosage of methyl jasmonate addition to the *Catharanthus roseus* cell suspension is day six of growth at either a concentration of 10µM or 100µM. The maximum ajmalicine production was 10.4 ± 0.6 mg/L ($8.67x10^{-5} \pm 5x10^{-6}$ lb/gal) and the maximum serpentine production was 1.15 ± 0.06 mg/L ($9.58x10^{-6} \pm 5x10^{-7}$ lb/gal). These concentrations were obtained with methyl jasmonate elicitation during a period of rapid and steady cell growth.

Conversely, while growth is restricted, the cell suspension decreased alkaloid production. Methyl jasmonate elicitation joined with agar immobilization did not successfully increase alkaloid production. *Catharanthus roseus* cell suspensions and heated cell suspensions obtained ajmalicine productions of 4.1 ± 0.65 mg/L ($3.42x10^{-5} \pm 5.42x10^{-6}$ lb/gal) and 4.4 ± 0.97 mg/L ($3.67x10^{-5} \pm 8.08x10^{-6}$ lb/gal) respectively and serpentine productions of 0.72 ± 0.12 mg/L ($6x10^{-6} \pm 1x10^{-6}$ lb/gal) and 0.77 ± 0.18 mg/L ($6.42x10^{-6} \pm 1.5x10^{-6}$ lb/gal) respectively. Lower concentrations were obtained with the agar immobilized suspensions as ajmalicine production was 1.5 ± 0.65 mg/L ($1.25x10^{-5} \pm 5.42x10^{-6}$ lb/gal) and serpentine production was 0.32 ± 0.16 mg/L ($2.67x10^{-6} \pm 1.3x10^{-6}$ lb/gal).

Recommendations

Further experimentation is recommended in order to narrow the findings of the two described above. Timing and dosage of methyl jasmonate elicitation can be further optimized by studying a range of methyl jasmonate concentrations between 10µM and 100µM with day six addition. If desired, it may be possible to pinpoint the optimal time of methyl jasmonate addition to the hour within the sixth day of growth.

Further exploration into cell immobilization could be beneficial with the study of a different material as the immobilizing agent. Cell immobilization could simply be an undesirable tactic to increase alkaloid production, or agar could be an undesirable immobilizing material. It also is possible that methyl jasmonate and agar immobilization together do not create an optimal environment for the cell suspension. Additional study into these issues could result in knowledge as to how alkaloid production in the *Catharanthus roseus* can be further increased.

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Acknowledgments

Experimental work was performed in the laboratory of Dr. Carolyn Lee-Parsons at Northeastern University. Further acknowledgments include Kevin Cash, Seda Ertuk, and Amber Royce for their gracious support as colleagues. The author would like to thank ISPE and AIChE for the opportunity to present this research to its members and for their support of undergraduate research. Northeastern University undergraduate research fund, NSF, and Louis Stokes Alliance for Minority Participation (LSAMP) all offered their support and helped make these studies possible.

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Jennifer Gaines graduated in May 2004 with a BS in chemical engineering from Northeastern University. She will continue attending Northeastern University to obtain a master's degree in chemical engineering. Gaines has had the opportunity to present her research at a national level to both ISPE and AIChE in the past year. She can be contacted by email: gaines.j@neu.edu.