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An Integrated Approach to Design, Commissioning, and Validation

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This article addresses opportunities to find efficiencies and savings along the spectrum of critical services that includes design, commissioning, and validation.

Introduction

The costs of bringing a Biopharmaceutical product to the domestic or international marketplace are enormous and growing. These include, but are not limited to, the cost of research and development, clinical trials, capital for facilities and equipment, expenses for operations, and controls infrastructure. Key components of these costs are architectural and engineering design for facilities and equipment, construction, start-up, commissioning, and validation. This article addresses opportunities to find efficiencies and savings along the spectrum of critical services that includes design, commissioning, and validation.

Food and Drug Administration (FDA) regulations (cGMPs), put in place to protect the public health, have increased in stringency and reach. An unavoidable result of this rigorous regulatory environment is that the cost of bringing a biopharmaceutical product to market continues to climb. Compliance requirements have extended the entire project delivery time frame, potentially delaying production start-up.

One area that increasingly impacts schedule and cost is the validation phase of the product-to-market process. This final substantiation of process and product is highly regulated and extensive; documentation requirements and the associated costs have grown considerably. Conversely, the design phase of a product process has remained stable and even been shortened by the increasing application of technology such as computer modeling and Computer-Aided Design and Drafting (CADD).

As validation costs continue to rise, a well-documented middle stage, the commissioning phase, becomes more critical to start-up and de-bugging activities. More stringent commissioning activities can reduce potential devia-

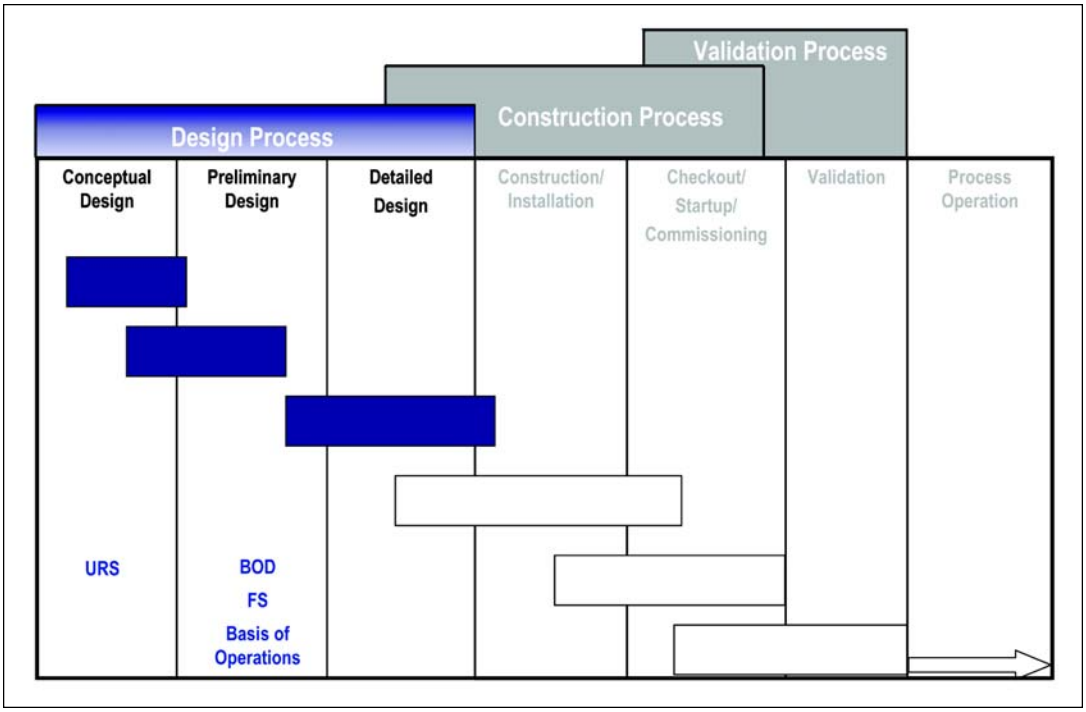

Figure 1. Traditional project process.

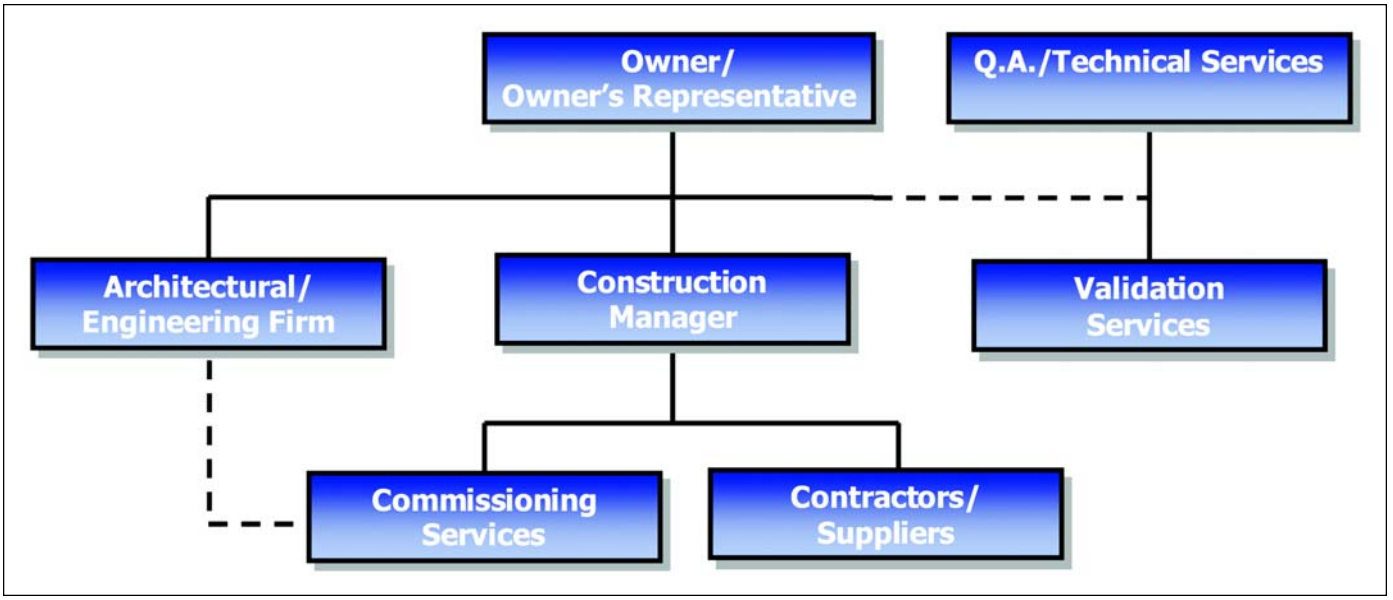

Figure 2. A traditional team organizational model.

tions and drive down validation costs. This understanding has led some design professionals to adopt "enhanced commissioning," a process by which start-up and de-bug are put to more rigorous testing prior to validation. When these activities are documented to a high degree they can be referenced in validation documents, saving a repeat of the activity at the validation phase.

All enhancements in design, commissioning, and validation have been developed to maintain the intent of the regulations and ensure a quality process. However, for varied reasons, design, commissioning and validation have evolved as independent, discrete processes. This inherently adds to cost, and leads to redundant activities and delays in delivering product to the marketplace.

By moving elements of commissioning and validation upstream or closer to design (Integrated Approach), a project team can better accomplish design qualification, and reduce schedule and cost of a project while at the same time meeting compliance measures and maintaining all checks and balances. This "Integrated Approach" is practical, and if structured and managed properly, works.

This article focuses on the three phases of the product process (design, commissioning, and validation) that are in reality intimately related. It addresses how the combined cost and schedule of these phases can be integrated to reduce lifecycle costs and time to market, and provide a greater assurance of a successful launch. The article also briefly examines the traditional approach to completing these steps and discusses some elements of a well-structured "Integrated Approach," the role of technology, and some case studies.

What is an Integrated Approach?

Definition - In·te·grat·ed Ap·proach to De·sign / Com·mis·sion·ing / Val·i·da·tion – a project approach that considers the elements of design, commissioning, and validation, and ensures all of these elements work together to improve efficiency, thus reducing project schedule and costs. The approach considers what each element requires and optimizes the individual elements to integrate with each other. The approach front-end loads the commissioning and validation elements during the design phase while at the same time, helps build in design quality.

Elements of an Integrated Approach

The elements of an "Integrated Approach" are design, commissioning, and validation. Each has a distinctive and unique role in the life of a successful project. However, the processes can be structured to work in tandem to improve efficiency.

Design

Design or technology transfer from Research and Development (R&D) to a production facility is the managed process of developing a conceptual design, to preliminary design to detailed design - *Figure 1*. This process includes the recommended steps of User Requirement Specifications (URS), functional specifications, Basis Of Design (BOD), as well as a basis of operation, training, etc. Design is developing a complete set of architectural, engineering, and controls deliverables such as specifications for building materials, equipment, instruments, and controls. It also includes directives as to how they are to be built, installed, and operated to produce a very specific (specified) quality of product. Drawings are developed as a deliverable to show exactly how everything is to be constructed and installed. Once the facility is built, and the process equipment and controls are installed in the facility, all must be commissioned and validated.

There are two obvious improvements to be made to the design phase.

Design Deliverables Must Become More "User Friendly"

"Know your audience" is good advice to anyone delivering a message and has relevance in the area of biopharmaceutical engineering. The audience is comprised of many stakehold-

ers, such as engineering, production, and quality groups within the client organization as well as the contractors who will implement the design. The design team assumes responsibility for delivering clear specifications to this audience. The validation execution phase of the project is not the optimum learning ground for the production and quality groups. All end users need to know some basic information about their new process: *What is it? What does it do? How does it do it?* If a design phase concludes with ill-informed end users, it is a poor reflection on the information flow related to the project.

There are many challenges in creating a team where each member is informed about the detailed design and the quality and production impact of that design. Among those challenges:

- Quality and Production team members do not always understand the engineering possibilities and restraints.
- Engineering team members do not always understand the quality and production implications of the design.
- Not all team members are aware of the project budget and schedule restraints.

URS is a useful tool to transfer information among the various disciplines. It provides an opportunity for early and sustained involvement by many stakeholders. As the name implies, it outlines the user requirements; however, it is not necessarily the users' sole responsibility to draft the document. Ironically in many situations, the designer may be the best informed to provide the preliminary draft of user requirements.

A URS is an appropriate prerequisite to the Enhanced Design Review Process. The format for the URS can be varied, but put simply, it should include the following:

- a system description (narrative)
- a Process Flow Diagram (PFD)
- a list of system inputs (utilities, user interfaces, materials)
- a list of system outputs (alarms, product, byproducts)
- a list of the processes contained within the system (controls etc.)

Once compiled, this information will provide the project team with a forum for discussion and clarification on the system.

Enhanced Design Review

The International Society for Pharmaceutical Engineering (ISPE) has published valuable guidance in the Baseline Guide® on Commissioning and Qualification, and has addressed the issue of "structured design review." Structured design review is a process by which selected stakeholders in the system's design and use come together in an organized way to review the design for compliance to cGMP and other user requirements. Typically, there are representatives of the design team, production team, quality, and regulatory groups. The concept is simple and can be executed at a suitable time in the design process, usually at the conceptual stage and then again at a later stage (typically 80% design) for a "system by system" review. The outputs are numerous, but can include:

- proof that the design was qualified, i.e., old fashioned Design Qualification (DQ)
- suggestions, objections, and clarifications between the design team and the other stakeholders
- identification of commissioning and validation needs (an excellent example of where integration can really impact team efficiency as design, commissioning, and validation disciplines work together up front to identify all the needs of each discipline; it is also practical to utilize design team personnel on the commissioning team)
- assessment of the system impact, i.e., is the system direct impact, indirect impact, or no impact

One method that works well is similar to the Hazard and Operability (HAZOP) or Hazard Analysis Critical Control

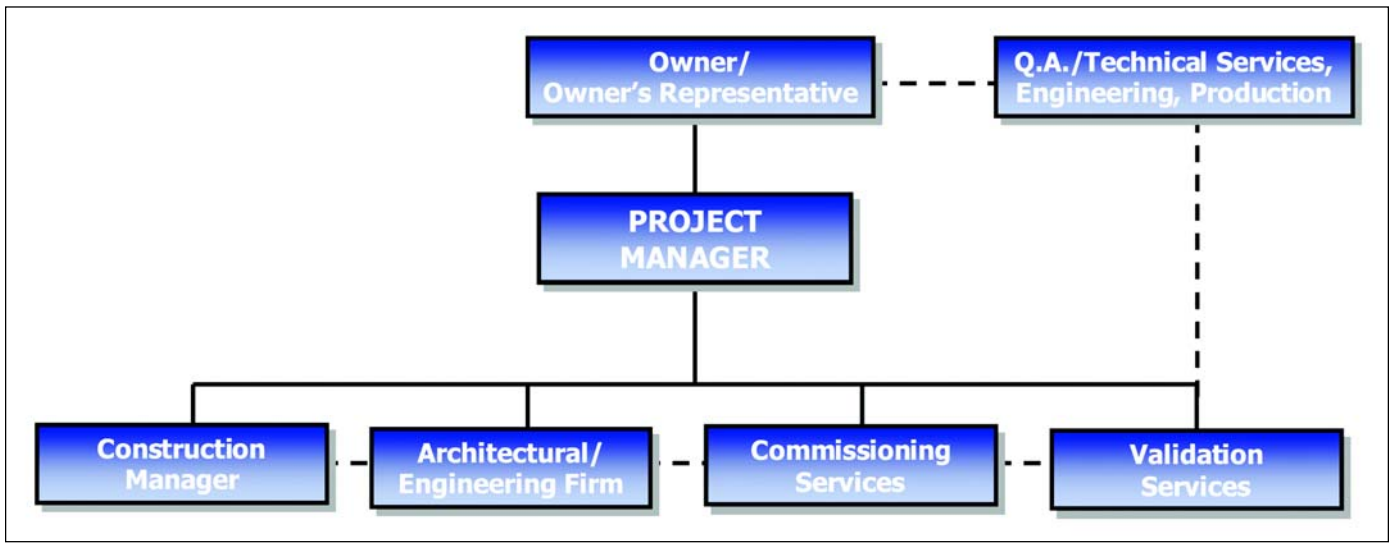

Figure 3. An integrated team organizational model.

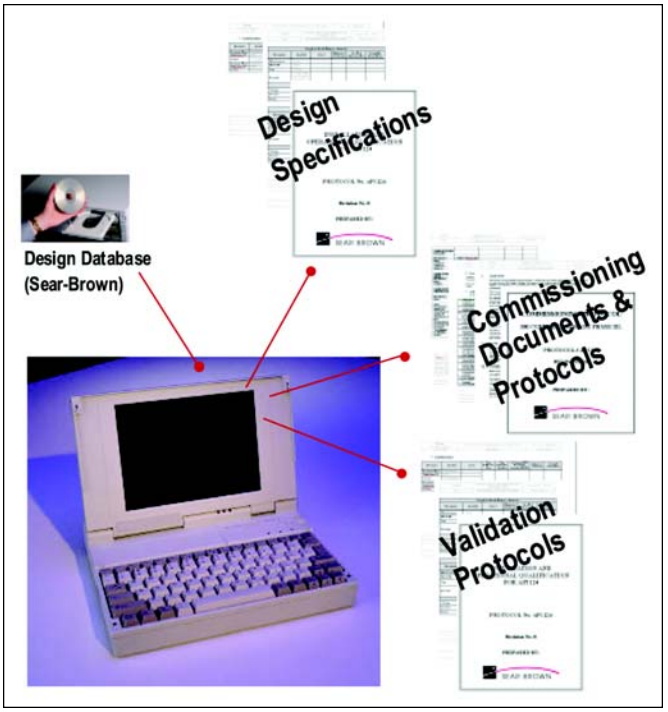

Figure 4. Design database system.

Point (HACCP) process. Each system is defined in terms of its boundaries. The system is described (typically by the designers) to the project team. The ideal format is the URS. Once the project team has been given an opportunity to understand the proposed system, a facilitator will take the team through a series of questions (evocative in nature) concerning the GMP impact of the system. Concerns are raised and changes are proposed. All this is documented with attendee lists, design document references, action items, changes, and concerns.

Many companies are beginning to add a greater degree of specificity and detail to the enhanced design review process, tightening up methodology and documentation, requiring use of a qualifications protocol.

Commissioning

Commissioning can be viewed as a process of proving that what was designed and specified was in fact installed and meets its intent from engineering design and business perspective, e.g., *does the air handler meet the design criteria for airflow, temperature, humidity, and air quality as specified? Does the pump put out the correct flow of fluid at the correct pressure?*

Commissioning is most beneficial when performed concurrently with construction activities. In fact, many of the subparts of commissioning documents focus on recording construction activities.

Proper tagging and identification of systems and equipment, if performed early in the design process, benefit all of the subsequent steps of commissioning and validation and provide a link to such things as training, spare parts, maintenance procedures, equipment records, operating procedures, and cleaning procedures.

Commissioning must become more rigorous if it is to be an effective partner in an "integrated approach." Although essential from a safety and business perspective, commissioning sometimes fails to deliver sufficient documentation and often falls short in addressing failures. Skilled commissioning professionals (and we include Site Acceptance Tests - SAT in that mix) are invaluable to a process start-up. These experienced individuals are ultimately charged with ensuring that everything works as designed and in concert. Here again, design team members can and do make excellent commissioning team members, not only in the documentation development phase, but also in the commissioning execution phase. The results, in some cases, can be better integration and impact to schedule and cost reductions.

Good Documentation Practices

- how the commissioning documents are created
- how the commissioning documents are executed

Commissioning documents do not need to be as rigorous as their validation document cousins, but they must have at a minimum:

- a clear scope (what is being commissioned)
- clearly defined acceptance criteria
- some degree of pre-approval (project dependant)
- some degree of data review and document post approval
- a mechanism for reporting failures
- a mechanism for reporting retests

If the commissioning documents are to be used as a reference for validation, they must be executed with the proper cGMP documentation practices such as 'no white out,' single line strikethrough etc. However, commissioning cannot be as rigid as validation and allowance must be made for failures and ad-hoc changes to tests if proper documentation is generated. In this way, commissioning becomes a controlling, but not implacable process.

Commissioning Scope

Commissioning requirements are often limited to those systems that are installed under the scope of the construction management firm, typically those systems that require multiple disciplines to install. Systems delivered as packages are often excluded from the commissioning scope. These systems may fall through the cracks unless the end user or engineer has specifically requested commissioning prior to start-up. The scope of commissioning must include all equipment and systems associated with the project and should not be limited to those systems that directly serve production processes and quality laboratories.

If commissioning is to provide value beyond the safety and business needs of the project, it must address the entire project scope and abide by the principles of good documentation practices. The greatest potential for commissioning lies in its use as a reference document for validation activities, and in many cases, it can be used as a replacement for Installation Qualification (IQ). Indeed, when commission-

ing is properly performed with an eye on quality documents, it can lead to abbreviated Operation Qualification (OQ) tests.

Validation

Validation can be viewed as the process of proving that what was designed and installed meets its intent from a regulatory perspective, *e.g., proof that controls are in place to ensure that the HVAC system will protect product quality; proof that the agitator provides the proper mixing action.*

Note: Under the enhanced approach to commissioning/validation, much of the "proving steps" of validation can be performed concurrent with commissioning, and in many ways, are a review of properly executed commissioning documents. This reduces the overall time required for this project phase.

In order for validation to reap the rewards of the changes to the design and commissioning strategy, it must better reflect the work that occurs during these earlier stages. Validation documentation should reference commissioning testing. Moreover, validation team members must support and deliver input to the structured design review. In order to accomplish this, the validation team members should be a part of the "integrated" team at the outset of the project.

Enhanced Design Review

This step described earlier in the design phase of a project is an optimum time for validation to influence a project design. At this stage, all requests can be considered, suppliers have not been selected, and the user requirements can be enhanced to include the following:

- What documents must the supplier provide?
- How are instruments to be calibrated?
- What training must contractors complete?
- What testing are suppliers required to perform?
- What test results (including format) must be provided?
- What system performance criteria have been set?
- What are the rules for pre-approval of contractors test sheets?

Certainly, these validation-related items are a part of Enhanced Design Review, but they also are included and executed during commissioning. By referencing the commissioning documents, in whole or in part, a condensed abbreviated validated IQ/OQ can be achieved.

Overall, the enhanced design review process provides the quality and validation groups a chance to outline their requirements during design and also allows potential suppliers to access the rigor of testing and documentation required for such a project.

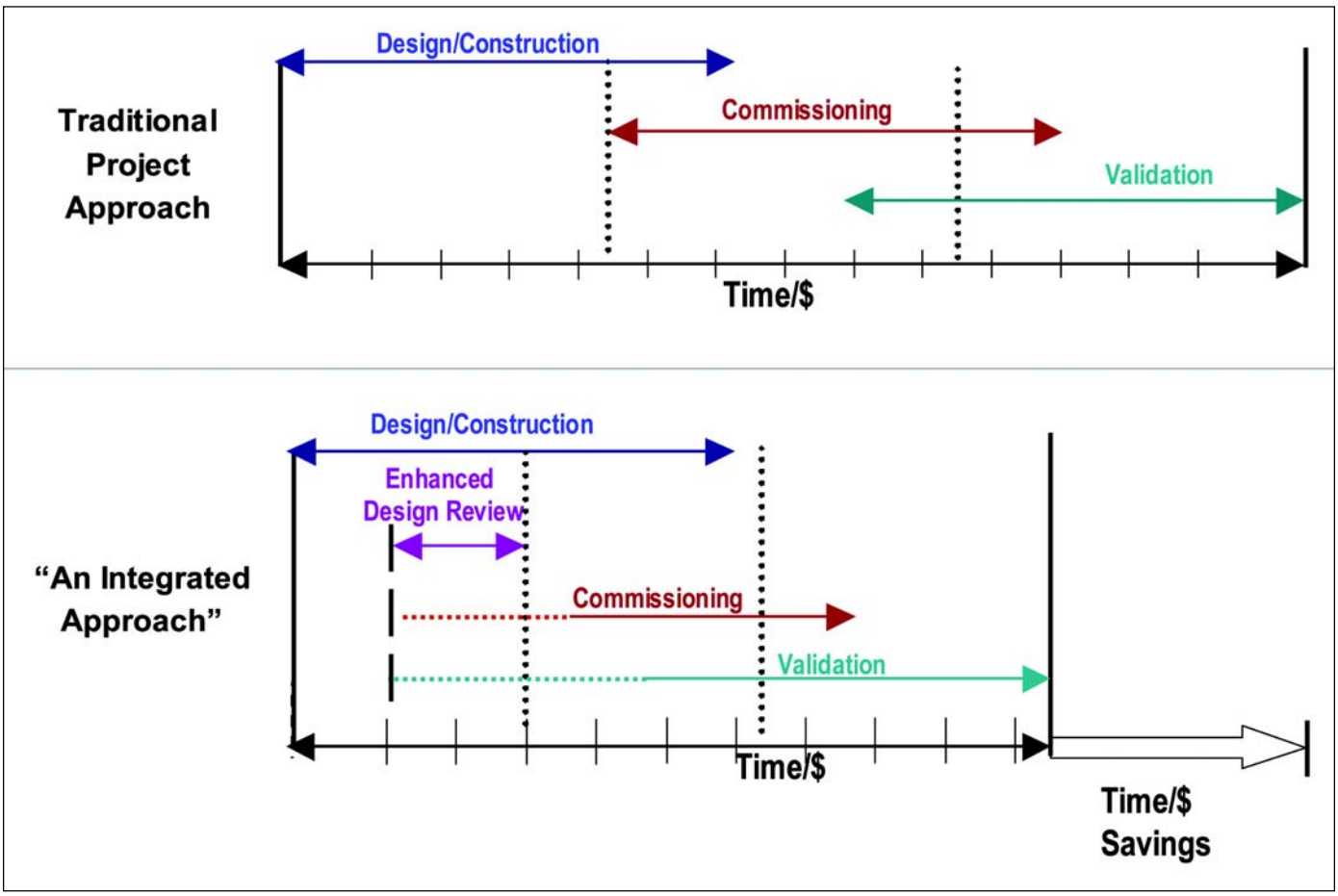

Figure 5. Traditional vs. integrated project approach.

Reference to Commissioning Documents

Many quality records are generated by technical experts with tools and capabilities outside that of the validation team. The "test and balance" of an HVAC system is a typical example; validation documents can be structured to allow for an 'either or' testing where the test can either be referenced or executed as part of the validation document. This approach provides the flexibility of using the commissioning reports or simply repeating the testing.

By using commissioning as a precursor, IQ/OQ phases will run more smoothly, reducing the time and costs required. This approach may actually dictate that the commissioning document now be considered a control document (depending on structure and interpretation). However, this approach has been proven successful and can play a greater role in the future to reduce schedule and costs of the validation process. Advantages of using a combined commissioning/validation strategy include:

- the same system boundaries are used for both commissioning and validation
- reduced duplication of testing
- fewer failures encountered during validation activities
- shorter schedule
- reduced overall cost
- streamlined project management

The commissioning and validation protocols are all developed and populated with data from the design specifications and lists. In design, one must establish the process (process description), develop Process Flow Diagrams (PFDs) and Process and Instrument Diagrams (P&IDs), which depict equipment, instruments, and controls (system components), and develop equipment and instrument and controls specifications and construction specifications (installation specifications), equipment lists, instrument and controls lists, drawing lists, and so on. All of this same data is compiled in the Design, Commissioning, and Validation documents.

Front-end loading of design data into protocol templates during the design phase, coupled with reduced deviations encountered during validation execution, could result in an estimated commissioning and validation cost savings of 10-15%.

The Integrated Team Model

In the traditional organizational model (Figure 2), a design team is set up and produces the facility and system drawings and specifications. For a multi-discipline project, a typical traditional team would include architects, engineers, and a construction manager. The team completes the design and respective documents and turns the design documents over to separate commissioning and validation teams. Both of these teams consist of document development specialists, execution specialists, and administration personnel. These teams usually operate independently of the design team. This traditional approach, some believe, facilitates the ability of the commissioning and validation teams to "challenge" the design.

The simple fact is this model works. However, it does not work efficiently or cost effectively. All too frequently, specifications are rewritten in several different formats using the same data.

Consider instead the formation of an integrated design, commissioning, and validation team comprised of a project manager, architects, engineers, suppliers, construction manager, commissioning specialists, and validation specialists - *Figure 3*. Under this model, the design team and commissioning specialists report to the Director of Engineering and the validation specialists report to the Director of Validation, thus maintaining an objective relationship to one another. These can be different firms, but it is not necessary that they be, as long as the team remains consistent.

The best model would be to integrate the sub-teams (design, commissioning, and validation) immediately at the start of the project. These teams truly work together as an "integrated" team. They share in the requirements each has for their specific project deliverables. In many cases, particularly between design and commissioning, individuals from the design team can take on commissioning document development responsibilities as well as commissioning execution responsibilities. This "integrated" model truly makes for better appreciation and knowledge of each sub-team member.

Crucial to the success of this team is strong project management by the client and the design and validation organization(s). Roles and responsibilities must be firmly in place with project plans, SOPs, and guidelines. If managed well, checks and balances remain firmly in place and the "Integrated Approach" works well. With Commissioning and Validation specialists on the Integrated team, Enhanced Design Review provides richly detailed input and requirements, which pays off down the line. In fact, Enhanced Design Review can be made a part of the process and a well-structured Enhanced Design Review protocol can be executed as the design is taking place.

The Construction Manager (CM) also should be a part of the integrated process. Indeed, the construction manager should be involved throughout design, commissioning, and validation together with their contractors and suppliers. Quality construction is paramount to the success of the commissioning process and the overall project success. CMs also can be of value in pointing out more practical ways to accomplish a design.

The Role of Technology

Databases are a powerful tool in today's workplace and should be used whenever possible and practical. They are an essential complement and enabler to the "integrated approach" of design, commissioning, and validation. When implemented properly, all design specification data is entered during the design phases of the project. Design specifications, commissioning protocols, and validation protocols can all become report functions of a well-structured database system.

The reputation of databases in pharmaceutical projects is mixed. Some industry experts swear by them while others frown on them as unnecessary and unreliable. The truth is that as with any other project tool, it must be used correctly and its role in the project must be defined and understood by the project owners. Controls system professionals often use databases in commissioning and start-up activities. It is relatively easy to create loop check-sheets and instrument check-sheets from an existing list of inputs and outputs (I/O). Some clients use databases to the extreme that all critical processing parameters are registered in databases and mapped to the various physical assets, control sequences, and operating procedures of the plant operation. Databases, as with any application, can be as simple or sophisticated as required.

A database can be described in terms of inputs, outputs, and processes.

- Database Inputs - typically this will be assets lists (equipment, instruments, I/O etc.) and design data.
- Database Outputs - what the database produces – typically these databases provide the project with asset datasheets and a variety of check-sheets and test plans. Commissioning and validation protocols can be set up as reports for database outputs.
- Database Processes - what the database does – assign tag numbers to categories, assign tests to categories, assign quality attributes to categories, etc.

The database can be an excellent tool in maintaining the integrity of the design/commissioning/validation approach. The assets lists and design data are usually readily available and in a format that makes populating the database easy. Design data sometimes must be manually entered (from various sources such as engineers, designers, shop drawings etc). Simple outputs for commissioning purposes such as receipt check-sheets are easily generated and offer the advantage of a standard format. At the end of the project, this data can migrate to the required enterprise operating systems.

As projects become more complex, the advantages of databases increase. Well-managed databases add a high degree of automation and can be very effective. Moreover, they provide legacy value by providing accessible basic design information that can migrate to the enterprise management system. These database systems also can be set up to be utilized for preventive maintenance, change control tracking, etc.

Is it more efficient to build a custom database, or to purchase a system off the shelf? That question can only be answered once an accurate picture of requirements is established. Therefore, a detailed User Requirement Specification for the project database should be prepared at the outset to aid in the decision.

With a well-structured design database system and tightly constructed commissioning and validation protocol templates (database reports), fields can be set up to populate protocols (at least to a 50 to 75% level) by the end of the design phase - *Figure 4*. As changes occur throughout design and construction, the database is amended and all documents and protocols are updated accurately. An estimated savings of 15-20% could be realized utilizing a well-structured design database system.

Case Studies

Elements of this integrated approach have been used on several recent projects with noteworthy success and a positive impact on schedule and budget. Key elements to project success were:

- project plans which defined roles and responsibilities
- strong project management
- excellent communication

API Facility 2002

An Active Pharmaceutical Ingredient (API) facility upgrade was requested and delivered in a 10-month period. The upgrade was designed, constructed, commissioned, and qualified.

This project offered some unique challenges in addition to the tight timeline. There was a much higher degree of process automation in the facility upgrade compared to the existing controls. There were four companies involved in bringing the project to completion including a construction manager, a design and commissioning firm, a process controls firm, and a validation consultant. The facility was to be upgraded and integrated into existing processes to allow for full production to resume at the required time.

Below are some key lessons gathered from the project team:

- Both a validation project plan and a commissioning plan were developed.
- System boundaries that were used by both the commissioning team and the validation team were developed.
- The construction management team together with the design and commissioning team executed the commissioning documents.
- The validation team had input into the commissioning protocols, software design specification, and the Site Acceptance Test (SAT) documents.
- Commissioning scope included a start-up of each equipment item and a test for its design performance. This applied to all pumps, agitators, etc.
- Site Acceptance Testing was completed with commissioning engineering functional runs.
- Validation documents were prepared to match the construction schedule, commissioning schedule, and the software installation schedule.

- Validation documents were prepared with an "either/or" scenario. If the testing could be referential in nature, the test need not be repeated. If rigor was deemed lacking, the test could be repeated in full during the validation phase of the project.

- Commissioning documents set forth a method for handling failures equivalent to the validation 'deviation' reporting method. Failures in commissioning did not require Quality Assurance (QA) approval.

- There were very few qualification failures; this was mainly due to the amount of pre-testing that was performed.

- Representatives of the process design team, commissioning team, and the software design teams were made available for the duration of the commissioning/validation phase of the project. Issues were managed and communicated within the team.

HVAC Facility Upgrade 2003

A recent major HVAC upgrade project utilized a totally integrated approach. An outside A/E design team, commissioning team, and validation team along with a client team comprised of stakeholders such as engineering, production, internal commissioning manager, internal validation manager (technical services), and maintenance were led by a strong, knowledgeable, and involved Project Manager. Other key integrated team members were the construction management team and the Building Management System (BMS) design/contractor team. The ultimate success of the "Integrated Approach" can be directly attributed to the Project Manager's lead role. In turn, each team member was assigned roles and responsibilities. These roles and responsibilities were delineated and documented at the start of the project.

Weekly team meetings were held and conducted by the Project Manager with schedules, progress reports, issues, and needs assessments for the week being discussed and all documented with meeting minutes. Total team cooperation existed among all members.

Design, commissioning, and validation staff had access to all the current design and control documents (drawings, Standard Operating Procedures (SOPs), Preventive Maintenance (PM) procedures, Function Requirement Specifications (FRS), and URS). Commissioning and validation team members sat with the design team members regularly as the design was developed. This structure allowed for input and suggestions by the commissioning and validation team members as it pertained to design specifications drawings, etc. that were critical components/data required for the compliance protocols (commissioning, IOQs and PQs). Immediate transfer of the data was allowable. Simple input to the design team with regard to writing specifications that would meet design criteria as well as allow for flexibility during protocol execution and also allow meeting the specification, i.e., providing ranges instead of single point specifications, proved beneficial in meeting execution schedules and reducing deviations. These simple types of collaboration with the integrated team allowed for critical schedules and budgets to be met.

The execution team members were educated in Instrumentation and Controls (I&C) as well as document development. These team members interfaced closely with the BMS design team as protocols were developed. Knowledge of I&C, along with development of protocols while working closely with the BMS design team, again allowed for meeting execution schedules and reducing deviations. Virtually every system is automated today; therefore, having knowledgeable I&C team members on the commissioning and validation teams, as well as a developing a close working relationship with the BMS team makes good business sense.

Communication, a strong Project Manager and front-end loading of commissioning and validation as part of an "Integrated Approach" allowed for meeting schedule and costs.

Summary and Conclusions

An Integrated Approach to Design/Commissioning/Validation will be adopted with increasing frequency as a successful model for bringing Biopharmaceutical products to the marketplace with control of the schedule and costs. Success will be dependent on well-planned approaches defining roles and responsibilities, the requirement of strong project management, clear communications, and utilization of technology such as database systems. The design, commissioning, and validation elements and their components will not change, but the integration or ability to perform simultaneous functions will become more urgent as pressures to control schedule and cost continue to mount. A well-structured and managed integrated team can meet all the requirements for checks and balances while meeting compliance objectives. Project successes have proven it works.

It is difficult to compare a traditional approach to an integrated approach as no one project is conducted with both methods so cost and schedule savings can only be estimated. However, there is little doubt that savings can be realized by reduction in duplication of effort by integrating teams and front-end loading documents. The integrated teams also help reduce deviations during validation. Again, if structured and managed well, the cost savings from front-end loading coupled with the ability to meet or reduce schedules can equate to significant overall project cost savings. - *Figure 5*.

About the Authors

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Kevin Scannell, BSc, has 13 years of experience in the pharmaceutical industry. He is presently Manager of Validation Services and is responsible for the management and execution of pharmaceutical validation projects. His extensive experience includes project start-ups, quality assurance, regulatory compliance, audits, and validation master planning. Scannell has overseen validation projects throughout North America. He received a degree in chemistry from the Waterford Institute of Technology in Ireland. He is a member and has been a featured speaker for ISPE and Institute of Validation Technology. Scannell is an employee of Sage Engineering in Toronto, Canada. Sear-Brown and Sage Engineering have worked collectively on various design/commissioning/validation projects.

Contributors

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This article discusses how to operate and maintain an effective cleanroom program to meet pharmaceutical industry compliance regulations.

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The Road to Cleanroom Compliance

by Bob Cates and Larry DeShane

In today's environment, pharmaceutical companies face a variety of challenges. In addition to struggling with patent approval, poor economic conditions, cost ceilings in terms of medication price, and a significant reduction in R&D funds available, pharmaceutical companies are grappling with how to best execute a compliant cleanroom program.

Many factors contribute to a compliant cleanroom program, including meeting certification/regulatory standards; understanding the types of contamination for the healthcare industry; developing the most-effective methods to combat contaminants; identifying the essential tools for a compliant cleanroom; and training and managing your cleanroom staff.

Meeting the Standards

Companies in the pharmaceutical industry must adhere to strict procedures in terms of making, handling and packaging in order to ensure the safety of their products and consumers. A compliant cleanroom in the healthcare industry is required to meet certain regulations and certifications in order to keep manufacturing and packaging areas free of microcontamination, which can destroy a product's integrity and characteristics. The design of the cleanroom, or any controlled environment, typically follows these standards:

- ISO Standard 14644-1 - current revision International Standards Organization (ISO) is a worldwide federation of standards that has a direct correlation to other critical governing bodies in the pharmaceutical industry, such as the FDA. The FDA examines the Standard Operating Procedures (SOPs) of all pharmaceutical companies. The ISO process systematizes the SOPs into an auditable, inspectable process before the FDA reviews it. This prepares a company for the scrutiny that comes with any FDA inspection. An internal audit should be conducted with quality managers and other personnel to ensure that SOPs are in place. A certifying agency also will conduct an external audit, providing ISO 9001:2000 certification.

- 21 CFR, parts 210, 211, 820, current Good Manufacturing Practice

- state and local building codes

The classes of cleanrooms generally range from Class 100 through Class 100,000 (ISO Classes

Table A. Commonly used disinfectants and sanitizers.

Disinfectant	Advantages	Disadvantages
Phenolics	• Not counteracted by organic matter	• Not effective against resistant bacterial spores • Pungent odor
Alcohols	• Acts quickly • Evaporates readily • Leaves no residue	• Little effect on spores • Flammable
Quarternary Ammonium Compounds	• Highly stable • Nontoxic • Odorless	• Affected by water quality • Soap interferes with action • Not effective against spores
Hydrogen Peroxide	• Excellent sporicidal efficiency • Nontoxic at a 1-6% concentration with 0.5% detergent	• High surface tension • Not compatible with all surface active agents
Formalin	• Effective against bacterial spores • Does not corrode metal • Effective in the presence of organic matter	• Toxic - irritating fumes • Residual • Odor

5 through 8). In a healthcare facility, there are separate cleanroom environments with individual gown rooms, whereas in an industrial facility, the cleanroom is divided into process steps. The room finishes are smooth, hard, and easily cleanable. For instance, flush joining of different materials, sealed jointed, and covered corners are critical features when it comes to cleanroom design. The selection of surface finishes must be compatible to the disinfectants used for cleaning.

In addition, the gown rooms must be divided into zones of cleanliness to protect the integrity of the cleanroom garment system. Airlocks and pass-throughs are used for the transfer of items into and out of the manufacturing areas. In aseptic facilities, it is a common practice to have a de-gowning room.

The Cleanroom Configuration

There are two types of cleanroom layouts - ballroom and tunnel. A ballroom layout is an open-spaced structure that encloses a large volume, which permits greater air space. The tunnel layout, which is a more confined structure that reduces airflow and allows for lesser volume, minimizes the cost for clean air and makes the maintenance of service chases easier. Pharmaceutical and biotech cleanrooms typically follow the tunnel layout.

Making Your Cleanroom Work

Designing, operating, and maintaining cleanrooms or controlled environments at the optimum level of cleanliness is an essential task that can affect the quality of the products manufactured and can impact the health and safety of consumers.

Types of Contamination

Understanding the types of contamination that can threaten these products is key to protecting a consumer from the harmful effects of contamination like illness or other adverse reactions. Particles of bacteria or contaminants can be carried into a cleanroom through air, fluids, people or objects, or moved via an electrical field. Some microorganisms like pyrogens and endotoxins – the most common type of pyrogen — can induce fever and other reactions and negatively affect the respiratory and immune systems.

While there are four kinds of contamination — particulate, chemical, biological, and energy — the two of primary concern in the healthcare industry are biological (sometimes called "viable," these are living) and particulate (sometimes called "non-viable," these are non-living).

The biological category includes bacteria, fungi (molds and yeasts), and viruses. Each of these main groups of biological contamination includes many different types, species, or varieties. They are living in that they grow, feed, and reproduce themselves. Biological organisms require food, moisture, and warmth to multiply and grow. However, lack of these three essentials will not necessarily kill microorganisms.

Bacteria are single-celled organisms, although some species, Cocci, tend to join in pairs. Other types of bacteria include Bacilli, Spirochaete, and Vibrious. Bacteria under optimal conditions (moisture, food and warmth) can divide in half once every 20 minutes. So in one hour, one bacterium will become eight and in 12 hours, more than 12 million.

Molds are forms of fungi. They come in different shapes and sizes and can look like a network on a surface. Yeasts are a form of fungus. Under a microscope, they look like a larger form of bacteria. Virus is defined as an obligate intracellular parasite. Essentially, they grow inside another living cell.

While some bacteria, molds, yeasts, and viruses can cause illness, not all microorganisms are harmful. However, even those that are normally harmless can be dangerous to people that are ill. All products that are used in the eye, an open wound, or inserted into the body cavities, tissues, or blood vessels must be sterile. A sterile product is free of all living organisms.

Particulate contaminations can be dangerous if fine particles are injected or inserted into the body. Therefore, it is necessary for the manufacturers to control the number and size of particles in injections and other sterile products. Additionally, most airborne bacteria and other microorganisms are usually attracted to particles. So if the level of particles can be controlled, the risk of biological contamination is reduced.

Biological contaminants have five sources — environment, water, raw materials, containers/closures, and people. People are indisputably the biggest source of biological contamination. People shed bacteria-carrying particles by the million from skin, hair, beard, saliva, nose, throat, and mouth. Bacteria can spread from person to person and from people to inanimate objects in a variety of ways. Coughing, sneezing, scratching, and shaking hands are all examples of how bacteria can be transferred in this manner. Since it is not possible to entirely eliminate these microorganisms, it is important to take special care to protect pharmaceutical products during manufacturing. As a result, a high level of restrictions and requirements for all personnel who enter the healthcare manufacturing areas is critical.

Class English (Metric System)	Maximum number of particles per cubic foot (per liter) 0.5 μm and larger	Maximum number of particles per cubic foot (per liter) 5.0 μm and larger
100 (3.5)	100 (3.5)	Less than 10 (0.35)**
1,000 (35)	1,000 (35)	Less than 10 (0.35)**
10,000 (350)	10,000 (350)	65 (2.3)
100,000 (3,500)	100,000 (3,500)	700 (25)
* Information derived from ISO and IEST (Institution of Environmental Sciences and Testing) standards and practices. ** Counts below 10 (0.35) particles per cubic foot (liter) are unreliable except when a large number of samplings are taken.		

Table B. Air cleanliness classes.*

Class	Number of particles per cubic meter by micrometer size					
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1 μm	5 μm
1	10	2				
2	100	24	10	4		
3	1000	237	102	35	8	
4	10,000	2,370	1,020	352	83	
5	100,000	23,700	10,200	3,520	832	29
6	1,000,000	237,000	102,000	35,200	8,320	293
7				352,000	83,200	2,930
8				3,352,000	832,000	29,300
9				35,200,000	8,320,000	293,000
10						

Table C. ISO Standard 14644-1 airborne particulate cleanliness classes.

Sterilization Methods

Terminal sterilization and the practice of aseptic cleaning are two methods that remove microbiological life from a healthcare product.

Terminal sterilization (heat, radiation, or gas-ETO) is the manufacturing of a product into its final container and then the sterilization of that product. All parenterals have to be filled in Class 100 whether terminally sterilized or not. Sterilization of a product at an earlier stage, generally by filtration (this removes the organism rather than kills the contamination and is only applicable to fluids, liquids, or gases), before filled or packaged, or working with an unsealed sterile product, requires using aseptic techniques.

The sequencing/scheduling of aseptic cleaning is as follows:

- All surfaces are cleaned and disinfected daily.
- Higher frequency of cleaning may be needed for the gown room.
- In case of shutdown, three consecutive cleanings are required. Fogging or fumigation requires specific training requirements.
- After cleaning you are required to complete a cleaning/sanitization form.

Terminal sterilization is defined as a final process step used to deliver a sterility assurance level of at least 10-6 power after the product is placed in its final container-closure system. This is used primarily with medical devices. It is rarely used for biotech.

There is a test that confirms the sterility of product batches. Per industry standards, this is a poor test because:

- only a percentage is sampled
- it is a destructive test
- not all types of contamination can be tested

Sterilization can be accomplished in one of four methods — moist or dry heat, radiation (gamma rays or electron beam), gas, or filtration. The purpose is to get rid of microorganisms. The methods all differ, and while heat, radiation, and gas kill or destroy microorganisms, filtration removes them.

The variety of categories in the healthcare industry, (e.g., injectable, tabletting, ophthalmic, ear drops, skin preparations, irrigation solutions), all call for effective cleanroom maintenance and operation.

Terminally sterilized products are generally manufactured in classified cleanrooms if the product is implanted or applied to open skin.

Clothing to Reduce Contamination

Gowning, and often de-gowning, of employees is a key step to maintaining compliant cleanrooms, and often relies upon standard operating procedures developed specifically for that location. Cleanroom garments can serve as barriers in protecting the product from people. However, some bacteria can still pass through the fabrics. Hence, it is important that all cleanroom procedures be strictly followed.

To enter any cleanroom or controlled environment, special cleanroom clothing is necessary. The first requirement is hand sanitization, which includes washing or the use of a foam product. In general, non-sterile gowning is a top-to-bottom sequence. Sterile areas may differ in this sequence. In sterile areas, fresh gowning is donned at every entrance. In non-sterile areas, gowning may be used for a defined period, but the frequency is generally higher than in an industrial account. Formal training and gowning testing is a requirement prior to work acceptance in any manufacturing area of a pharmaceutical company.

Tools for a Compliant Cleanroom

The effectiveness of any disinfectant will vary depending on its target. Keep in mind that the ideal disinfectant does not exist. The Quality Control Department selects the type(s) of disinfectant used in the cleanroom. This selection is based on particular product needs and process requirements. Cleanroom compatibility also is considered; however, it is not the only factor in the selection process.

Essentially, the way all disinfectants work is to react with the cell's protein to interrupt metabolism or destroy cellular integrity. Both lead to the death of the cell. Frequency of disinfectant application will vary from cleanroom to cleanroom. Environmental monitoring needs to be implemented to determine the schedule for all applications. Strict care must be taken if applying the disinfectant. The surfaces must be cleaned and prepared to prevent the application of a

ISO	FED STD 209E	
1		
2		
3	1	M1.5
4	10	M2.5
5	100	M3.5
6	1,000	M4.5
7	10,000	M5.5
8	100,000	M6.5
* Information derived from ISO and IEST standards and practices.		

Table D. Airborne particulate cleanliness classes comparison.

disinfectant over dust, dirt, grease, or other debris. Dirt, grease, or films can inactivate disinfectants.

Disinfectants

There are thousands of products available today that claim the ability to disinfect. Table A provides a list of commonly used disinfectants, including advantages and disadvantages of each.

Disinfectant rotation, a process that prevents the build up of resistant microbial populations, should not be changed unless:

1. Microbiology isolates and confirms the presence of a resistant organism from a manufactured product.

2. Product contamination increases to an unacceptable level and a joint decision between QC and Manufacturing determines that a change in rotation is needed.

3. Cost-effective and equivalent replacement is identified and implemented.

It is important to understand that if a change in the rotation is implemented, this may continue for a period of time, usually six to 12 months. During that time, information will be gathered to determine the effectiveness and stability of the product. At a time determined by adequate testing and approval by the customer, the primary disinfectants will be reinstituted.

Materials and Equipment

Materials and equipment are another key factor for a compliant cleanroom. All cleaning materials must be approved specifically for cleanroom use. Equipment designated for cleanroom services should be used **only** in the cleanroom. All equipment and materials must be cleaned to cleanroom standards prior to admittance into the cleanroom. Equipment for use in aseptic areas must be sterilized.

Materials and equipment for the cleanroom can include:

- mop - low-linting materials with a handle of stainless steel or reinforced plastic

- cleanroom wipe - approved process wipes

- bucket - dual, stainless steel

- approved chemical disinfectants

- cleaning/sanitization work forms

- materials used in aseptic areas must be sterilized

Techniques to Reduce Contamination

Using good cleanroom techniques will remove organic matter such as dirt prior to decontaminating with a disinfectant solution. Surfaces must be cleaned and prepared to prevent the application of disinfectant over dust, grease, or other debris. This type of contamination could render the process ineffective. Smooth surfaces such as walls, floors, ceilings, and bench tops are most conveniently disinfected by using approved wipes and mops. Mops are used for large areas such as floors, walls and ceilings.

In an aseptic area, the two-bucket method should be used. The mop is placed in the first bucket and used on the surface after which it is rinsed in the second bucket. The disinfectant solution must be changed after each room or every 300 square feet, whichever occurs first. The mop must be thoroughly rinsed after use and returned to the preparation area for re-sterilization, or to discard.

When sanitizing a curtain, apply the disinfectant directly to the sterile wipe. Wipe in a straight-line fashion, moving from top to bottom. Begin at the most critical part of the operation and proceed to the less critical area. Spraying can be used as an acceptable method. Spray until the entire surface is wet.

All disinfectants require a defined "kill" time. This is the amount of time required for the disinfectant to react on a surface. Generally, surfaces must remain moist for a period of two to 15 minutes as mandated by Standard Operating Procedures.

The sequence and schedule of cleaning is mandated by the Standard Operating Procedure of a particular pharmaceutical company. Generally, the cleaning progresses from the most critical process areas to areas of less critical nature. In a vertical cleanroom, the cleaning sequence should be ceiling first, followed by walls, windows and doors, and finally floors.

The custodial staff should not clean equipment. Equipment cleaning is usually done by production or a designated crew that has been trained by the customer utilizing the various protocols for that particular piece of equipment. The equipment needs to be cleaned prior to the cleanroom/controlled environment cleaning and then re-cleaned prior to use.

In non-aseptic facilities, floors are generally cleaned daily. In an aseptic facility, all surfaces are disinfected daily and a higher frequency may be required for the gown rooms.

If an incident or shutdown should occur, three consecutive, full cleanings are typically required. Some companies use fogging or fumigation procedures depending on the extent of the microbial situation. Fogging or fumigation requires specific training and qualifications. Any incident or shutdown cleaning is governed by Standard Operating Procedures.

After all cleaning, it is necessary to complete a cleaning

and sanitization form. This form typically includes the date, time, type of disinfectant used, any batch or identification number of the sanitizing solution, and name.

Surface Sampling to Test Success

Surface sampling supports or disproves the quality of housekeeping and aseptic cleaning procedures. Sampling is often done before and after cleaning. This will help determine the cleaning effectiveness and ensure that the environment is safe for the product.

To accomplish this, the bioburden of an area must be defined by various test methods. Surface samples are generally collected by Microbiology. Samples are taken and acceptable test parameter levels must be in accordance with Standard Operating Procedures. Rodac plates and swab samples are used. Plates are used on regular surfaces, while swabs are used on irregular surfaces such as grills, lights, and door hinges.

Results of any unexpectedly high levels of microorganisms or the presence of certain organisms will be reported and generally the room must be re-cleaned until within acceptable limits.

Training the Cleanroom Team

Most larger pharmaceutical companies conduct their own training due to the idiosyncrasies of their particular cleanroom environment, including:

- the equipment being used
- the product that is being made
- the people inside the cleanroom
- the chemicals being used
- the many protocols governed by current Good Manufacturing Practices (cGMPs) and controlled by 21 CFR (Code of Federal Regulations) regulations and audited by the FDA for each product

In Closing

Careful consideration must be given to the development and implementation of cleanroom operation in order to ensure the health and well being of consumers. When it comes to manufacturing and packaging products, meeting the regulatory demands of the FDA and other governing bodies can be a challenge for pharmaceutical companies. Above all, a compliant cleanroom must be carefully developed, implemented, and managed in order to attain and maintain the highest level of these standards.

Reference Guide

Tables B, C, and D serve as a reference for understanding standards and practices.

References

1. ARAMARK Cleanroom Technology Manual, Revision No. 2002-1, 2002.
2. International Standards Organization (ISO), ISO Standard 14644-1 Airborne Particulate Cleanliness Classes.
3. Cleanroom Housekeeping: Operating and Monitoring Procedures: Institute of Environmental Sciences and Technology, Recommended Practice CC018.3
4. US Code of Federal Regulations: 21 Series, cGMP.

About the Authors

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This article demonstrates how the risk analysis guidance in GAMP 4 can be applied to GMPs and Good Distribution Practices (GDPs).

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Risk Assessment for Use of Automated Systems Supporting Manufacturing Processes

Part 2 - Risk to Records

by the ISPE GAMP Forum

Introduction

Risk Assessment is a vital component in determining the appropriate validation and data integrity for automated systems used in supporting pharmaceutical and healthcare processes. Risk is considered in this article in terms of the impact an automated system can have on public health. The underlying assumption is that validation and data integrity controls should be established to commensurate with risk. Although the philosophy is not new, it has found recent prominence in relation to the FDA's current Good Manufacturing Practice (GMP) review in relation to electronic records/signatures.[1,2]

This article sets out to demonstrate how the GAMP 4[3] risk analysis guidance can be applied in relation to these topics in the context of the GMPs and Good Distribution Practices (GDPs).[1,4] This article begins by explaining how regulatory documents can be used to identify electronic records, goes on to discuss the impact

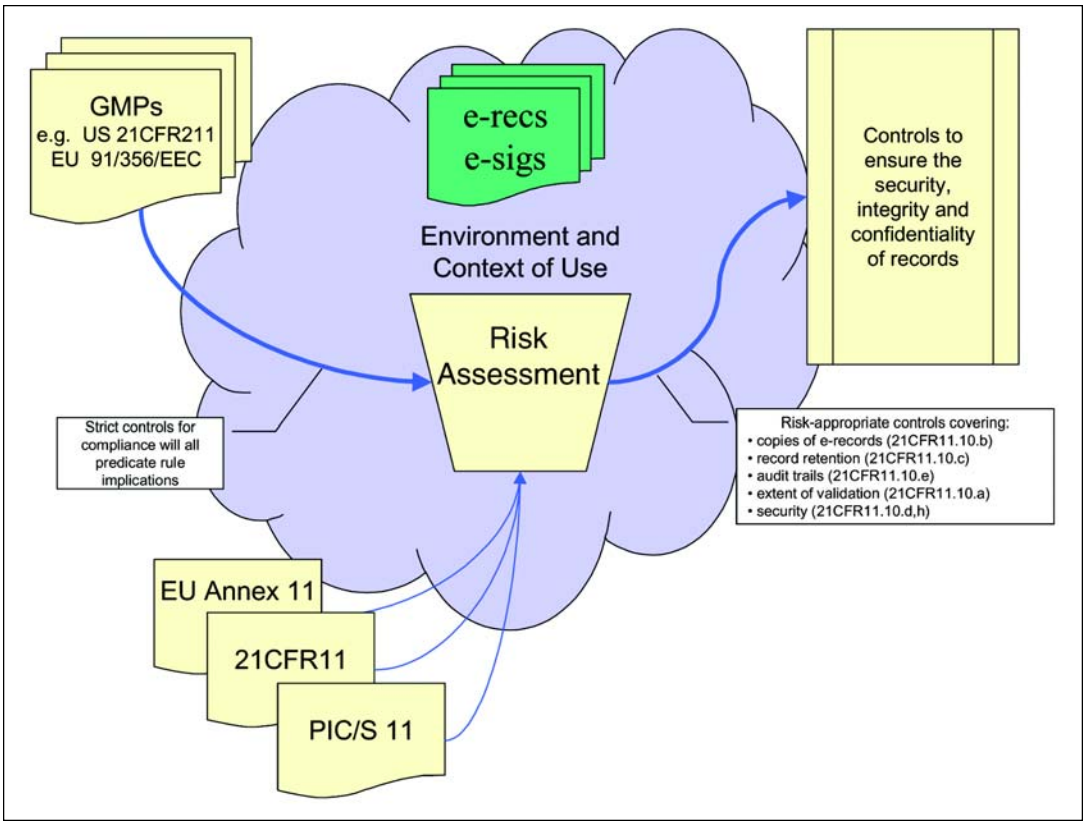

Figure 1. Role of regulation in risk management of electronic records.

of records, and then proposes guidance on appropriate risk mitigation with some illustrative examples. It is acknowledged that the context of different automation systems will vary and that this may alter the outcome of the risk assessment.

The structure of this article has been specifically chosen to complement a companion article on functional risk assessments for use of automated systems supporting manufacturing processes.[5] It is anticipated that both functional risks and risks to electronic records will be combined into a single risk management process. Guidance to industry, including just such a single risk management process is currently being developed by GAMP.

For consistency with other publications on risk management, the terminology defined in ISO 14791 'Application of Risk Management to Medical Devices'[6] is adopted throughout this article.

Records in Automated Systems

The now almost universal use of automated systems across all aspects of pharmaceutical manufacturing means that there are electronic instances of all the records required by the GMPs. While the GMPs might be expressed slightly differently within different legislation around the world, the record requirements that they identify are broadly the same.

The FDA have clearly steered the focus of Electronic Records and Electronic Signatures (ERES) thinking away from legalistic compliance with the technical requirements of 21 CFR Part 11, toward a more pragmatic concern for reliable and secure records that adequately support the predicate rules. Their latest draft guidance[2] mentions the predicate rules no less than 27 times in only five pages of guidance.

The key role of predicate rules (GMP regulations) is shown in Figure 1. Once electronic records have been identified then US Part 11, EU GMPs Annex 11, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) guidance,[10] and other regulatory expectations for record controls can be considered. A risk assessment to determine necessary controls must take into account the environment and context of use of those records. Controls should be appropriate to ensure the security, integrity, and confidentiality of records.

In Part 1 of this article, the functional risks arising from different types of automated systems were discussed. The high-risk issues identified by the Canadian Health Products and Food Branch Inspectorate[7] were mapped onto the FDA's 'systems approach' to inspection.[8] Figure 2 maps the examples of GMP records onto six main operational aspects of pharmaceutical manufacturing.

Risk Assessment Process

The GAMP risk assessment methodology provides a means of identifying the relative priority that needs to be assigned to

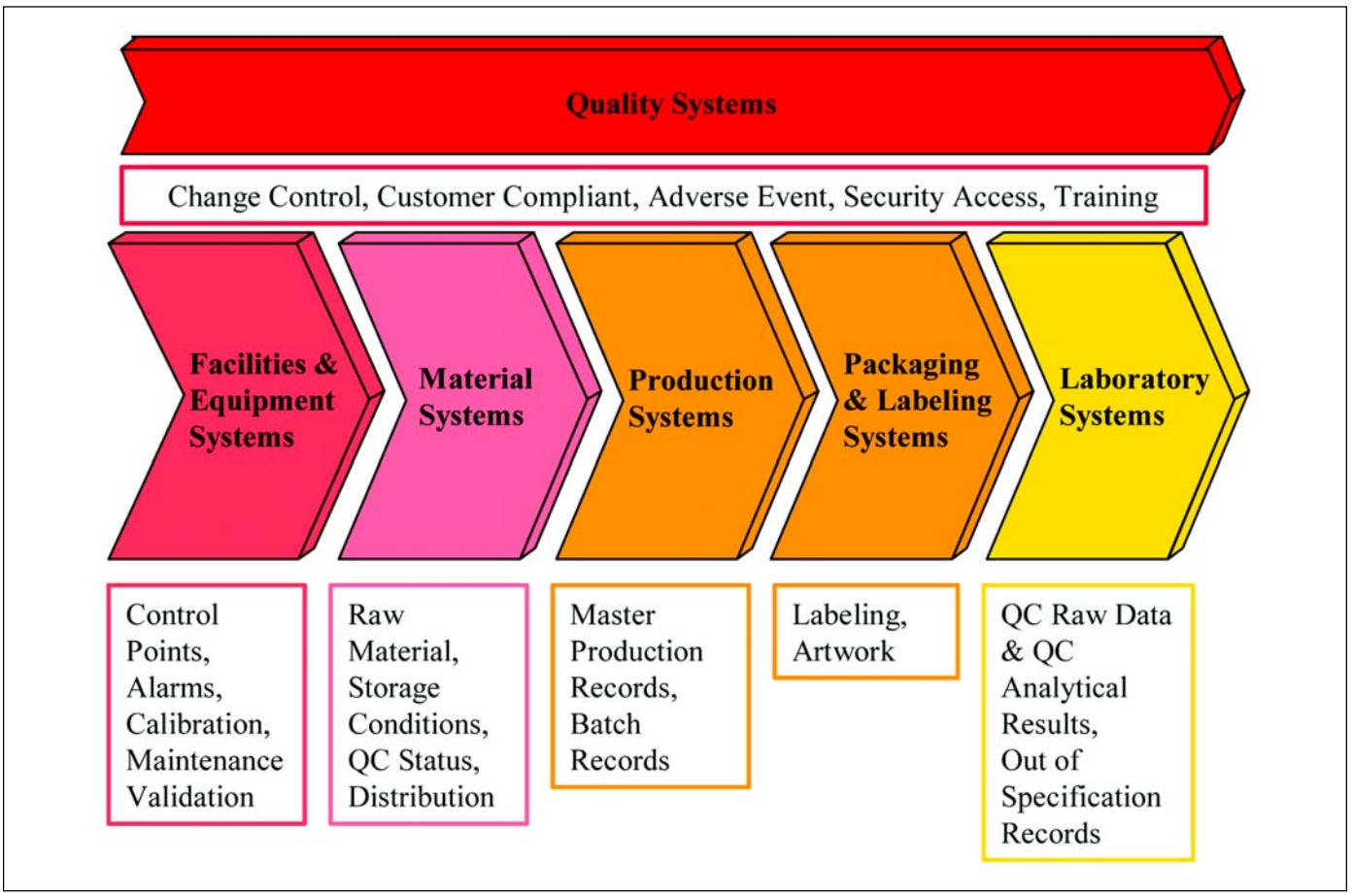

Figure 2. Records in automated systems.

Record Type	Severity			Commentary
	L	M	H	
Equipment cleaning and maintenance records		■		While the cleanliness of product contact equipment has immediate potential to create harmful product, GMPs require Quality Control (QC) checks before product release.
Master production and control records			■	These contain all the critical instruction and control points supporting product release decisions.
Batch production and control records			■	These contain the final record documenting decision to release potentially harmful product.
Out of specification (OOS) investigations		■		Often OOS investigations provide feedback prompting improvement in the Quality Management System (QMS). If OOS were used for batch release decisions then it would be deemed HIGH severity.
Customer complaint records		■		As customer complaints are used to prompt OOS investigations, similar arguments on their impact will apply.
Distribution and shipment records			■	Records that support product return and recall processes are HIGH severity. Others, like intervening logistics are LOW severity with the exception of distribution of controlled drugs.
Adverse event reports			■	Adverse events management is clearly to do with control of potentially harmful product, implying HIGH severity for associated records.
Validation Reports		■		While the correct function of equipment and systems has immediate potential to create harmful product, GMPs require QC checks before product release.
Training records, Job descriptions and Organogram	■			Critical decision points are governed by SOPs, and typically involve more than 1 responsible person.
Self-Inspection Records		■		No immediate potential to compromise individual decisions on product quality, but self-inspection has broad impact on an organization's QMS.

Table A. Typical severity for generic record types.

various examples of electronic records. The risk assessment process is slightly modified to address the generic nature of potential hazards arising from electronic records.

The risk assessment process can be conducted by examining record types to see if they are GxP or non-GxP, and then applying severity checks, likelihood, and probability of detection criteria as illustrated in Figure 3. The most critical records should be linked to direct patient/consumer impact. GxP non-compliance and broken license conditions are severe in their own right, but not as critical as patient/consumer health, in this analysis. Likelihood will be influenced by the degree of human error in how the record is input and/or used. The probability of detection needs to take into account the probability of the impacted record being used and its susceptibility to corruption or loss.

Once the hazards are understood, the appropriate design controls can be introduced. Controls should be specified and validated as part of established system development practices.

Class of Record

The first step in the risk assessment process is to identify records and determine their class in relation to impact and probability.

Criticality Impact of Records

Given that the first GAMP Risk Assessment step concerns the impact of failure rather than its likelihood or visibility, then it is reasonable to assume generic severities for hazards arising from a given record, based on the use of the record, rather than its implementation. The decision making supported by the records required by the GDPs are to some extent also defined within the GMPs, and therefore, generic. Table A proposes typical severities for the hazards arising from various example records identified by the GMP and GDP regulations.

Special consideration should be given to SOPs. Clearly, SOPs used in electronic form constitute electronic records. The criticality of SOPs (or potential severity of hazards arising from the SOPs) will depend on the nature of the SOP or set of SOPs concerned. For example, a set of SOPs that are used to govern the validation of computerized systems should not be considered as critical as SOPs that are used to govern QC operations including final batch release. The criticality of a set of SOPs should, therefore, be assumed to be the same as the most critical of the GMP records that the SOPs are used to manage.

Probability of Failure

The probability of failure of an electronic instance of a GMP or GDP record is dependent upon context. The system architecture, the type and quality of software used, and the nature of the business process that creates and uses the records can all have an effect on the reliability of the record. For example:

- Electronic records stored within a highly redundant storage device (such as RAID arrays) will be more reliable than records stored within a non-redundant architecture.

- As discussed in Part 1 of this article, bespoke software developments (GAMP Category 5) will have had less opportunity to prove their reliability than COTS developments (GAMP Category 3).

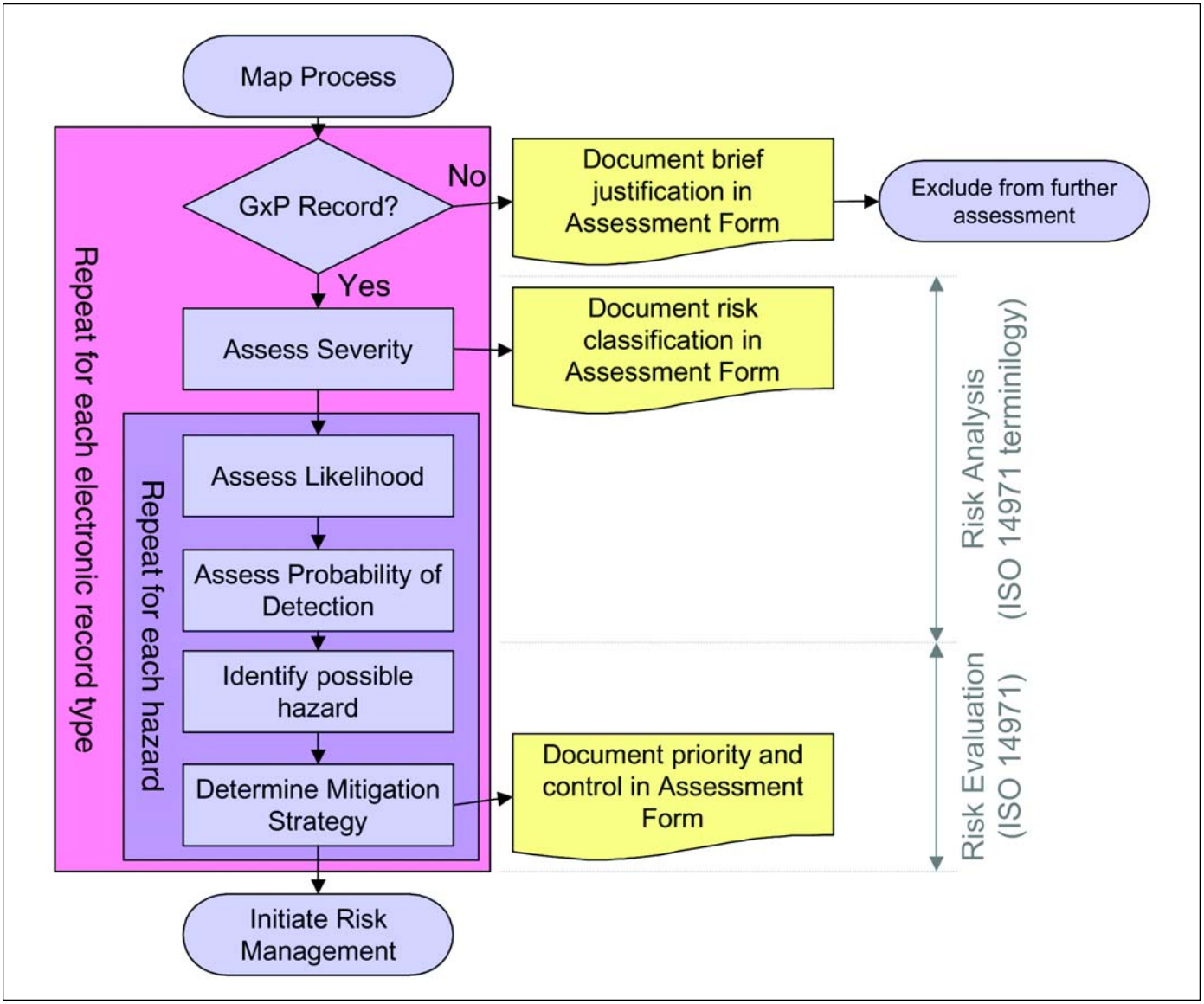

Figure 3. GAMP risk assessment process applied to electronic records.

- In some business processes, there may be call for high volumes of data entry, or multiple data entry, or very infrequent use of complex user interfaces, all of which can lend themselves to an increased human inaccuracy in data entry into electronic records.

- With all systems, the frequency of failure is linked to the frequency of demand.

Therefore, it is not possible to make generic statements about the probability of failure for specific classes of record. Instead, when assessing a specific system and its associated records, the risk assessment must include context specific estimation of the likelihood of all identifiable potential failure modes.

Level of Susceptibility

The second step in the risk assessment process is to determine the level of records in relation to their exposure to loss or corruption and likelihood of detection.

Likelihood of Detection

As with the probability of failure, the likelihood of detection of any given potential failure mode is very dependant on its context. For example:

- Some data file structures such as Relational Database Management System (RDBMS) files include a *checksum* that proves the integrity of electronic records, and allows immediate detection of any corruption to the data files. Such data file structures can only be successfully manipulated through the proper application software, whereas simple ASCII file structures may be easily edited with basic editing tools without the application detecting the record corruption.

- Many user interfaces for data entry include some form of data verification to ensure that manually entered data fall within sensible ranges, or that related data is sensible (for example day of the month field should fall inside a range

(1- 28, 29, 30 or 31) depending on the month and year values). It should be noted that this is a stated requirement of Annex 11 to the EU GMPs.

- Some applications support business processes that must have independent data verification (for example, in Clinical Study Data capture), whereas others are verified only by the individual entering data or even not verified at all (for example, automatically captured raw data).

Exposure

Probability of detection is a bit more complex than in the GAMP 4 model, which is geared toward system failure instead of record integrity. This is because of the additional mode of loss of record integrity which involves alteration or deletion of the record through knowledgeable human actions. These will inevitably be harder to detect through electronic means; indeed, this is the major principle by which the need for an audit trail should be judged. Hence, the GAMP 4 risk assessment model is modified slightly by adding a second "first tier" risk assessment that gauges exposure (the likelihood of unauthorized human changes) versus detectability. Clearly, if a system has an audit trail or a *checksum* verification built in, detectability will be high; whereas if detectability is dependent upon human observation, it will be low.

When critical data is manually entered, sometimes it is very difficult to spot erroneous information (analogous to your own spelling mistakes that you just cannot see), whereas other manually entered data may be presented in such a way as to make errors very easy to spot.

Risk Priority

The risk priority can be determined by assessing the relationship between the class of record and the level of susceptibility. A risk mitigation strategy is then developed to reduce risks to an acceptable level. Technical controls are discussed later in this article. The Medicines and Healthcare products Regulatory Agency's (MHRA) definition of critical deficiencies[9] provides valuable guidance (Table B) when prioritizing risk controls.

Illustrative Examples

In order to illustrate the full risk assessment and risk management process in practice, seven example electronic record classes have been selected for further discussion as follows:

- Computer Aided Design (CAD) drawing files, generated using a standard CAD tool on a LAN, used to generate, maintain, and print equipment design drawings. The paper drawings are subject to manual review and approval with hand-written signatures. Only paper copies of the CAD drawings are used in plant construction and maintenance activities.

- SOPs stored and accessed over a corporate intranet. Standard software products (Microsoft® Word, Adobe® Acrobat®

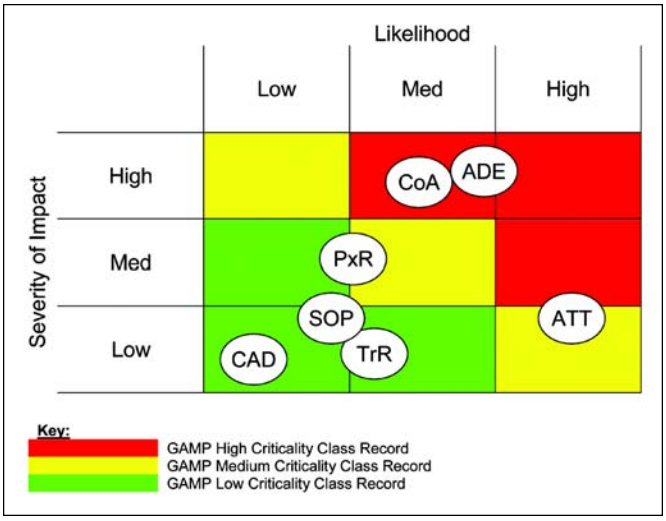

Figure 4. GAMP risk classifications.

PDFWriter) are used to publish and electronically sign each SOP. They are made available on the intranet using only standard network operating system file services. This specific set of SOPs govern IT development and maintenance.

- Automatic Test Tool (ATT) records from a GxP significant computer applications (such as SAP). The ATT is used to define test procedures with associated test criteria, and then to execute and capture test results. In this example, there is no further testing after the ATT. The ATT records are not signed.

- Production Record (PxR) generated by a stand-alone PLC/SCADA combination that controls a discrete item of process equipment. The PxR is not electronically signed, but when printed forms part of a full batch record that is approved with handwritten signatures. It is, therefore, a hybrid record. The batch parameters captured in this partial batch record are subsequently verified through QC controls.

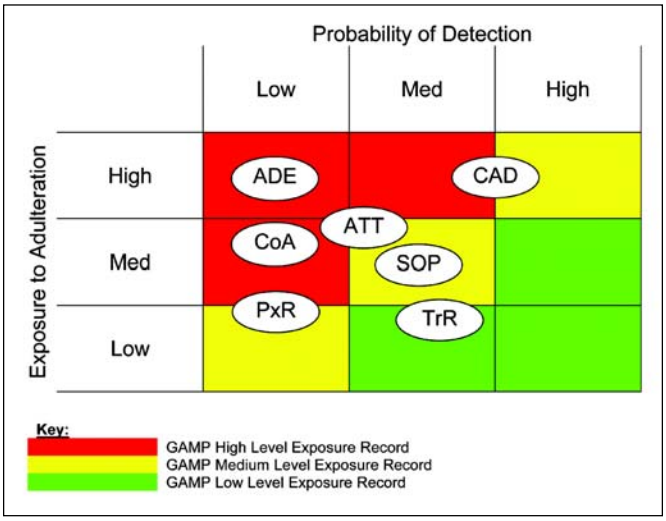

Figure 5. GAMP levels of record susceptibility.

Impact	Explanation
Critical	• A critical GMP failure occurs when a practice could give rise, or has given rise, to a product that is harmful to the patient. • A critical GDP failure occurs when a practice or omission could result, or has resulted, in the supply to a patient of a harmful product. • A combination of major deficiencies that collectively indicate a serious systems failure may also be classified as a critical deficiency.
Major	• A non-critical deficiency which could or would produce a product which is not in compliance with its marketing authorization • A non-critical deficiency which contravenes significant provisions of the manufacturer's license • Repeatedly failing, or significant failure, to fulfill legal responsibilities • Any non-critical deficiency which indicates a significant and unjustifiable deviation from GxP regulatory requirements
Other	• Deficiencies that cannot be classified as critical or major, possibly because of lack of information, but which nevertheless indicate departures from good practices.

Table B. MHRA's definitions of criticality.

- Certificate of Analysis (CoA) generated from automatically collated and analyzed QC samples by a LIMS system. The LIMS system prints the CoA to paper, where it becomes part of the Batch Release documentation, and is approved with handwritten signature.

- Training Records (TrR), created using a word processor, printed and stored in an employee's personal training dossier.

- Adverse Event Reporting Records managed using a database to capture call information from multiple users.

Class

Taking the generic records' typical severities from above, we can deduce the following relative severities:

- CAD documents form part of the design and validation evidence of manufacturing equipment, and therefore, inevitably have potential to impact the eventual product quality produced through that equipment. However, the equipment is always subject to equipment validation, the production process manufactured through that equipment is always subject to process validation, and then all product manufactured through that equipment is always subject to rigorous QC controls prior to release to the public. Given these three levels of subsequent controls, it is safe to classify any failure arising from CAD records as **L**ow severity.

- The IT SOPs have no direct impact on manufacturing processes or manufactured product. Their accuracy is important to the security and availability of electronic systems; however, production using systems controlled by the computers developed and managed under these SOPs is subjected to process validation, and then manufactured product is subjected to QC controls prior to release. These SOPs are, therefore, classified as **M**edium/**L**ow severity.

- The ATT records form part of the Validation Records of a GMP significant system, and would, therefore, be classified as **M**edium severity (Table A).

- Production Records (PxR) provide information used to decide whether to release the batch. As in this case, there is independent QC of the quality significant parameters, these PxRs may be considered as **M**edium severity.

- The CoA is the record used as part of the decision on batch release, and has no additional verification. Errors arising within a CoA should, therefore, be considered as **H**igh severity.

- As discussed in Table A, the training records should be considered as **L**ow severity.

- As Adverse Event (ADE) records are required to manage potentially harmful product, they must be considered a **H**igh severity.

As discussed above, the likelihood of failure of each of these illustrative examples is context dependant, as follows:

- The CAD records have a closed file structure and are manipulated using industry standard CAD software with almost no scope for application specific configuration. The software is, therefore, extremely unlikely to introduce errors. The CAD tool has a graphical data entry mechanism, and strong drawing identification and versioning functions, minimizing the possibility of erroneous data entry, so that it is reasonable to consider CAD records as having a **L**ow likelihood of failure.

- Like the CAD records, the IT SOPs are created using industry standard software. However, the likelihood of human error within the IT SOPs is slightly higher than the CAD records as typical word processing tools have no document identity and versioning functions, making the likelihood of failure **L**ow/**M**edium.

- While an ATT tool is typically a COTS product delivering standard functionality, the test scripts themselves entail high volumes of data entry that are relatively meaningless to those entering the data. This gives rise to the potential for a **H**igh likelihood of errors.

- The final PxR is all automatically generated data, and has no dependency on manual entry; however, it is dependant on the correct configuration of the PLC and SCADA, both of which offer opportunity for error. It is, therefore, reasonable to assume that the likelihood of error is **M**edium/**L**ow.

- Like the partial PxR, the main data content of the CoA is

automatically collected, which like the PLC/SCADA system, is subject to potential configuration problems. This likelihood of failure is slightly increased by the fact that some manual data is also entered, so the potential for human error is introduced. This leads to a classification for the CoA as having a **M**edium likelihood of error.

- As the training records in this example were generated using the same technologies as the SOPs, they also should be considered as having a **M**edium/**L**ow likelihood of error.

- The ADE records in this example are entered by several different users, each using the system infrequently to capture complex information. Even with data entry validation select lists, etc., the likelihood of inaccurate data entry due to operator error must be treated as **H**igh/**M**edium.

These criticalities and likelihoods are plotted on the GAMP 'risk classifications' grid depicted in Figure 4.

Level of Susceptibility

As with likelihood of failure, the probability of detection for each example record type within its context is considered, as follows:

- Errors in CAD records have a **M**edium/**H**igh probability of detections. Technically, the CAD file structure is binary and complex, so it is extremely unlikely to be able to corrupt or change the file structure without the CAD application software detecting the change. The possibility of human error is largely (although never completely) mitigated by the manual review and approval process.

- Like CAD records, the main potential for undetected errors in IT SOPs lies in human error. Given that it is arguably less easy to spot errors in written text than in drawings, it is reasonable to assign a **M**edium probability of detection to the IT SOPs.

- Following this same theme, the probability of detection of errors within ATT records centers on the likelihood of spotting human errors. This time, the records tend only to be reviewed locally (subjected to peer review for example, not full QA approval), and are less intelligible, so the probability of detection is reduced to **L**ow/**M**edium.

- The final PxR is generated from automatically collected data (from the PLC), so the QA inspection has no easy reference for these data. It is, therefore, potentially difficult to detect corruption of batch record values so the probability of detection must be ranked as **L**ow.

- Like the partial PxR, the main data content of the CoA is automatically collected with no easy reference against which to check for errors. The probability of detection, therefore, for the CoA also must be ranked **L**ow.

- Like the IT SOPs, the training records can easily be manually inspected for errors. However, training records have very little information content, so error detection would be easier, rendering a probability of detection of **M**edium/**H**igh.

- As the ADE records in this example are the sole or primary source of information about an adverse event, there is no obvious means of identifying entry error, so the probability of detection should be considered **L**ow.

As discussed in the Exposure section, the probability of detection is not the only factor that contributes to a record's

Level of Risk	Vulnerability/ Rigor of Technical Control	Example Technical Controls
GAMP Priority 1 Vulnerability	Increasing vulnerability, increasing need for rigorous technical controls — High	• Full, immutable, automatically generated audit trail for all manual record changes. • Full, validated, automated archival and restoration processes for record retention and inspection. • Electronic signature for record signing requirements. • Physical or high integrity logical access controls (e.g., password aging, idle-time log-out, auto account barring). • High availability system architecture or frequent (dependant on business requirements) and validated automated backup mechanism. • Computer system validation
GAMP Priority 2 Vulnerability	Medium	• Partial or implicit audit trail (e.g., last changed by, copies of old files, manually linkage with change records). • Ordinary logical access controls (unique user id and password) with procedural controls to ensure account integrity. • Hybrid signature for record signing requirements, with unambiguous linkage between signed printout and electronic record. • Procedural controls governing electronic copies for retention. • Procedural controls governing system backup and restore. • Computer system validation
GAMP Priority 3 Vulnerability	Low	• Procedural change controls of electronic records only when change records are required by the GMPs. • Simple logical access controls (unique user id or group id, and password). • Procedural controls governing system backup and restore. • Computer system validation

Table C. Example technical controls.

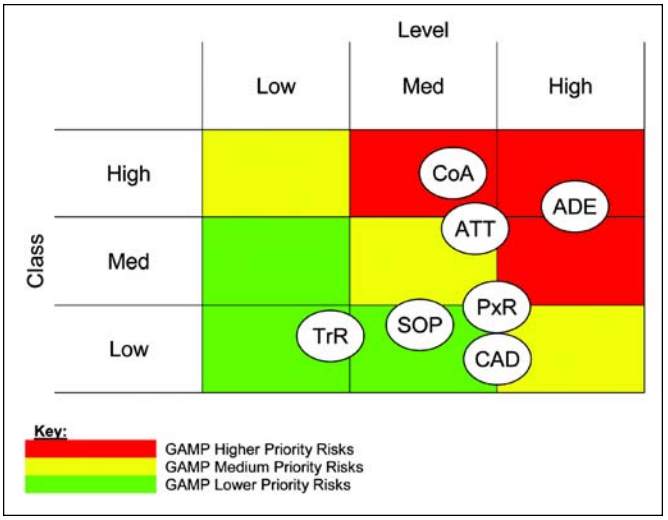

Figure 6. GAMP risk prioritization.

overall susceptibility to corruption. In the examples discussed in this article, relative exposures to adulteration are proposed as depicted in Figure 5. For example, the information contained in ADE records or CAD records would be seen as highly important to an organization, giving possible motive for falsification and would be very easy to change without 'hacker' type skills, whereas PxR records are largely automatically generated and do not represent an easy opportunity for changing. ADE and CAD are, therefore, ranked as having **H**igh exposure to adulteration, whereas PxR is ranked **L**ow/**M**edium. In cases where a high exposure to adulteration is identified, this could be treated as a specific hazard, and separately ranked, leading to controls designed specifically to defeat that risk.

Risk Priority

Therefore, building on the GAMP risk classifications depicted in Figure 4, and the Level of Susceptibility in Figure 5, Figure 6 presents the relative priority of the risks presented by each of our seven example record types.

A scoring system could be used to complement the approach outlined in this article. Threshold scores would need to be determined to set relative risk priorities. Rationales supporting these threshold scores would need to be documented. In general, scoring systems work better with system assessments. Scoring can become burdensome when dealing with numerous records within systems.

Appropriate Controls

The illustration of the seven example record types demonstrates that simple risk assessment techniques can be used to differentiate different electronic record types by their relative threat to public health from drug safety, quality, and efficacy. As with the demand for increasing validation rigor discussed in Part 1 of this article, increased record vulnerability demands increasingly rigorous electronic record controls. Building on the FDA's proposed areas of risk appropriate controls, Table C outlines some typical technical responses to the general requirement for secure, reliable, and confidential records.

All controls should be clearly specified, giving clear evidence of what was decided against each hazard. For the highest priority risks, a rigorous process for designing controls should be used, covering option analysis, residual risk evaluation, risk/benefits analysis and other generated hazards. Such a process is described in ISO 14971.[6] In all cases, where a technical control, such as an audit trail, is selected, it should be validated.

Conclusion

This article has illustrated how the GAMP 4 Risk Assessment process can be used for electronic records and electronic signatures. The principles applied are consistent with those previously published by the GAMP Forum in *Pharmaceutical Engineering* for dealing with functional risk in automated systems. Although the US regulation 21 CFR Part 11 was taken as the prime example of electronic records/signature requirements, the concepts suggested are equally applicable to other GxP record-keeping requirements.

The GAMP Forum is currently preparing further detailed guidance on risk management for electronic records and electronic signatures. This work will shortly be available and discussed at forthcoming ISPE events before final publication as a GAMP Good Practice Guide.

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Recommendations for Implementing a Calibration Program

by Yefim S. Gudesblat, PE

This article presents the infrastructure of a GMP compliant Calibration Program based on technical and metrology methods.

Introduction

This article is limited to the principles of organization for calibration work in relation to cGMP and other pharmaceutical standards. Calibration and metrology methods related to actual calibration techniques, statistics, and theories are not explored in our discussions.[1] Each class of instruments requires specific techniques and approaches to achieve stated accuracies. All members of the calibration team should be educated in metrology techniques and skills necessary for the successful calibration work.

In pharmaceutical applications, performance and accuracy of instrumentation devices are governed by Current Good Manufacturing Practices (cGMPs). Verification of proper process instrumentation operation is an important factor for finished product in Quality Assurance (QA) programs. In GPM processes, outside of validated parameters weighing additions, sterilization temperatures, compounding pressures, and other factors are most likely not recoverable and costly to the business. Mistakenly released products within an established QA program could be detrimental to patients' health and manufacturers' reputation, including legal implications.[5]

Proper operation of process systems and laboratory equipment in the pharmaceutical environment is critical for product quality, manufacturing cost, and research development. Processes controlled by instrumentation outside of defined tolerances, presumably irreversible, will lead to distraction of affected materials and rise of production costs. Incorrect data of laboratory instrumentation and measurements could delay development and

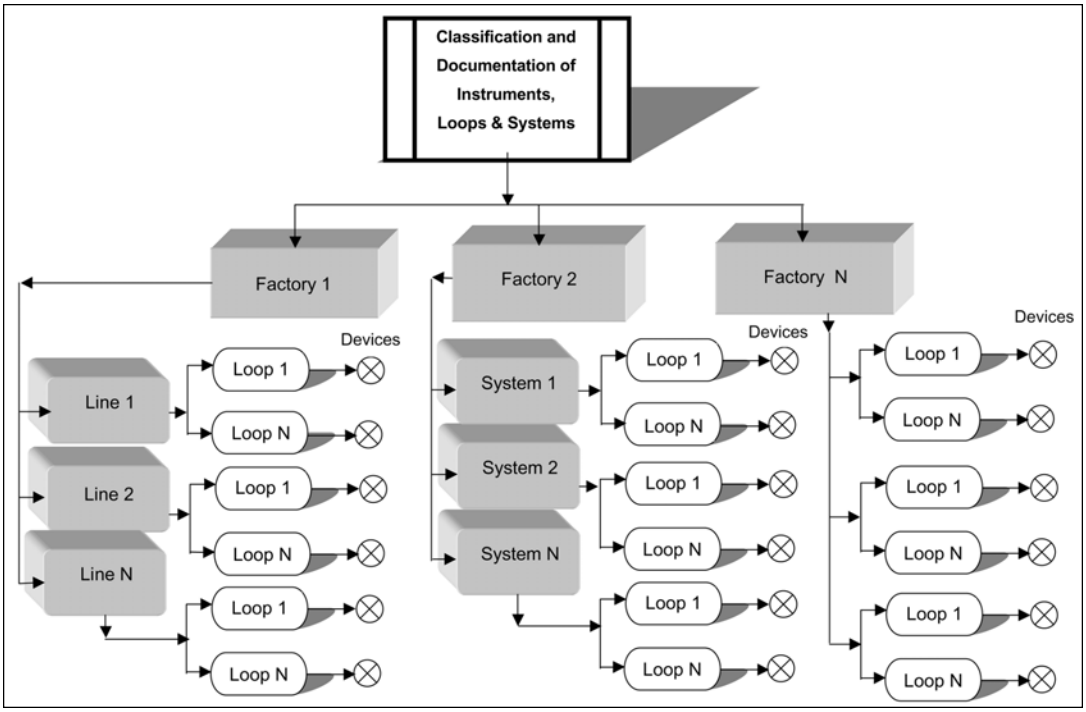

Figure 1. Facility instrumentation configuration diagram.

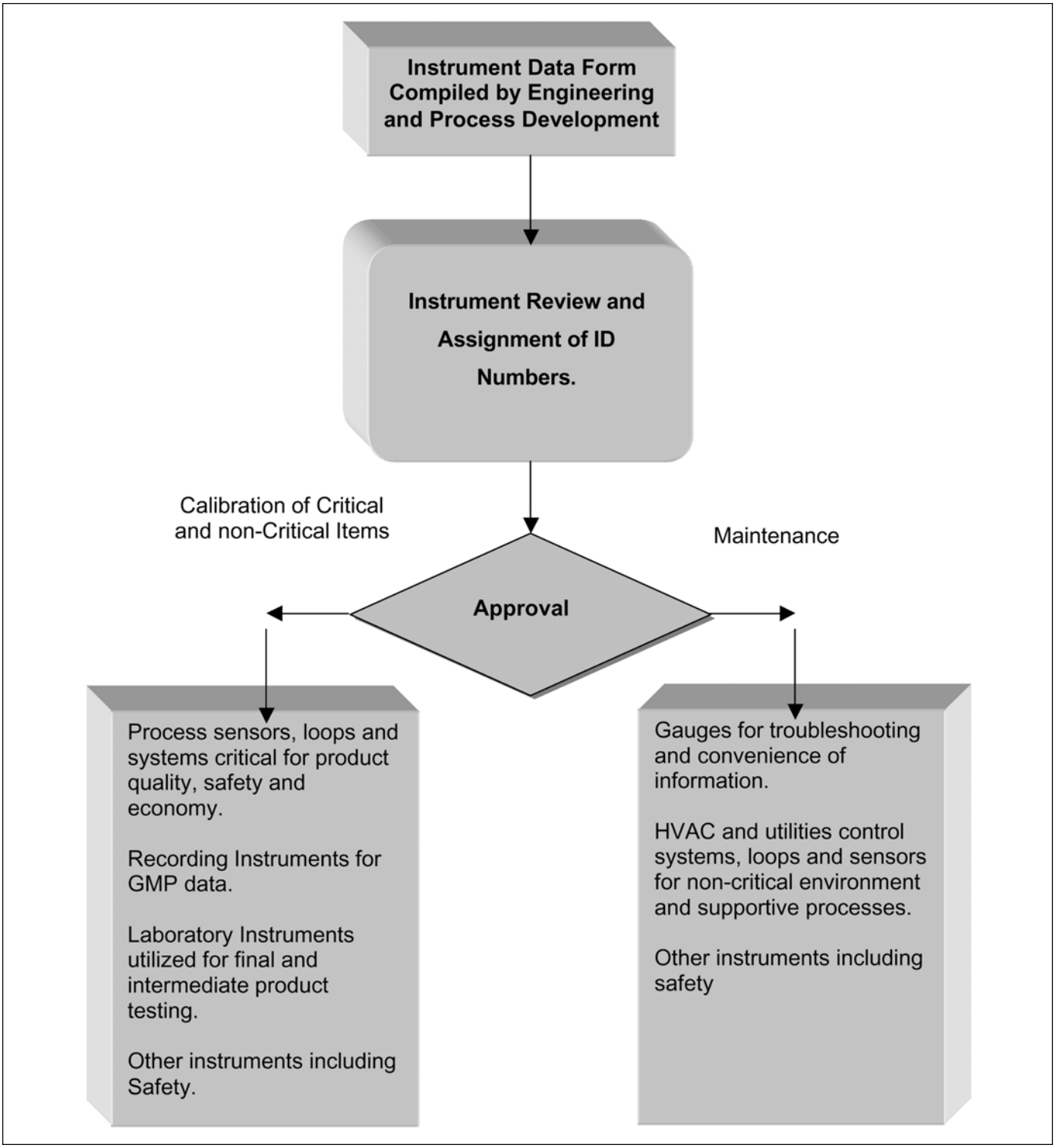

Figure 2. Interactions between preventative maintenance and calibration programs.

release of new products resulting in potential losses of the market share.

The Product Master File and Batch Records contain information concerning weighing specifications, sterilization requirements, compounding parameters, and other details of scientifically developed process tolerances. Production recipes include sequential order of all process activities and permitted fluctuations. Maximum and minimum temperatures for sterilization, weights of each chemical addition, mixing time, and feeding rates are examples of windows for validated parameters critical in determination of final pharmaceutical product quality.[2]

Precision of data in research and development applications is one of the requirements associated with current Good Laboratory Practices (cGLPs). Good calibration record keeping and maintenance of standards and instruments are

Selected Functions of Calibration Program	Functions of Preventative Maintenance Program in relation to Instrumentation and Measurements	Description of Differences or Comments
Field calibrators are certified as traceable to NIST. Failures of field calibrators will result in product hold and investigations.	Field calibrators are functional but not necessarily traceable to NIST. Calibrators functional or calibration failures will be limited to equipment retests only.	Instruments subjected to calibration program require greater functional analysis than devices under preventative maintenance program. For example, failure of calibrators used for sterilization processes and calibrators used for balancing temperature in office areas will generate different responses.
Calibration and process tolerances are specified for the process operating range and instrument operating range.	Instruments and loops functional performance are defined for control and monitoring processes of non-GMP areas.	Product quality could be directly or indirectly affected by out of tolerance instruments in the Calibration program. Instruments under preventative maintenance program have functions of convenience, energy cost, effectiveness or comforts.
Documentation of performed calibration is filed under calibration program.	Documentation of performed preventative maintenance is filed under preventative maintenance calibration program.	There should be no difference in documentation filing and retrieval between calibration and preventative maintenance programs.
Calibration schedules and frequencies are under periodic review and approval.	Preventative Maintenance schedules and frequencies are under periodic review and approval.	Both programs could be defined by one database and divided by Critical, non-Critical and Maintenance categories.
Instruments, loops and systems calibration failures will trigger notification, investigations, product hold, etc.	Instruments, loops and systems functional failures will necessitate repairs and possible notifications.	Calibrated instruments and loops are traceable to calibrators and standards. It is a good practice to use calibrated instrument in preventative maintenance work. However, strict instrumentation traceablilety is not necessary.

Table A. Similarities and differences between calibration and preventative maintenance programs.

necessary for expected reliability of experimental outcomes. Introductions of new drugs to the market could be affected by failures of upholding metrology standards in science laboratories.

The purpose of this article is to review in a general format a Calibration Program suitable for the pharmaceutical industry. In addition, a discussion of engineering methods for process specifications and theory of calibration requirements in reference to pharmaceutical process procedures, operation/laboratory methods, and standards for instrumentation tolerances will be outlined.

Weighing additions of chemical components, process temperatures, pressures, flows, etc., will naturally fluctuate from batch to batch. Therefore, cGMP requires that Standard Operating Procedures (SOPs) for validated pharmaceutical processes will cover maximum allowed fluctuations for specified parameters. Products made outside of critical control defined specifications will oblige sanctions of product "on hold" for investigation. An almost certain outcome from investigations will lead to destruction or rework of manufactured material.

Permitted variations in processes need to agree with the equipment and instrumentation capabilities. Qualification tests and procedures for instruments in validated processes will provide the necessary assurance of accurate process executions. Verification of the instrument's compliance to the process requirements is an important phase for the system qualification and validation. Selections of calibration procedures, calibration frequencies, and certification methods for instruments, sensors, control loops, and systems depend on applications, accuracies, and characteristics of instruments stability.

Data of pharmaceutical manufacturing processes and laboratory testing are limited by the instrumentation accuracy. Product quality compliance requires calibration standard certification traceable to National Institute of Standards and Technology (NIST). Calibration procedures work with formats of records to establish documentation layout and flow designed to assure traceability of collected data. Verification of instrumentation measuring devices performance is comprised from two parts. One is a calibration certification and the other is a calibration check. The calibration certification summarizes a methodical process defined by a written and approved procedure developed for a range of measurements. A calibration check is a simplified confirmation of the instrument, loop, or device performance. Usually calibration checks are represented by one or two test measurements.

A successfully executed calibration procedure confirms that manufacturing processes and laboratory experiments are not affected by the tested instrument within the last calibration time interval. Calibration failure in the "as found" data will necessitate an investigation of the product produced within the last calibration period. In the laboratory environment, all tested lots will be affected by an instrument calibration failure. Strict procedures are required for notification of calibration failures. Adjustments of the instruments found out of tolerance should be controlled by Standard Operating Procedures (SOPs). Each SOP should contain instructions for adjustments or reference them to published literature. For investigation purposes, some instruments could require additional testing and may not be adjusted or repaired inimitably. Investigational tests may be needed to determine a magnitude of losses or requirements for application/design/replacement of an instrument.

Properly established instrumentation tolerances, calibration procedures, and instruments functional tests are very important issues for product development, quality assurance programs, and production costs. CGMP/cGLP metrology program issues related to laboratory instruments, manufacturing capabilities, process tolerances, and calibration methodology are addressed in this article. Actual calibration tech-

niques and metrology requirements related to standards, uncertainty rations, instruments bias, precision, and accuracy are outside of the scope of work for this article.

Managing a Calibration Program

A modern pharmaceutical facility is dependant on thousands of instruments installed in operations, utilities, laboratories, and development areas. Proper functions and accuracies of those instruments are maintained by a Calibration Program. Tasks of a Calibration Program are interfaced with a Preventative Maintenance Program and Quality Assurance activities.[6]

The process of review and approval of Preventive Maintenance activities needs to address requirements of pre and post calibration data. The critical path formula of Pre-Calibration, Preventive Maintenance work, and Post-Calibration is necessary for the system integrity assurance. Calibration and Preventive Maintenance programs cannot function as independent programs. In many cases, Preventive Maintenance could disturb instrumentation and unfortunate discoveries during Calibration work will lead to quality investigations, production loses, and poor business reviews.

Interfacing of Calibration and Preventive Maintenance work requires maintenance, engineering, and quality reviews. Preventive Maintenance and Calibration tasks for all systems and devices need initial and periodic evaluations for assurances of production/experimental consistency and repeatability. The outcome of these reviews should be outlined in specific procedures. For example, Preventive Maintenance work associated with control valves, removal, and reinstallation of instruments will necessitate coordination with calibration activities. Bearing greasing, belts replacements, and other mechanical work may not require links to the calibration program.

An established Calibration Program needs to address the following functions:

I. Documentation records of instruments for traceability and application requirements in accordance with the industry standards of metrology.
II. Continued enforcement of approved calibration SOPs. Reviews and recommendations for modifications of calibration SOPs based on the inputs from Preventative Maintenance and Quality Assurance. Development of new SOPs.
III. Notification of calibration failures to appropriate departments. Investigations of calibration failures and assistance to affected departments by providing technical expertise and improvements.
IV. Maintaining calibration schedules and coordination with production and maintenance activities.

Each of the above functional topics represents specific responsibilities and procedures of a comprehensive calibration program.[3] Descriptions of internal and external configuration correlated to functional topics are very important for understanding the scope of calibration work.

I. Documentation Records of Instruments for Traceability and Application Requirements in Accordance with the Industry Standards of Metrology

All instruments should be recorded on an approved single format Instrument Data Form. The form should be able to describe and identify a single instrument, sensor, loop, display, system, etc. The information from the manuals and cutsheets of instruments include manufacturing model, serial number, input/output units of measurement, resolution, and accuracy. This information should be properly placed on an Instrument Data Form. Consequences of instrument performances and failures related to processes should be provided by engineering, process development groups, and technical services. This information is needed to identify each instrument as critical or not critical, calibration frequency, and tolerances in reference to the final product quality requirements.

Each of the critical and non-critical instrumentation could be divided into several subcategories. That division may be necessary to establish multi-level procedures for calibration failure notification and actions. The following sections of this article will provide a general discussion of critical and non-critical categories without subcategories.

Instrument review procedures in a calibration program need to identify each device, loop, and system with a calibration number. This number will stay with each instrument, loop, or system and will be retired from the program after removal of the instrument or loop/system modification. Calibration numbers need to work within an establish database to assure historical traceability (replacements and modifications) for all control elements of production and research equipment. Figure 1 represents a sample diagram for configuration of facility instrumentation. The Instrument Data Form requires the location of an instrument, loop, and system (including interconnected references) to be recorded. For example, a form for a temperature sensor, transmitter, or controller should identify the location in the loop, system, and plant area (factory). Each loop or system needs to reference instruments and devices employed in the application. Bi-directional referencing is a very important factor for effective performance of a calibration program.

Instrument calibration numbers need to be interfaced or in many cases integrated with the preventative maintenance program for production machines and devices. It is acceptable for the function verification of non-critical instruments to be addressed by the plant preventative maintenance program. Non-critical gauges and displays utilized for reference only could be checked or periodically replaced within a preventative maintenance program. The Calibration Program could employ a separate category of maintenance devices. For example, some HVAC control loops may be covered by the preventative maintenance (calibration) program. Table A demonstrates similarities and differences between calibration and preventative maintenance functions in relation to instrumentation testing.

The process of an instrument calibration review flow

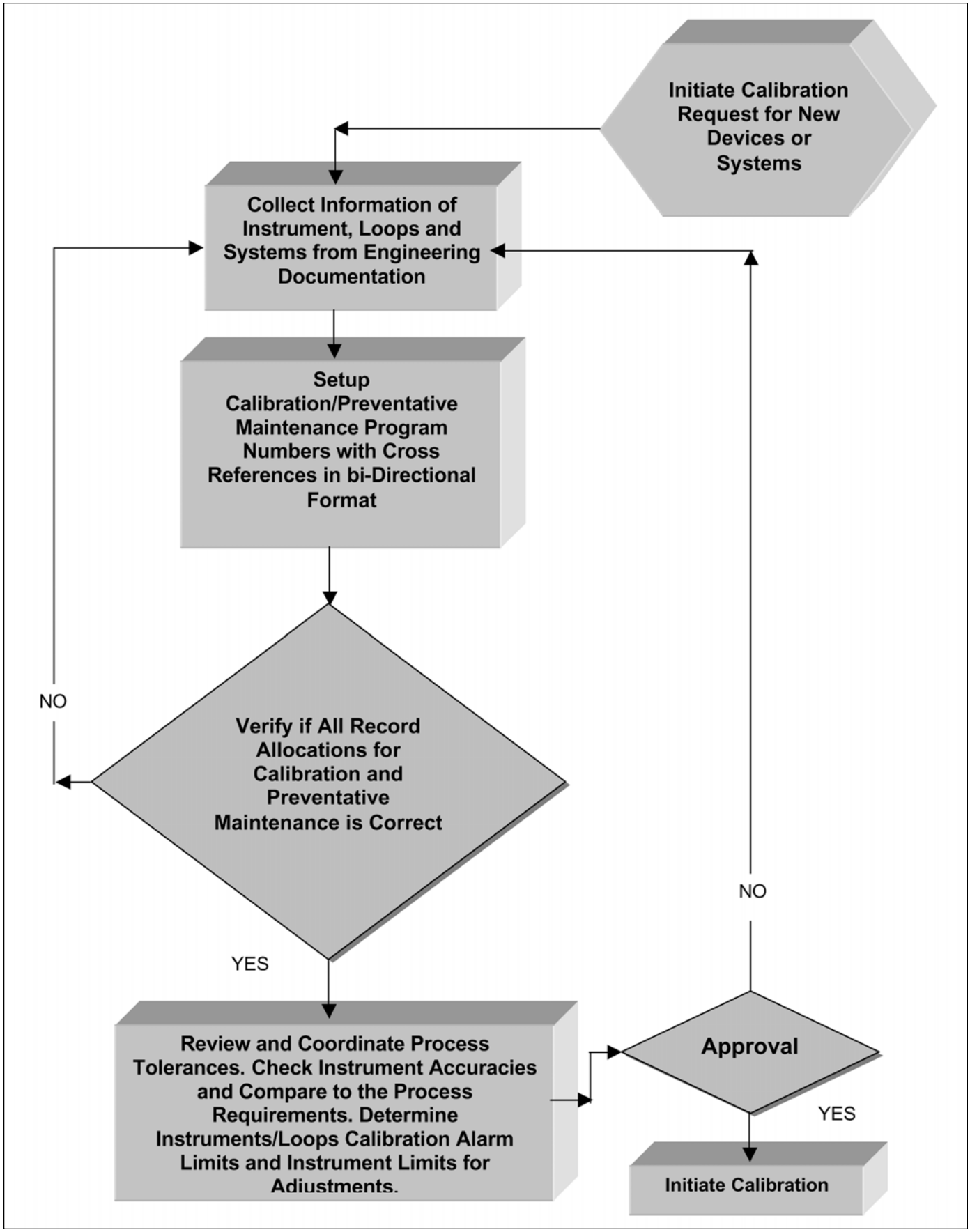

Figure 3. Process of calibration request approval.

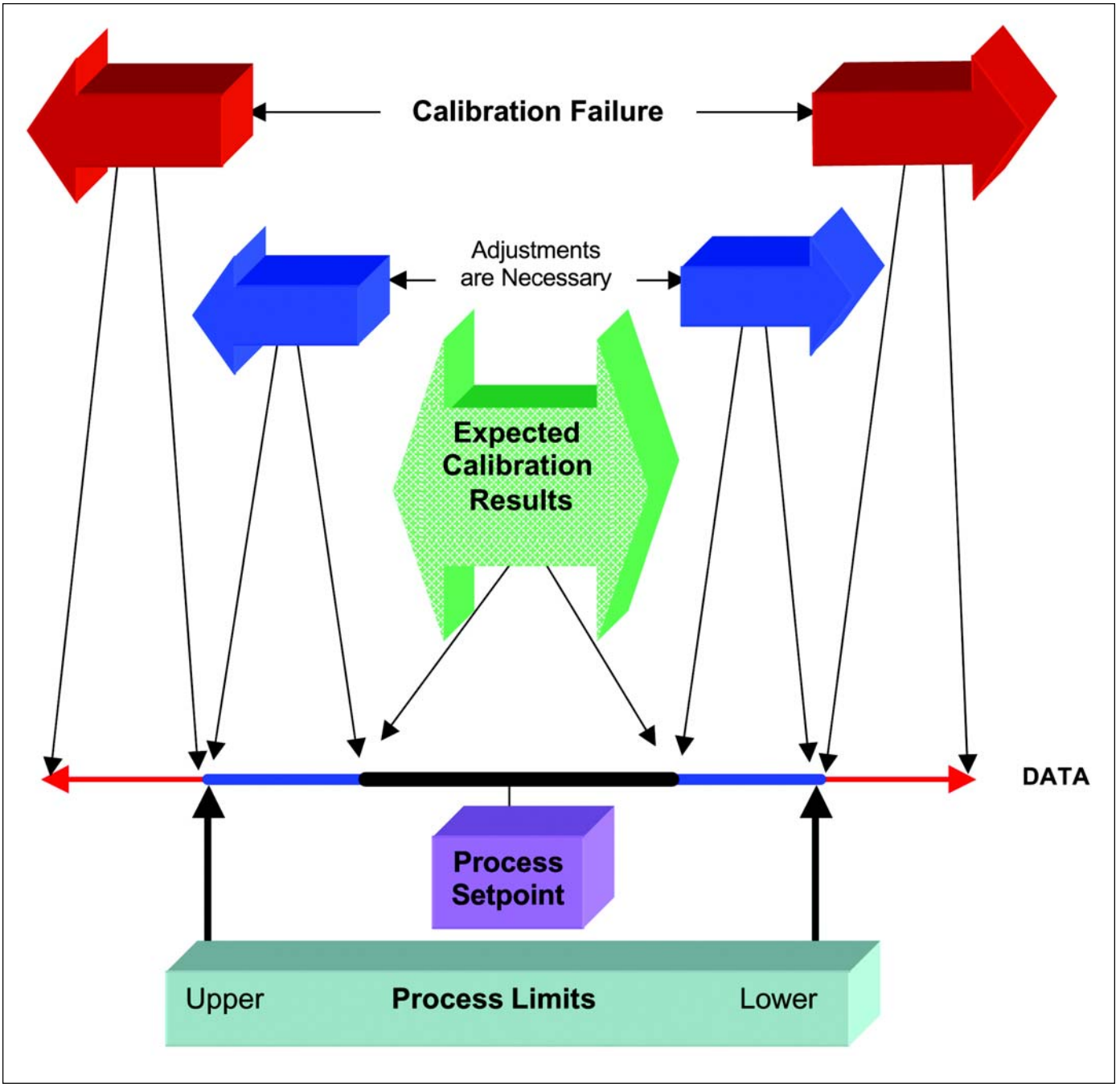

Figure 4. Limits of calibration process and tolerances.

chart is presented in Figure 2. The Maintenance and Calibration work need integration for the following reasons:

- Calibration schedules must be coordinated with preventative maintenance schedules. Preventative maintenance of a system immediately after calibration will void all calibration efforts. Calibration should be a conclusion of preventative maintenance work.
- All instruments require performance verification. However, the detailed periodic calibration with documented traceable standards is not necessary for maintenance gauges, HVAC controls, and many other devices. The preventative maintenance functions within the Calibration Program can satisfy the need for verification for such devices without traceable documentation for standards and detailed records.

Figure 3 summarizes the necessary steps for finalizing and approving calibration documentation. In the process of development or modification of a calibration program, those steps could be subdivided or combined to satisfy company policies, personal need of technical staff, or availability of equipment and software. A brief description for each step is presented below:

1. The first step is dedicated for instrument identification

with cross-reference to control loops, systems, and locations. References of the instruments to loops and system should be bi-directional. In this step, information is recorded about manufacturing operational data, devices models, operating software, serial numbers, I/O inputs, etc.

2. The second step requires review of the instrument's impact on product quality. This step will collect information necessary to determine instruments, loops, and system alliance and placement under calibration or preventative maintenance programs.
3. This step is allocated for instruments under calibration program and will require coordination of tolerances. Calibration limits will be determined from coordination of tolerances. Recorded and approved calibration limits will be used to initiate suitable procedures to notify appropriate departments of calibration failures.

Coordination of tolerances is a very important factor for setting process calibration limits.[4] This information should be extracted from engineering and process development information. Based on instrument/loop capabilities and process requirements, calibration procedures should include two sets of limits. After exceeding the first set of limits the instrument or loop should be subjected to adjustments. No calibration failure notices will be necessary. If the instrument or loop calibration data exceeds the second level of limits then calibration failure notifications will be necessary. For graphical interpretations see Figure 4. Calibration limits usually are determined by experience, but process limits are established from the process requirements and engineering calculations.

II. Continued Enforcement of Approved Calibration SOPs. Reviews and Recommendations for Modifications of Calibration SOPs Based on the Inputs From Preventative Maintenance and Quality Assurance. Development of new SOPs.

Periodic SOP reviews and GMP training are very important factors for a successful calibration program. SOP reviews should reflect changes in facility processes, quality assurance, and preventative maintenance programs. GMP training is a requirement for maintaining personnel qualifications at an acceptable level.

New and modified processes will require creation or modifications of specific SOPs. Periodic reviews will assure that single changes of one SOP have not created contradictions and discrepancies in the integrity of the calibration program. Those reviews or audits should be conducted by quality, engineering, and production representatives.

Training of personnel should be focused on actual documentation procedures and metrology techniques. It is advisable for members of a calibration team to join professional societies. Participation in the Instrument Society of America and National Conference of Weights and Measurements will improve and broaden technical skills of technicians and engineers. The staff responsible for implementation of technical tasks within the frame of a calibration program must maintain and continuously improve their knowledge in instrumentation and metrology.[3]

III. Notification of Calibration Failures to Appropriate Departments. Investigations of Calibration Failures and Assistance to Affected Departments by Providing Technical Expertise and Improvements.

Procedures of a calibration program for pharmaceutical applications should be able to categorize instruments, loops, and systems in several levels of criticality. Instruments involved in the final product quality tests will be the most critical and devices collecting duplicate data will be less critical. Different organizations may adapt specific and most appropriate terminology for a system to categorize instruments.

The majority of calibration programs choose the use of primary standards. Primary standards are instruments, materials, and devices utilized for testing (calibrating) field calibrators. Primary standards are directly traceable to NIST traceable laboratories. Field calibrators are traceable to primary standards. Sometimes primary standards are used for field calibration also. All instruments, loops, and devices must be traceable to calibrators. Calibration failures of primary or field calibrators will trigger investigations of processes affected by instruments traceable to failed calibrators.

A failure of an instrument or a loop calibration indicates that all product or testing material affected by the instrument requires investigation for quality of compliance. Investigation periods will be extended to the date of the previous calibration. All products manufactured and tested between the last acceptable calibration and the current failure of calibration require an investigation.

Instruments of a failed calibration in different applications will require:

a) immediate adjustment, repair, or replacement, or
b) no adjustment or repairs until additional testing of the failed instrument and process is conducted

The actions above must be pre-selected for each instrument, loop, and system, and clearly identified by specific SOPs. The actions 'a' and 'b' could be associated with the level of criticality of instruments and processes. Therefore, instrument calibration frequencies should be set with considerations and risk assessments of processes.

Calibration failures will affect all processes and instruments calibrated with the defective calibrator. Calibration failure of instruments in a quality assurance laboratory could have the same or larger specter of issues. Calibration failures of critical instrumentation could put product on hold, recall and/or destruction.

Properly engineered systems with correctly selected instruments and a practical calibration program will effectively minimize nuisance calibration failures. One part of the calibration program consists of continuous/periodic evaluations of the processes and instrumentation to assure good cGMP compliance.

IV. Maintaining Calibrations Schedules and Coordination with Production and Maintenance Activities

Calibration instruments, loops, and system must be carefully scheduled for calibration. Calibration work requires shutdown of production and laboratory testing. In production environments, calibration of water systems, continuous sterilizers, and other systems will necessitate a major shutdown. Calibration work requires diligence, dedication, and objectivity. Therefore, system shutdowns should be scheduled with adequate time delegated for calibration and coordination with other perhaps preventative maintenance activities.

Calibration schedules must be very closely monitored. Overdue scheduled calibrations should be considered as serious events and treated with commitments to avoid any possible future delays. If an instrument calibration is overdue, then production/laboratory stop notices should be immediately forwarded to appropriate departments for shutdown of instruments and associated processes. Accidentally manufactured products or laboratory work performed with instruments affected by a calibration overdue date will require investigation and hold of products.

If a cGMP equipment or system is due for removal or modification then calibration work should be scheduled before work begins. Calibration should be conducted immediately after production ends and before project work starts. To assure product integrity calibration work is necessary to verify instrumentation performance as production ends. After project completion (in case of modification), calibration work will be part of commissioning or validation. If equipment is removed, then the last calibration report will be a record that product manufacturing was performed under specified controls.

Conclusion

Calibration work in a pharmaceutical plant should be focused on the specific applications and not on the capability of instruments in wide varieties of their potential performances. The rules of calibration cannot require that all instruments must be calibrated over the full range of the instrument to the expected manufacturing accuracies and with a complete ignorance to the processes. Each system, loop, and instrument should be carefully reviewed for calibration methodology and applicable techniques.

Process instrument calibrations should be done in place, without instrument removal, and within the loops. Loop calibration is one of the most desirable methods. Calibration of instruments before installation and manufacturing certification should be considered as a reference only and acceptable for commissioning. In regulatory environments, calibration procedures of an approved program must be exercised prior to the beginning of qualifications and validations.

The relationship between an instrument range, process limit, and instrument tolerances is very important. Process limits cannot exceed instrumentation ranges and range of instruments cannot exceed the required process resolution. For example, gauges with ranges of 0 to 1000 psi and 0 to 25 psi cannot be used in the processes of 20- 30 psi.

In a large number of pharmaceutical processes, an application loop calibration at process limits is acceptable and considered as a reliable verification of the controlled accuracy. Loop calibrations could be supplemented by individual device calibrations. For example, if frequency of a loop calibration is quarterly or semiannual then device calibrations could be set for an annual schedule. After completion of individual device calibrations, a loop calibration should be done to assure proper operation of the loop. Functionalities of alarms, emergency algorithmic, and sequence of operations at critical points could be included in calibration procedures.

This article in a general format outlines an infrastructure of a Calibration Program dedicated to a pharmaceutical facility. The purpose of the program is an assurance of instrumentation integrity. A successful calibration program must be interfaced and integrated with other functional programs of engineering, production, and quality departments. At the present time, a facility calibration program is one of the most important factors in the plant compliance and business performance.

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This Guide discusses the considerations which should explain this activity and suggests a process to be followed in order to assess and validate Legacy Systems.

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GAMP Good Practice Guide: The Validation of Legacy Systems

by the ISPE GAMP Forum

1 Introduction

In view of the rapid evolution of both new technologies and regulatory expectations over recent years, it is crucial that pharmaceutical organizations take positive action to maintain their existing cGxP-related systems in a validated state. This Guide discusses the considerations which should explain this activity and suggests a process to be followed in order to assess and validate Legacy Systems.

2 What is a Legacy System?

There is no formally accepted definition of 'Legacy System,' but for the purposes of this GAMP Good Practice Guide (GPG), a Legacy System should be considered to be any GxP relevant system that is in place and in use, and which is deemed not to satisfy current regulatory expectations.

It is **not** acceptable under any circumstance to implement a new system that has not been validated. Legacy System validation "is not equivalent to prospective validation and is not an option for new systems." (Ref: PIC/S PI-011-1.)

3 Typical Issues Encountered with Legacy Systems

There is a risk that a Legacy System, which has not been the subject of a recent validation program, will fail to comply with current regulatory expectations, e.g., 21 CFR Part 11. Therefore, there is a need to review existing systems for compliance. Typically, the issues are associated with:

- ownership of the system
- validation package
- security
- system functionality
- data integrity
- archiving of data

3.1 Ownership of the System

The owner of a Legacy System has the responsibility to ensure that:

- the system continues to be relevant to the (GxP) process being supported
- the operating procedures are up-to-date
- user training is sufficient to maintain the competence of the users
- a formal change control procedure is in place and is followed
- any necessary maintenance agreements, (e.g., Service Level Agreements,) are in place and valid

Essentially, the owner of a Legacy System should ensure that an appropriate validation package exists.

In this age of mergers, acquisitions, divestments, outsourcing, and reengineering of organizations, operational responsibilities are frequently reorganized. As a result, the ownership of existing systems may become poorly defined or unknown. Without a formal and controlled hand-over process, it is unlikely that the knowledge associated with a particular system will be passed to the new owner, or even that the

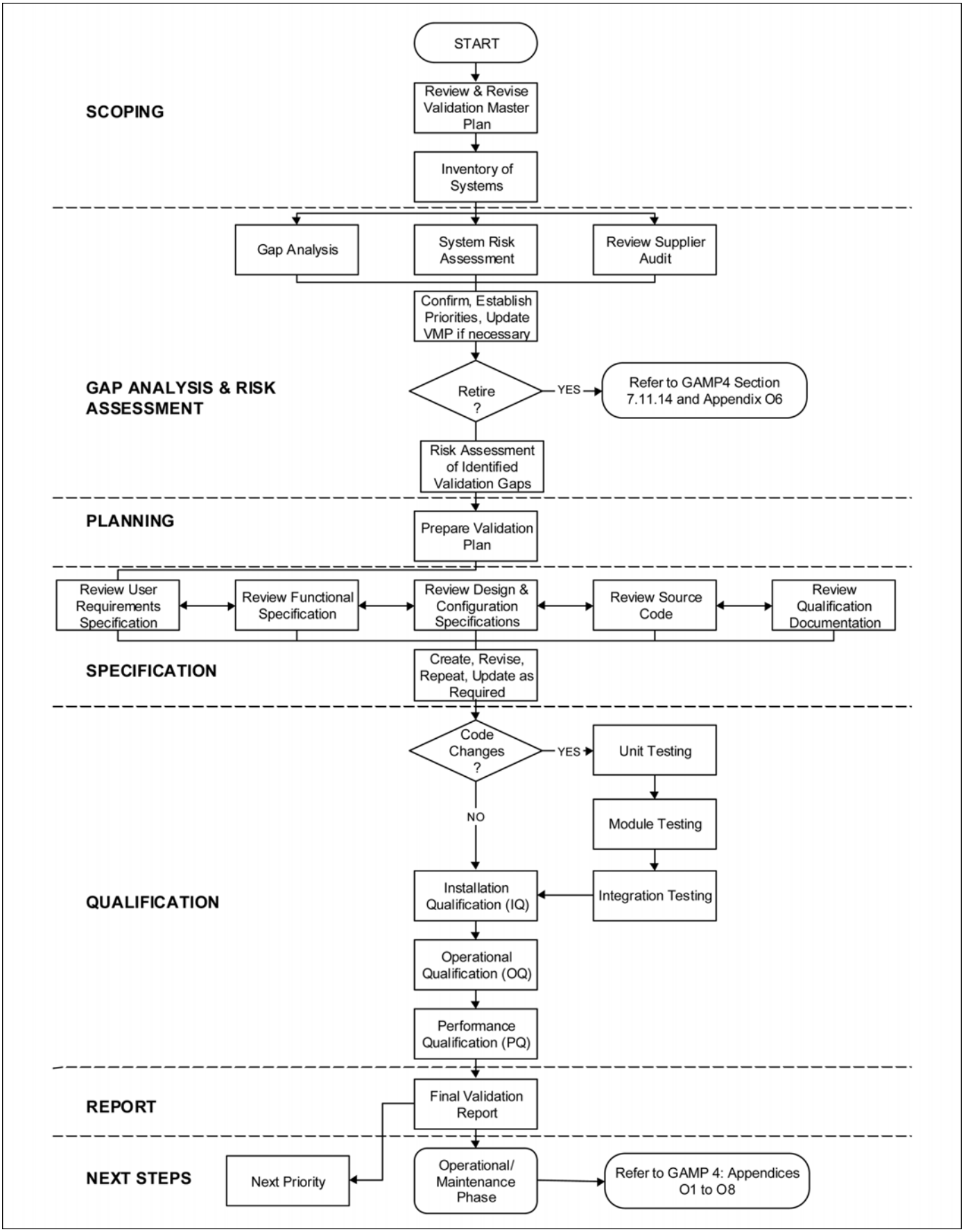

Figure 1. Legacy Systems Validation Activities.

location of critical system documentation will be made known to the owner. An incoming owner must take appropriate steps to identify those systems under his ownership. When a system has no owner, it will fall into an uncontrolled state.

It is, therefore, critical that the system owner be clearly identified, whether an individual or a representative team accountable for widespread or enterprise systems.

3.2 Validation Package

It is usually the case that documentation associated with Legacy Systems is no longer up-to-date or complete. The Legacy System may have been validated to an earlier regulatory expectation that is no longer adequate. With changes in the use of a Legacy System, parts of the system documentation may no longer reflect accurately what the system does, how it does it, or how it should be used. All such issues need to be remedied in a Legacy System validation program, which should produce a validation package for the Legacy System.

The required validation package consists of the system documentation, together with the qualification documentation, fronted by a Validation Plan and concluded by a Validation Summary Report.

3.2.1 System Documentation

In the context of this GPG, system documentation should be regarded as the 'live' documents, such as specifications (e.g., URS, FS, design/configuration specifications, source code), Requirements Traceability Matrix, Standard Operating Procedures (SOPs), user reference manuals, and 'Help' text. Without the application of a formal change control procedure, the 'live' documents will fail to represent the system accurately.

3.2.2 Qualification

Qualification provides the documentary evidence that the system does what it is supposed to do, accurately and consistently. For Legacy Systems, the qualification documentation may not be available or may not be adequate in terms of current regulatory expectations. Existing documentation also may have failed to incorporate the qualification of any changes that have been made to the system since it was first implemented.

3.3 Security

Security is frequently an issue with Legacy Systems; particularly with the advent of ISO17799, there is an increasing focus on the physical and logical security of the system and its data. All systems which contain electronic records and are subject to validation, must be able to demonstrate that access to the system is properly controlled. It also is a requirement that, where appropriate, there are multiple levels of security, e.g., users may have different access rights from supervisors, who should have different access rights from the system administrator. The way in which access rights are granted also may need to be addressed.

Issues relating to security are addressed in the Good Practice and Compliance for Electronic Records and Signatures, Part 2: Complying with 21 CFR Part 11: Electronic Records and Electronic Signatures and in GAMP 4, Appendix O3.

3.4 System Functionality

Changes to regulations or their interpretation may have caused the capabilities of the Legacy System to be regarded as inappropriate or inadequate. For example, the Legacy System might not have the capability to record audit trails that are now required for compliance with 21 CFR Part 11.

With increasing concern about the control of electronic records and signatures, the availability of audit trails has become a prominent issue. The audit trail needs to record who did what, when they did so, and retain the original value for any altered data; again, this is addressed in the Good Practice and Compliance for Electronic Records and Signatures, Part 2: Complying with 21 CFR Part 11: Electronic Records and Electronic Signatures. Many Legacy Systems do not have an audit trail facility although some will provide a transaction history for a limited number of batches and then overwrite that data.

These are issues to be addressed when reviewing the status of Legacy Systems and deciding appropriate actions to remedy those issues in order to bring the Legacy Systems into compliance with current regulatory expectations.

3.5 Data Integrity

Where a Legacy System failed to demonstrate the accurate and consistent capture, change, and retention of data during a prior validation effort, and for systems which have never been validated, it may not be possible to show the integrity of the data now residing within the Legacy System.

3.6 Archiving of Data

Data archived from the Legacy System is often overlooked, but must be retained in a secure and accessible manner. Further guidance is provided in GAMP 4, Appendix O6: *Guideline for Record Retention, Archiving, and Retrieval*.

4 Objectives of Legacy SystemValidation

The objectives of validating a Legacy System are fundamentally the same as for prospective validation except that, being accomplished after the system is 'in place and in use,' some elements of the validation process have already occurred.

Typical objectives of Legacy System validation include:

- to ensure that the Legacy System properly supports the process
- to ensure that the Legacy System has been properly installed, is operated correctly, and that procedures and practices are in place to allow it to be maintained in a state of control throughout its useful life
- to establish a complete set of system documentation providing a precise definition of the operating environment, functionality, hardware and

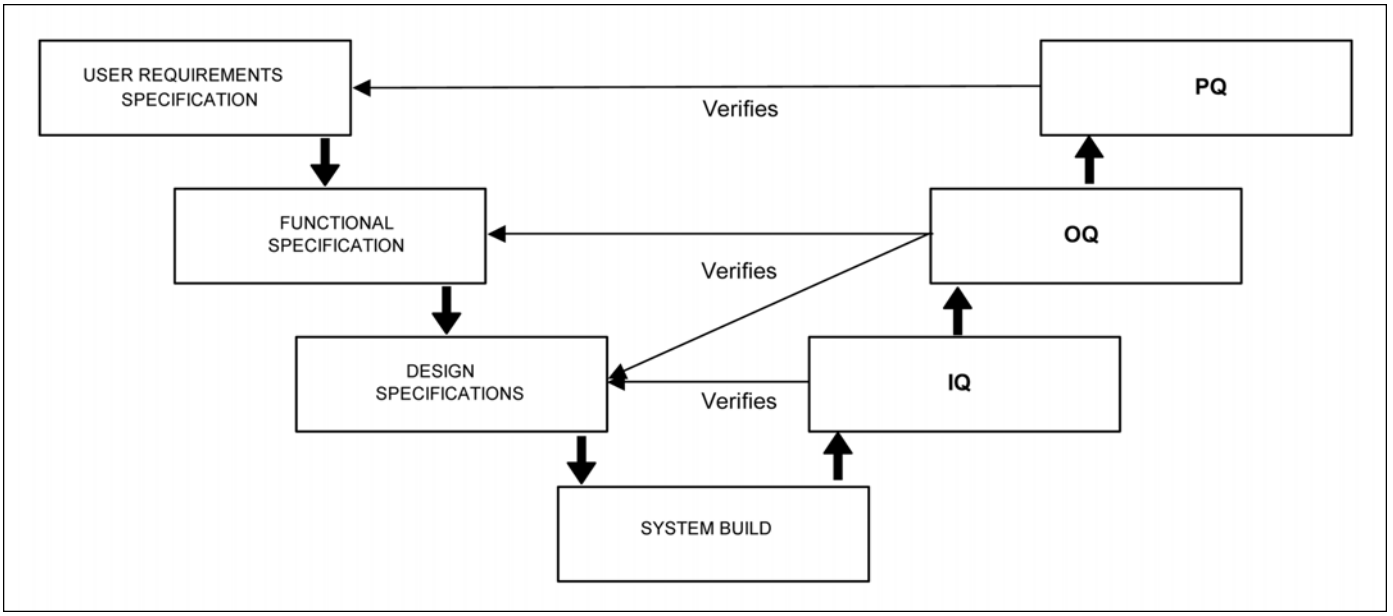

Figure 2. A basic framework for specification and qualification. (This figure is reproduced from GAMP 4).

software, procedures, and reference manuals associated with the Legacy System

- to provide indexes to the documentation set (i.e., by the use of traceability matrices for documents and user requirements)
- to provide a framework to demonstrate regulatory compliance

5 Benefits of Legacy System Validation

Undertaking Legacy System validation has valuable benefits and should not be perceived as having regulatory compliance as its only objective. These benefits include:

- assurance that the system is fit for purpose and relevant to the process that it supports, from both a business perspective and a GxP perspective
- understanding of the actions required to achieve compliance with evolving regulations, e.g., 21 CFR Part 11
- enhanced confidence in the engineering of the Legacy System
- demonstration that users are competent to operate the Legacy System to an appropriate level and are provided with approved procedures
- provision of a baseline from which to manage change control
- potential to reduce system maintenance costs

6 Typical Process for Legacy System Validation

6.1 Scope

It is assumed that a Validation Master Plan (VMP) (see GAMP 4, Appendix M1), or equivalent document, already exists and formally identifies the Legacy Systems under review. As an initial step, this document should be reviewed and updated to ensure that it includes all Legacy Systems and references all Legacy System validation activities.

Figure 1 shows a typical process for Legacy System validation. This process is detailed in Sections 6.2 - 6.9.

6.2 Gap Analysis and Risk Assessment

Once the inventory of a Legacy System is in place, a Gap Analysis can be undertaken, which should be conducted against the V-model, shown in Figure 2 and include a review of the Change Control history for this system (see GAMP 4, Figure 6.2: Basic Framework for Specification and Qualification, and GAMP 4, Appendix M4: Categories of Software and Hardware).

The Gap Analysis should determine the difference between what is in place and what is required to demonstrate that the system has a complete documentation set, is in a state of control, and can be operated and maintained properly. At the same time a Risk Assessment (see GAMP 4, Appendix M3) should be undertaken to determine the criticality of the system to the process (with respect to product efficacy or patient safety).

The Gap Analysis and the Risk Assessment together will help to determine the strategy and the priority in which each system should be addressed for remedial action. High criticality systems with poor compliance will result in a high priority for remedial action, whereas, low criticality systems with poor compliance may fall below the threshold for remedial action, the definition for which shall be described in the VMP. For medium and low GxP criticality systems, it may be acceptable to establish the quality of the documentation set by sampling (or 'spot checking') as recommended in GMA/NAMUR Guideline NE68: Retrospec-

tive Validation of Control Systems.

In the analysis phase, it may be necessary to collect historical evidence of the successful operation of the system (e.g., review of product batch records, event and incident logs) to support the continued use of the system. This approach should be used with caution, as it will be difficult to assure the integrity of historical data unless it is possible to demonstrate good operational control throughout the life of the Legacy System.

If this is part of the Legacy System validation strategy, then this activity should be included in the Validation Plan, as a deliverable, or discussed in the Validation Report, as part of the rationale for not having a complete validation documentation set. For example, if the volume of data is large enough, it may be possible to demonstrate that the system works properly at the boundaries of an alarm range. However, considering the example of a line running at a certain constant speed setting, the limits of the process may not be stretched, and validation testing of the control system at maximum and minimum line speed might be necessary.

The status of the Legacy System supplier should be reviewed to determine whether there are any outstanding issues from any previous audit(s) and, if so, to ensure that all actions are closed out. The review process should also take into account whether there will be a continuing relationship with the supplier. If there is, or because further upgrades are expected, then consideration should be given to when the first, or next, audit should be conducted. Any new audit should encompass a review of the ability of the supplier to meet the requirements of any legislation introduced since the last audit, e.g., 21 CFR Part 11. The result of the supplier review may impact the degree of testing required within the validation program of the Legacy System.

Where no prior supplier audit exists and no further upgrades are expected, the Legacy System is assessed as low risk, or the Legacy System is wholly supported with internal resource, there is little or no value in conducting a supplier audit as part of the Legacy System validation.

6.3 Planning

Once the Gap Analysis and Risk Assessment are complete and a priority has been set, the Validation Plan (VP) for the system can be established. The VMP sets out what activities will be undertaken to validate the system, who will be responsible for the various activities, and in which order those activities will be executed (see GAMP 4 Appendix M1). The VP should, in principle, follow the outline given in the GAMP Appendix, but may be amended to take into account the findings of the Gap Analysis.

At this point, an additional Risk Assessment, which considers the risk category of the identified gaps may further influence the validation tasks (i.e., the gap may be determined to be acceptable). Where gaps exist, reference may be made to existing specifications and historical records (e.g., error logs, change requests), particularly where they add clarity to the scope of the validation activities, provide positive evidence of reliable performance, supplier status etc.

6.4 Specification

The business process or production process being supported by the Legacy System must be understood in detail and will be reflected in the documentation describing the user requirements for the system. For Legacy Systems, this may be included in the Functional Specification (and a URS is not required) or conversely a URS may be in place (and an FS is not required). However, care must be taken to ensure that the current documentation reflects what the system is intended to do at present. It may have changed since first implementation, and indeed, the process this system is supporting also may have changed. (GAMP 4, Appendices D1 and D2 give guidance on the preparation of User Requirements Specifications and Functional Specifications.) The specification document(s) should contain the up-to-date system description covering hardware, software, and the system environment (physical and logical, i.e., operating environment, hardware platform, interfaces), as well as a definition of the functions and facilities provided by the system.

The specification document(s) should be understandable by both the operational users and the technical support staff/system administrators, and be readable, usable, and maintainable.

6.5 Design

Taking into account the criticality of the system determined by the GxP Risk Assessment, the route through the Legacy System validation process is now determined by the availability or not of the design documentation - *Figure 3*.

Where design documentation already exists this should be reviewed and brought up to date to ensure that each element of the Functional Specification is met.

Where design documentation does not exist and the application is not category 5 software, the configuration must be specified. (See GAMP 4 Section 8.1.3 and Appendix M9.)

Where the design documentation does not exist, some part of the application is category 5 software, but no further development is expected or the GxP risk is low, the configuration must be specified, and the system development 'frozen.' (If future code changes are unavoidable, the design documentation must be generated, but can be limited to the scope of the change.)

Where the design documentation does not exist, some part of the application is category 5 software, further development is required and the GxP risk is high, the Design Specification must be reverse engineered from the source code. When such 'reverse engineering' is required, it will be necessary to ensure that:

- The critical algorithms are correct, lacking defects, anomalies, and nonconformance to standards and best practice in the code, which would adversely affect the reengineering of the design documentation.

- The source code and the executable code are the same. (This will largely depend on how well the change control and program promotion procedures are/were controlled in the 'development' and 'live' environments.) (See GAMP 4, Appendix D5).

A properly executed Code Review will give a good indication of the overall integrity and maintainability of the code. The review should result in a report of the findings and any remedial actions that are necessary.

On completion of the Functional Specification and, if necessary, a Code Review, the Design Specifications are required. Guidance on the production of Design Specifications can be found in GAMP 4, Appendix D3 and Appendix D4.

In the event that specifications and source code are absent, the only possibility is to develop a Functional Specification from the process requirements and the system's functionality, as used. However, this in itself is insufficient and must be supported by evidence of reliability in use, such as a formal report of the history, use, maintenance, and change control records of the system, and by functional testing or Operational Qualification (OQ). The continued use of the system will depend on factors, such as the criticality assigned by the Risk Assessment process, and a replacement strategy may need to be considered. To ensure that each element of the user requirements is met by a design, a traceability matrix must be built which will subsequently ensure that each part of the design and each user requirement have a corresponding test. Guidance on Traceability Matrices may be found in GAMP 4, Appendix M5.

Prior to commencing the qualification phase, there is opportunity to review the data held within the system for continued relevance, accuracy, security, and integrity.

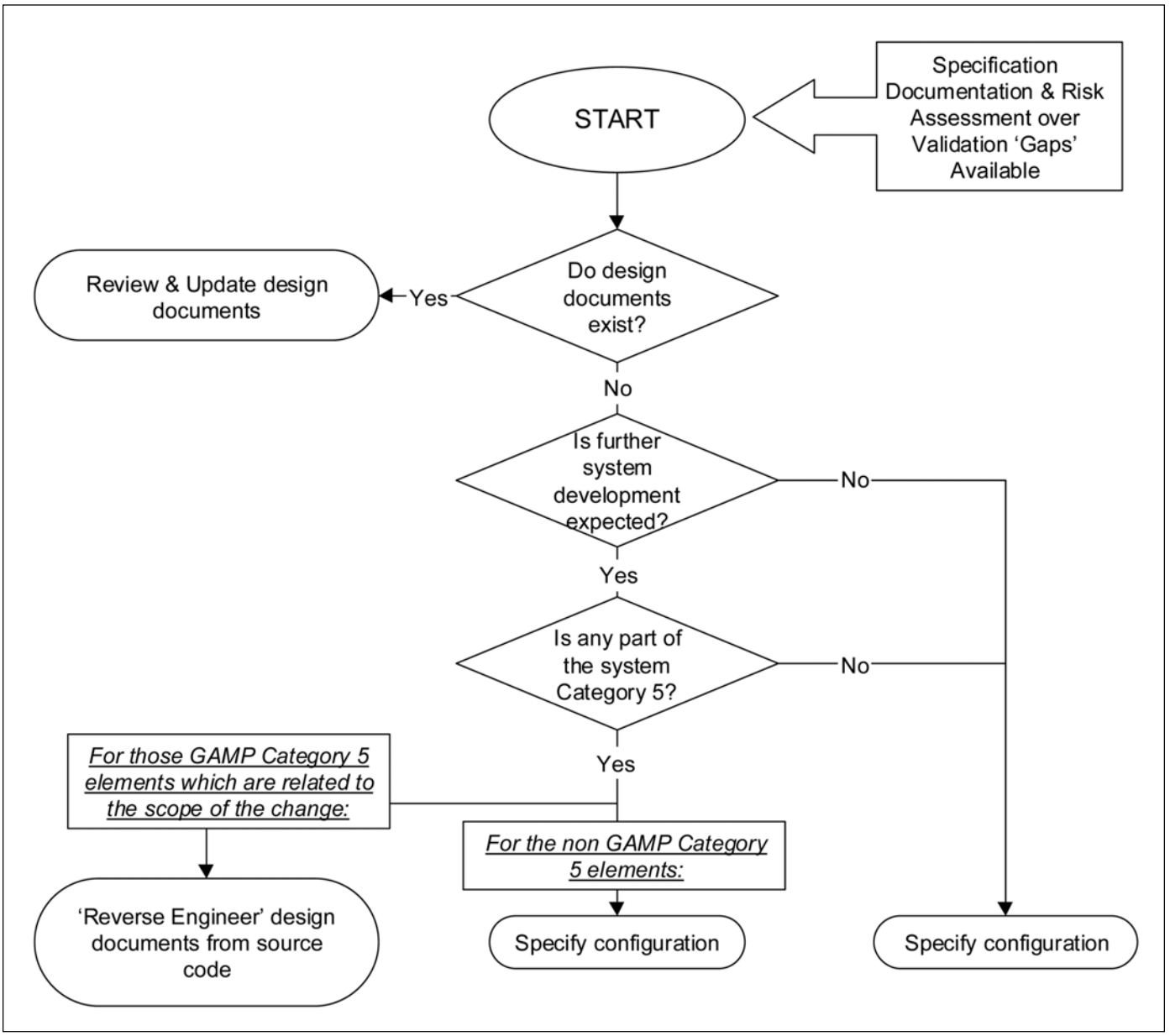

Figure 3. The Legacy System Validation Process.

6.6 Configuration Management

The design level review must address Configuration Management (see GAMP 4, Appendix M9) to ensure that all items subject to configuration control are identified in the design level documents and to provide a baseline for ongoing configuration management.

6.7 Qualification

Using the V-model (see Figure 2) as the framework for the Legacy System validation program, the left hand side of the V is now complete (Specification – Design – Code Review), leading to the right hand side, and the testing phase. Guidance on the scope of the testing phase, in particular Installation and Operational Qualification activities, is given in GAMP 4, Section 6: Validation Overview. Guidance on the details of each test specification may be found in GAMP 4, Appendix D6. It may be possible to review and reuse all or part of the existing Test Specifications. The Test Specification must include tests for all the critical processes in the system and for all anticipated routes through those processes. If any modifications have been made as a result of the review of the specifications or the code, then regression testing must be part of the testing program. If code has been amended as part of the Legacy System validation, then there should be properly documented module and integration testing prior to qualification activities.

When this stage is successfully completed, an appropriate Installation Qualification (IQ) can be executed, which will confirm compliance with the controlling specifications and create the new baseline against which to manage ongoing change control. (This does not require a re-installation of the hardware and software, rather it is a confirmation that what is already in place is what is required.) The IQ will be followed by the Operational Qualification (OQ), which will demonstrate that the system works across its expected operating ranges, and will challenge the system in critical areas, e.g., to demonstrate that it will fail safe when inappropriate entries are made.

The qualification phase also will assure, as with any system, that the procedures for the operation and continuing maintenance of the Legacy Systems are in place to ensure that the system remains in a state of control (see Section 6.9).

Finally, if substantial change has been made to the system as a whole, it may be necessary to confirm its performance in the 'live' environment by executing a Performance Qualification (PQ). All of this testing and qualification must be documented and the results retained as evidence of the success of the testing.

6.8 Reporting

When all of these activities have been completed and the procedures are in place, the validation program will be closed with the preparation of the Final Validation Report, which responds to the Validation Plan. The Final Validation Report should review the results and draw a conclusion on the continued use of the system. (GAMP 4, Appendix M7 gives guidance on preparing the Final Validation Report).

6.9 Maintaining the Validated State

It will now be necessary to ensure that the operational part of the Legacy System's life cycle is maintained in its validated state by ensuring existing operational procedures are kept up to date, clearly defining who is responsible for what.

The system owner is responsible for maintaining the validated state, which involves ensuring that the following operational procedures are in place and followed:

- Operational Plans and Procedures
- Operational Change Control (including data)
- Training
- Security Management
- Problem Management and Resolution
- Performance Monitoring
- Service Level Agreements
- Record Retention, Archiving and Retrieval
- System Management
- Business Continuity Planning
- Backup and Recovery
- Periodic Review and Evaluation
- Configuration Management
- System Retirement

Further details on these topics are provided in GAMP 4, Section 7.11: 'Maintaining the Validated State' and Section 7.11.14: 'System Retirement' and GAMP 4, Appendices O1 to O8.

Appendix O1	Guideline for Periodic Review
Appendix O2	Example Procedure for the Production of a Service Level Agreement
Appendix O3	Guideline for Automated System Security
Appendix O4	Guideline for Operational Change Control
Appendix O5	Guideline for Performance Monitoring
Appendix O6	Guideline for Record Retention, Archiving, and Retrieval
Appendix O7	Guideline for Backup and Recovery of Software and Data
Appendix O8	Guideline for Business Continuity Planning

7 References and Reading List

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This article presents current trends and technology in laboratory and development facility projects.

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Evaluating Current Trends and Technology for Laboratory and Developmental Facilities What's Right for Your Project?

by Bob McCleskey

The purpose of the article is to assist clients and project management professionals in evaluating some of the current trends and technology in laboratory and development facility projects. The applicability of new trends and technology should be based first and foremost on a clear understanding of them along with the functional needs and business drivers for each individual project. The development of preconceptions and the force fitting of concepts and ideas from other projects almost never results in a successful project. The article is written from a project management point of view and has an emphasis on project execution.

Most of the articles and seminar presentations on current trends seem focused on showcase R&D and discovery type laboratory facilities. The trend setting concepts which garner a majority of the attention tend to be in this arena. Determining how these concepts might be applicable to facilities that focus more on analytical procedures, clinical testing, and process development is often unclear. But some do, and a better understanding of them can lead to better solutions for these types of projects. Certainly, some of the new trends in design, technology, and project execution can be beneficially applied in varying degrees to all projects. The key is determining which ones and to what degree.

The functional, operational, cost, and schedule impacts of these advances, in many instances, cause major changes in the very way these facilities are perceived and how the tasks are accomplished. Determining which of these new trends and technologies may be appropriate for your project and to what extent has become increasingly difficult due to the ever-increasing rapidity and number of innovations and advances along with the renaming, repackaging, and renewed emphasis of previous concepts.

Trends are not always new. Many are a new emphasis, perspective, or angle. Some are a resurgence of an earlier trend that the time is now right for and current technology developments now make more feasible, or they might be a return to something that worked before because the latest trend did not pan out. What we are looking to identify are trends that better meet critical user requirements for our specific project. These are core trends and have staying power. We should be wary of the ones that resemble fads — here today and gone tomorrow, leaving behind a bad and costly experiment that has to be dealt with for a long time. Remember that the scientists are the ones that do the experiments.

Trend as used in this article refers primarily to an approach or concept, while *Technology* is defined as an applied science, the underlying systems and equipment that make the concepts possible. The *Dancefloor* concept is a trend in design, while the flexible casework and utility service systems utilized in its execution are technologies. Similarly, *Sustainability* is a design trend, while the materials, mechanical, electrical, and controls systems utilized as part of its application are technologies.

Few individual projects push the envelope to the extent of causing the development of new

technology. The time, money, and risks are almost always perceived as too great to offset the benefits. All this is to advise you to ensure as early as possible in the project cycle that proven technologies are available to support the concepts you are considering.

We will overview some of the current trends and technology as they pertain to design and project execution, identify issues to consider, and provide some guidelines to utilize in evaluating which applications are right, and to what degree, for your project. These are divided into the following three classifications:

- Design Trends
  - Flexibility
  - Sustainability
- Technology
  - Casework and Utility Service Systems
  - Fume Hoods and Local Exhaust Systems
- Project Execution Trends
  - Program Management
  - Teaming and Partnering
  - Early Project Definition
  - Decision Making

There is a wealth of in-depth information on the trends and technologies discussed in this article and others available in publications such as this magazine, at seminars, and in vendor literature. Some that are getting a lot of exposure such as currently popular terms *Dancefloor* and *Ballroom* which are variations for providing increased flexibility are not specifically covered here. Automation is another critical area with numerous developments, concerns, and issues. It is recommended that you thoroughly research any trends you feel may be applicable or are being considered for your project including visits to projects utilizing them.

Design Trends

Recent design trends have considerable impact on cost and operations of new lab facilities as well as the environment in which the scientists and technicians work. New trends whose cost justifications rely on significant savings in operational, facilities, and maintenance costs often are difficult to get approved. Correspondingly, those that require significant changes as to how the facilities will be operated and maintained can frequently have disappointing results, even with extensive re-training. There are sometimes significant differences in opinions as to how successful some of the concepts were in reality. Do not base your decisions on one perspective.

The following are two of the frequently considered design trends:

Flexibility

Flexibility is included as an initial goal or objective of most projects. The allure is too tempting. It has been a predominant theme of laboratory projects over the years with the usual constraints being the increased cost and the effort required making the conversions. Finding the right balance has always been the challenge with the optimum goal being no additional cost, or something you get for nothing. In recent years, technology has accelerated the development of new systems and products, which better support the development of flexible, open plan concepts. Two of the key technological drivers today are major advancements in the ease of conversions, some even at the push of a button, and competitive pricing due to the increasing number of products in the marketplace.

Flexibility Must be Defined for Each Project

Accepted meanings for words such as flexibility are much too general and open to broad interpretations to be utilized when setting requirements and expectations on projects. Flexibility is defined in dictionaries as the ready capability to adapt to new, different, or changing requirements.

- When used to state a goal or objective, flexibility must be clearly defined as to what it means for the specific project.
- Answers have to be developed to the questions as to what needs to be flexible, why, to what degree, and at what cost?
- Anything defined as having or needing "ultimate" flexibility should raise a red flag and get a closer look.

Project managers and financial people often almost instinctively interpret words ending in "-bility" as meaning spending additional money beyond what is absolutely necessary to meet the needs of the business plan. To this group, the best "-bilities" are those gained through better planning and design without any additional pre-investment. In essence, when the business needs it, the business will have the money to pay for it.

Popular Terms and Concepts

As mentioned earlier in this article, two of the more popular terms being utilized currently to denote flexible concepts are *Dancefloor* and *Ballroom*. The names are derived from an analogy of having an open floor and when the music changes, you easily change partners and the type of dance without disturbing others. These are interesting concepts that have been around awhile, but now have new names and most importantly new technology.

- These concepts are intended to allow multiple, quick, and cost effective reconfigurations with minimal impact on other operations.
- The high cost, time, and risks of disruptions of frequent reconfigurations are the factors used to offset the increased initial capital expenditure.
- In most instances, there is still the need for a "fixed grid" of utilities and lab services to provide for the flexibility

- The reconfigurations need to involve people trained in lab and space planning.

The ability of the space, furnishing, and equipment to be flexible and easily reconfigured should not be to the point of becoming a distraction to the scientist and technicians working in the area. In some instances, these folks can become seemingly more interested in moving things around to produce the optimum environment at the expense of the work they are suppose to be doing.

Recommendations

- The best solution always starts with the determination of the actual needs and benefits.
- First evaluate how much you can get without paying more such as allowing space on the site for expansion and locating areas that need expansion where they can be expanded.
- Then consider those solutions requiring additional cost and payback times to justify.
- Priority should be given to the core elements where a little more gains a lot or where changes later are extremely expensive or disruptive.

The above is not meant to be negative on the need and benefits of providing flexibility. It is an extremely important and beneficial element of most projects. But for it to be so, its meaning, cost, and benefits must first be clearly and measurably defined and analyzed as they pertain to each project. If a survey could be done to total all the money spent on flexibility that was never utilized, the amount would be staggering.

Sustainability

S*ustainability means meeting our needs today without compromising the ability of future generations to meet their own needs*.

The facts and figures regarding energy and natural resource consumption are frightening. We all need to do a better job in this area. Many of the things that can be done and have a positive impact are just good design and construction practices. Decisions, which impact this one way or another, will be made by team members throughout the execution of the project. Develop a plan to guide and manage these decisions and ensure maximum benefit. Do not ignore this issue and write it off on the premise it is too expensive, without developing awareness and understanding specific for your project.

Some of the Goals

It may be easier to understand what it entails and the applicability if sustainability is broken down into the following three main emphasis areas:

- Energy Efficient Design: conservation of energy use during the operation of the building.
- Conservation of Natural Resources: conservation and use of renewable resources and materials and the energy used in manufacturing them.
- Quality of the Environment Created: the environment within the building and the impact on the surrounding environment.

These are not new ideas, but rather a renewed emphasis. Sustainability is an expansion beyond just the operational energy efficiency of the building to include a focus on the materials and construction approach utilized. With planning, the pieces can always be put together a better way. Here are some potentially no or low cost applications and approaches to consider:

- use of *green* and local construction materials (Green refers to the use of renewable resources and energy efficient manufacturing.)
- construction waste recycling
- daylighting
- rainwater and condensate collection and reuse

What has Changed?

- Better design tools such as computer modeling and simulation allow for the development, study, and actual performance testing of various scenarios quickly and cost effectively.
- Advancements in the development of materials, equipment, and systems provide more options and increase competition.
- Globalization, the merging and consolidation of companies, is bringing with it a richer blend of wants and needs along with concepts, materials, technology, and systems.
- Competition for the best and the brightest employees is driving clients to want better quality environments.

Recommendations

- Do as much as your business plan can afford and to the extent your company is willing to commit.
- Start with a plan to address the no or low capital cost items. Then identify those with the shortest payback periods.
- Avoid “fuzzy math” by getting facility operations and maintenance involved.
- Be conservative in your calculations and promises.

Technology

Increased flexibility, energy conservation, and safety also have been the major themes for technological developments in laboratory casework, fume hoods, and control systems over the years. Casework products have been introduced such as C-Frame, Rail Supported, and Moveable Systems which are major advancements from the fixed floor supported systems, but the flexibility potential of these systems, particularly the ease of flexibility, seemed to be too constrained by the static nature of fume hoods and laboratory utility services. Recent advances are now continuing to break through these barriers, which are allowing laboratory design to get closer and closer to ultimate flexibility on demand with little or no impact on ongoing operations.

- Now that the technology is available to support "ultimate" flexibility, how much does your project need and at what cost?
- Give the users the tools and environment to help them accomplish their tasks in a productive manner, but not to the point of distraction, not to the point that technology becomes the focus.
- Fortunately, advances in design technology have kept pace. Computer modeling and simulation help designers develop and test options and variations quickly and cost effectively. These can be utilized interactively with the user groups.
- Technology is not a substitute for good planning and design.

Laboratory Casework and Utility Service Systems

There are numerous choices and options available for laboratory casework. If you have not been involved in the development of laboratory facilities lately, take the appropriate amount of time to study and evaluate the products that are available. Visit with your team installations of the systems being considered and talk with the users and facilities people when possible. Utilize mock-ups and let your user groups and facilities people interact with the proposed systems.

Do not feel as though you have to select one system for the whole facility. Determine which systems best fit the needs and requirements for each application. Utilizing enough of the main system in order to be able to interchange components is an important consideration for flexibility, but not all applications require the same degree of flexibility.

While increased competition has helped, these new systems do initially cost more, sometimes significantly more, than basic, fixed, floor mounted systems.

Some Things That May Help

- For each application, make your best assessment of whether or not modifications or reconfigurations to the system will be necessitated over time, what those modifications will be, and when and how often they will be required.
- If there will need to be modifications, assess the potential impact on the ongoing operations, the costs and how much disruption can be tolerated.
- Many projects incorporate functionally appropriate blends of flexible and fixed systems. In fact, this may be the norm. Avoid buying flexibility for areas where it will most likely never be used. Just in case is usually not enough a justification.
- Projects are evaluating more objectively the type of casework materials and finishes appropriate for each application. Almost all casework is modular and many of the different type systems and components can work together.
- When you use the new systems, maximize the benefit of the ease of flexibility with little or no impact on ongoing operations. Utilizing the new systems like the old systems usually results in buying too many of the wrong components. After all, they are flexible and easily added or changed out.
- Buy only what is needed to meet the immediate program requirements. If you want to be conservative, buy some additional components as inventory as a contingency.
- In the past, a lot of bench casework was bought for the main purpose of holding up tops. The storage that came with it was often the wrong kind, in the wrong place.

Utilization of the inventory as a contingency can help encourage people to take a closer look at their immediate needs without the fear of having to get it now or never. This approach allows flexibility in the use of an inventory to accommodate changes in users' needs that develop during the design, construction phases well as during operations.

The use of overhead, laboratory utility service distribution systems such as the "wing," is a trend gaining popularity and is frequently utilized in concepts such as *Dancefloor* and *Ballroom*. Most often located above the bench and at overhead shelf height, they are out of the way, while still reasonably convenient. Laboratory gases, water, drains, electricity, data, local ventilation, and task lighting can be incorporated within the "wing" concept. The development of safe and dependable "quick connectors" for lab utilities and services and "re-locatable" exhaust systems has not only greatly improved these concepts, but added flexibility to others. All this can provide a lot of flexibility, but it can come at a high premium cost.

Fume Hoods and Local Exhaust Systems

The following statement best sums up the ultimate goal for fume hoods in laboratories:

To ensure safe operation at minimum possible operating costs while maintaining the capacity and flexibility to meet user demands.

Discovery and Research and Development facilities tend to require significantly more fume hoods than the laboratory and development facilities projects that are the focus here. As a result, the conditioning of air to be exhausted is one of the larger potential energy users in these facilities. It is therefore an understandable focus for energy conservation. There are two basic variables, volume and velocity, that can be changed on hoods to achieve better energy conservation. For accessibility reasons, users really did not want to reduce the size of the face opening, so that left the reduction of the face velocity as the option.

Manufacturers of fume hoods are showing themselves equal to the challenge, with each of them introducing new products that get closer to the ultimate goal for fume hoods as stated above. The progress is impressive. The results are reflected in the use of the following new terms:

- Low Flow Fume Hoods: designs that provide a reduction in required exhaust volume from the traditional 100 fpm at sash full open vertical position.

- High Performance Fume Hoods: designs that provide a reduction in required exhaust volume from the traditional 100 fpm with the sash full open vertically and provide equivalent containment with the sash full open vertically at 60 fpm or less.

When considering the use of these new hoods, it is important to remember some causes of fume hood failure:

- room cross drafts
- insufficient exhaust airflow
- insufficient make up airflow
- improper room pressurization/air balance
- improper design of exhaust stacks and reentry of exhaust fumes

Some other trends in laboratory exhaust systems to consider include the use of local, point of exhaust systems, and minimal hoods. Technology and product development has come a long way in these areas with new options continually being introduced. Again, buy what you need, not what you don't. If you do not really need a fume hood for the application consider auxiliary exhaust systems.

While it is important in all areas at a project, it is critical in the design of the HVAC and exhaust systems to have an expert on the design team. This is even more the case when utilizing the low flow and high performance systems. As with any new technology or products, you do not want your project to be the experiment. Review existing installations and talk to the users and facilities people.

Project Execution

Program Management

Project Execution approaches continue to evolve, but mostly new names and phrases have been developed to describe the basic techniques that have been employed over the years. Fast track, hyper track, flash track, etc. are all catchy phrases, but if you look back in history you will find well known examples of large, complex projects done with unbelievably compressed schedules and tight budget constraints. What did most of them have in common? They had one team in charge of leading the project execution, in control and accountable for the scope, schedule and cost. This is now what is referred to on large, multi-firm projects as Program Management. It is being re-emphasized for the same reasons it was originally developed.

Projects are much larger and complex with tighter budgets and compressed schedules. Time-to-market requirements, while maintaining cost competitiveness, have become critical to success in many markets and the future well being of companies. With the amount of money and risks involved, clients are looking to a single company to manage the total project delivery process from inception through start-up, commissioning and qualification. In many instances, they are also requiring that these Program Managers share some of the risks.

Program Management starts with the basics of first defining and then controlling the scope, schedule, and costs. It requires the integration of all the resources, pieces, and parts into one baseline for the overall project that can be measured and controlled to bring certainty to the outcome.

Recommendations

- Projects are always, first and foremost, about quality and capability of both companies and people.

- You need a company that has Program Management experience on successful projects of similar size, types, and complexity. You do not want to be the project that helps them get into the business.

- The company's management must be committed to your project. Executive sponsors, the decision-makers, need to be assigned for each project team member and client company to a steering team that meets on a scheduled basis. There will be issues and concerns that are best addressed and resolved face-to-face.

- Open and honest communication is extremely important. You must be able to disagree and resolve disagreements without getting mad. You are paying your consultants for their expertise. Do not destroy the benefit by punitive actions against those who express differing opinions.

- The company must commit the right people to your project with experience on successful projects of similar size, types, and complexity. Require personal, former client references, and verify them for the key people proposed.

- Understand how they propose to execute your project and why. There are always alternatives to be considered. Find out what they are and why they selected the one being proposed.

Teaming and Partnering

Complexity, speed of change in design, and rapid advancements in technology make it difficult for any one firm to keep up with everything. An approach being utilized more frequently on large projects are multi-firm teams. These can either be assembled by the clients, the firms, or a joint effort of the two. Here are some suggestions:

- The best team is not always made up of all the best players at each position. They may be all-star players, but is it an all-star team? Do they work together?
  - All parties should be open about it. Discuss the needs and options and develop the solution together.
  - There should not be side agreements and hidden agendas.
  - The firms have to be aligned as a team and understand and respect each other's roles and responsibilities.

- With the need to be more inclusive of specialists and experts early on in the project definition process, teams, or at least portions of teams need to be assembled and aligned before the start of the project definition phase.

- Teaming can help ensure you have the design and project execution expertise to deliver consistent quality for the total facility. It can help to add strength and focus to critical areas where one firm may be weak or is not "cutting edge." Get the right resources involved.

- Do not buy the argument that each firm must report directly to you, the client, or they can not do their job. The concern may be that their ideas and concepts will not get fair consideration; however, there are other ways to better address these issues.

- Clients' team members have to stay engaged, particularly in the early phases. Popping in and out of the process creates confusion and backtracking.

- There must be a leader and a leadership team to set the vision, framework, and keep it all together and on track.

If you need to add or change a team member or refine their scope or their role, do so immediately. Few things on a project get better with time. Unresolved issues usually come to a head at times you and the project can least afford it.

Early Project Definition

Reflecting the need within their companies, clients are requiring that projects develop more certainty, earlier, that they are going to meet the functional and regulatory requirements within the schedule and budget contained in the business plan. The business need for a project is identified, the feasibility studied, and commitments made to a business plan as part of an internal strategic planning process prior to the initiation of programming and the conceptual phases for most projects. Financial and accounting people are extremely important team members during this strategic planning process and are increasingly continuing in prominent roles as members of the client conceptual phase team.

For the type of projects that are the focus of this discussion, cost/benefit calculations and analysis for the buildings, systems, and operations are applied as rigorously as they are for the manufacturing and production areas. If it is not necessary to ensure the quality, quantity, lowest cost per unit of the product, then it is probably not in the approved project funding.

In order to meet these needs to provide certainty earlier, additional emphasis is being placed on the early definition phase of projects and the inherent need to establish a baseline for the project that will bring certainty to the desired results - meeting the business plan.

Project Baseline

The project baseline needs to be a clear, complete definition of the project that can be utilized to track and control it. There are a number of different terms utilized, but the major components are the same:

- Project Approach and Execution Plan
- Scope of Facilities
- Scope of Services
- Integrated Project Schedule
- Detailed Estimate

In order to bring certainty, the project baseline needs to go beyond the normal design basis or conceptual design report to include the overall project approach and execution plan. The team needs to be expanded to not only include those normally involved in the design, but also procurement, construction, start up, and commissioning, qualification, and operations.

Multi-Discipline Team

From the design standpoint, having a team composed of multi-discipline specialists experienced in the programming and conceptual design process for the specific type of project has become critical. For developmental and process related projects or portions of projects, the trend is to refer to these experts as Facilities Integrators, and for laboratory projects, as Lab Programmers. Almost all firms have capabilities to varying degrees to provide programming and conceptual design services. But in order to develop a complete definition and layout for these types of projects at an earlier stage that has the required degree of certainty, you need specialists on the team.

Estimates

The estimate has to be tied to the design, schedule, and execution plan in order to establish a credible baseline. The trend is away from relying solely on design generated, factored estimates. It is important that the estimating process involves the entire team and quantifies and breaks down the project into a structure that can be utilized to track and control the project. By doing so, the tools and responsibilities

can be given to designers to design to the estimate. If changes need to be considered, they are identified early enough that viable options can be developed and considered in order to ensure the most cost and schedule effective solutions.

Caution, there are a lot of numbers out there. Historical data, benchmarks, and factors are available in abundant supply. Before utilizing any of these, make sure you know where they came from, what the basis is, and when they were developed.

The wrong numbers can lead to development of unrealistic and unattainable expectations.

If changes need to be made in order to meet the budget, then they need to be made in the early definition phase with the users' buy-in. These are the best people to identify what can be cut and still meet the objectives of the business plan. If the changes are made without their involvement and buy-in, the cuts tend to creep back into the project in the later phases, at premium costs, and with schedule impact.

Do not leave this phase until the project is fully defined and has a corresponding estimate and schedule that the team and management have confidence in.

Decision Making

As mentioned earlier, there are a lot of acronyms and slang utilized to describe executing projects faster and some excellent techniques and tools to utilize in doing it. One easy-read resource that offers a somewhat different perspective is a book titled *Critical Chain* by Eliyahu M. Goldratt.

No matter what phrase you utilize for needing to do a project faster, it boils down to the compression of the project delivery process with the key, critical ingredient being the absolute necessity to make better decisions, faster. There are literally thousands of decisions that need to be made on a project and they cannot all be made at once. A well-defined decision-making process must be established to identify the critical decisions, the inner dependencies and accountability for making the decision in support of the overall schedule.

It is normally the chain through critical, inter-dependent decisions that in fact become the critical path for the project. The making of decisions in a consensus driven organization is usually the hardest area to compress in a schedule-driven project. This is especially true when the key decision-makers are spread throughout the organization with no real time commitment to the project.

There has to be a commitment from the real decision-makers, from people who can make decisions that stick. A trend on some projects, with the concurrence of the client, has been to employ a default mechanism. Each decision presented to the client identifies the default recommendation. If the decision is not made in a certain timeframe, then the recommendation becomes the decision. This is not the preferred approach and can result in key people becoming less involved in the project. Decision makers have to be able to make decisions in a "time is of the essence" manner that stick.

Final Notes

There are many additional important trends or areas of increased emphasis, which need to be understood and their applicability to new projects evaluated. Two in particular result from expanding project execution to include the total project with a focus on the final result. These are Start-Up and Commissioning and Documentation and Qualification. The inclusion of both efforts in projects from the start can result in significant savings in time and money while helping to increase the certainty of meeting the needs of the business plan.

- Incorporating new trends and technology will not have as positive an impact on a project's success as will good project planning, design, and execution.

- At the beginning of projects, you can have the biggest positive impact at the lowest cost. However, spending a disproportional amount of the schedule and money on determining the design and not leaving enough to adequately develop and convey it to construction is just as bad - achieving the ultimate design concept does not accomplish much if it cannot be executed.

- There is a determined amount of need, time, and money to deliver a completed project. Maybe it's a novel, a short story, or an article for a magazine, but all the execution steps still have to done, all the gates gone through. The goal is to balance scope, schedule, and money, and deliver a completed project that meets the business plan. The best projects are those that reach a proper balance.

- Before adding new trends and technology to the other tools in your bag, make sure you understand what they are, the whys and the wherefores, and how and when to use them. Just because you have them does not mean you have to empty your bag on each and every project.

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About the Author

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This article describes a new, cost-effective design method for increasing productivity in new or renovated laboratories.

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New Laboratory Design Helps Speed Up Research

by David Withee

It may be a bit obvious to state Thomas Edison did a lot of things right. What may not be so obvious is that Edison was ahead of his time in the field of laboratory design! Edison kept his laboratories simple; his "benches" were primarily four-legged tables that he could drag anywhere he wanted them, whenever he wanted to do it, and he could do it himself. There was no need to schedule facilities management staff to reconfigure his laboratory for him; he just did it and went on with his research.

Of course, times have changed. Computers, robotics, analytical instrumentation, and other instruments have changed the way we do research, and they also make it more difficult to change the research methods we use. Networks, high purity gasses and waters, wireless systems, and other services required for the modern laboratory both enable our research and immobilize our laboratory designs.

Yet, the pressure to bring research solutions to market faster continues to build. For example, it now takes $800 million to $1 billion[1,2] to bring a new drug to market. More important, it takes 10 to 11 years of the life of a patent before a drug is developed, successfully gone through trials, and met regulatory approvals. That doesn't leave much time to recoup the investment and generate funds for additional new drugs. Industry consolidation in the hope of generating economies of scale only adds to the pressure. As a result, anything that can help speed up the process is being given consideration.

This article describes a new design for laboratories, called the Open Lab. The design is particularly cost-effective for laboratories that use many instruments and/or robotics, which are frequently rearranged and/or replaced. The design also is useful in laboratory facilities that are frequently reconfigured to meet the needs of ever-changing project teams, incubators, leased facilities, etc. While the design is cost-effective even for laboratories that do not change even once a year, if at all, such as quality assurance labs, it may not be comfortable for researchers in those labs. The key question to ask is not does this design work for my size or type of lab, but will I need to reconfigure my lab and/or instruments (for whatever reason) at least once a year? If the answer is "yes," then the initial installation savings combined with the later productivity and reconfiguration savings are a boon both to the researchers and the accountants.

Figure 1. The open lab concept includes overhead service carrier for utility distribution combined with mobile casework and instrument carts for easy reconfiguration by researchers.

Figure 2. An occupied open lab looks like any other lab but can be easily and quickly reconfigured at any time by the researchers themselves.

The Design Problem

The newest design in robotics assemblies must be integrated into the high throughput screening system. A new mass spectrometer must be installed where a workbench currently resides. Oops, corporate priorities have changed and this must now be a nanotechnology lab instead of a bioinformatics lab. How do you quickly and cost-effectively make any of these, or other, changes happen? By using a different laboratory design.

Laboratory design hasn't really changed much over the years. Cabinets made out of steel or wood, arranged in "islands" or "peninsulas" with sinks at the ends pretty much describes the state of the art in laboratory design over the last 100 years. Some innovations have developed over the years, such as c-frame in the 1960s and so-called "flexible" systems in the 1980s, but generally speaking they only have provided minor incremental gains in adaptive use of laboratories. Our plumbing and electrical services often are located (either up from the floor or between cabinets) where they impede the redesign of a laboratory without closing down the laboratory and bringing in contract labor to move everything around. That's neither cost-effective nor timely.

Bench design isn't the only problem. We spend inordinate amounts of time trying to design the laboratory so everything is in just the right place for the specific needs of each researcher and project team. Here's the time problem again. Laboratories are often in the final stages of being built or renovated without the actual project teams and Principal Investigators (PIs) who will occupy and use the labs having even been identified! Even when they have been identified, the odds are pretty good they will change – maybe more than once – before they even get into the labs. And the science! New types of science are being developed faster than we can learn how to pronounce them: nanotechnology, bioinformatics, proteomics, and more that spell checks just don't recognize.

Add to that the fact that the instruments, computers, robotics, refrigerators, and freezers, etc., that the researchers will use will often themselves change before occupancy of the lab takes place as new, more productive, and more cost-effective generations of products are developed and delivered. "Oops, that doesn't fit into our lab design" isn't an acceptable response. The design and the lab must be able to adapt at a moment's notice to changing conditions.

Everyone who supports the researcher – architect, laboratory designer, facilities management, and laboratory management – must be open to new ideas to help the researcher be more productive. Don't forget the researcher; as cutting edge and innovative as they are in their research, PIs are often the least accepting of change in their environment.

So, how do we use laboratory design to help make the researcher more productive? Can a laboratory facility actually encourage the advancement of science and technology? Can it also be cost-effective?

The Open Lab Concept

This article would be short if the answer to those questions was "no." Actually, there is a new concept in laboratory design, and it has taken the design community by storm since Bayer Corp. was awarded the R&D Magazine Renovated Laboratory of the Year Award in 2002 for their High Technology Center in West Haven, Connecticut.[3]

The Open Lab is simple in concept as well as in execution: design the lab so the researchers themselves can reconfigure everything within the lab when and where they want to do so - *Figure 1*. That's what Edison did, and it worked for him. The question is how do we make it work for us in today's research environment with all the additional resources we now use for our research?

To make an open lab work, we have to plan for four elements: utility distribution, movable components, casework, and the ability for the researcher to personally reconfigure the laboratory. These four elements are designed into a "dance floor" arrangement, that is, where everything that must be fixed is on the perimeter and everything else in the room can move to wherever its "partner" takes it.

The results can be outstanding. As one Project Engineer at a major pharmaceutical company stated, "We wanted the flexibility and adaptability for now and in the future. Our goal was to be able to accommodate any science with little or no disruption." - *Figure 2*.

Utility Distribution

Typically, services are often stubbed up from the floor or are brought down from interstitial space above the laboratory. It is then routed between cabinets or through "flexible" systems modules. Obviously, as soon as something comes up through the floor it creates a barrier to the free movement of design components. No need to discuss that further as the implications are obvious.

So-called flexible systems were actually pretty innovative when they first came to the design community. They are composed of service modules that attach together to make a semblance of a wall and provide a means to run services through the module. Casework also can be suspended from or placed in front of the modules. If a laboratory is going to be reconfigured at least once a year, it is typically less expensive to use a flexible system than dry wall and fixed casework when you take into account landfill costs of removed drywall, laboratory down-time, contractor costs, etc. Also, some firms are quite adept at reconfiguring these systems with their facilities staff, and rightfully proud of their ability to reconfigure a laboratory literally overnight. The problem with flexible systems is that they require someone else to do the actual reconfiguration. The major reason someone other than the researcher must do the work is because those services are typically hard-plumbed and -wired through those service modules. "Someone other than the researcher" translates into additional time, and we don't have time to spare.

If we don't want the services in the floor, and we don't want them between the cabinets, the only place left to go is up. Yes, put the services overhead. This isn't any different than what is done with air hoses in auto repair shops or in manufacturing facilities. Get your services up and out of the way. Now you have removed one obstacle to rapid reconfiguration by the researchers themselves - *Figure 3*.

Does it work? At Bayer, the researchers totally reconfigured their 5,000 square foot (465 square meters) lab nine times in the first year without the assistance of facilities staff or outside contractors. They credit the lab design as one reason why they were able to more than double the number of weekly screenings they were able to accomplish.[4]

Bayer actually tried two different overhead distribution designs. One was a vertical drop from the ceiling that stopped about seven feet above the floor. The other was a horizontal system, suspended from the ceiling and similar in appearance to a lighting fixture. Bayer has now standardized on the horizontal system, finding it is much easier and cost-effective to run additional lines than in the vertical drops, whether plumbing to bring in a new gas for a new instrument or the new data line or upgraded power requirements. Even the initial installation was more cost effective than past practice because the plumbing and wiring could be installed in the service carrier while it rested on saw horses. The service carrier was then lifted into place, final connections made, and leak tests performed. Installation of services was faster with better quality. Bayer also found the horizontal system gave them increased capability to move instruments anywhere on their "dance floor" since service fittings can be located as frequently as desired anywhere along the length of the overhead carrier.

Implementation is simple. Suspend the service carrier from the interstitial space above the ceiling. Locate it so

Figure 3. Overhead service carrier keeps services up and out of the way of mobile casework and carts underneath, yet handy for quick instrument connections.

Figure 4. Laboratory-grade instrumentation cart capable of holding 1,000 lb. loads comes with push-button electric height adjustment for improved ergonomics, productivity and safety.

connections to service fittings are typically seven feet off the floor. Additional services can be added later. Instruments can be as easily connected as they are in traditional lab designs.

Not all services were put overhead, of course. Due to building code requirements regarding venting, the water and waste lines could not be located in the service carrier (although this is frequently done in European laboratories.) To support the open lab concept, they were merely located along the walls on the perimeter of the laboratory. Other services, such as HVAC for fume hoods, or biological safety cabinets, also are typically located along perimeter walls.

Another pharmaceutical company, which we'll refer to as Pharma since it prefers to not be named for competitive reasons, toured the Bayer facility and applied the same Open Lab concepts to their renovated facility. Pharma found a way to improve the overhead distribution system, purely accidentally and purely out of necessity.

It doesn't seem like any construction project is completed fast enough, and renovations experience even more pressure because of the distribution that exists in the rest of the operating facility. This was the case with Pharma. As the owner representatives, contractor, mechanical contractor, and architect met to discuss ideas for speeding up the project, someone realized the service carrier was going to be pre-plumbed and -wired on saw horses on site before being lifted up into place. The question was asked if this could occur offsite and in parallel to other activities rather than in sequence to them. This action alone cut the total time required by the mechanical contractor for plumbing (wiring also was done) from six weeks to three weeks, and only one of those weeks was on site.

This simple, incremental step of taking the work off-site adds benefits everywhere. With the mechanical contractor doing work off site, there was less trade stacking on site with less jockeying for use of the elevators and other hassles that are standard fare on a construction site. Fewer staff on site means fewer orientations and hopefully fewer safety incidents, which helps lower worker's compensation premiums for the contractor. The quality of the plumbing and wiring was better because it could be done in an environment more conducive to quality work, rather than crawling between cabinets. Improved quality – and initial testing at the mechanical contractor's facility – meant less likelihood of on-site quality fixes being necessary.

Movable Components

Now that the services are out of the way, you can plan to make almost everything else movable. "Almost" because some items still aren't going to move well, such as sinks and fume hoods. If we can move everything else, we can reap enormous dividends.

- Instruments no longer used in one location can be quickly moved elsewhere where they are needed.
- Instruments can be placed back to back. When servicing is needed, they can be rolled out into the aisle and serviced. This means you no longer have to include in your design a service chase space between cabinets, which is rarely used. The result is more space in which to put more instruments and work stations (or less space is required).
- As new instruments and equipment arrive, existing casework can be rolled out of the way to make room.
- Since they are all mobile, everything can be "installed" later than is typical in the construction process, putting less stress on the other trades.
- Actual installation cost, which can be as much as 40% or more of the cost of fixed casework and flexible systems,[5] virtually disappears. Everything is just rolled into place! Researchers can move items around to preferred locations as they occupy their labs.
- New project teams taking over existing space can easily reconfigure mobile components to meet the needs of their team.

All that is needed is to add casters. Casework doesn't have to be fastened to the floor or suspended from the work surface. At Bayer, they realized it wasn't just the casework they wanted to be able to move, they also wanted to move the work surfaces above the casework. (Moving simple tables as Edison did won't work today because of the much greater loads being placed on the work surfaces).

The idea of moving work surfaces has been around for at least 10 years, when the first laboratory-grade cart systems

began to appear. Built for heavy load bearing and stability, they provide reassurance that it is okay to move those expensive instruments around the lab. Bayer wanted a next-generation cart, though. The then-current state of the art cart could move horizontally easily, but not vertically. Vertical movement required staff to physically remove the work surface from the cart and relocate it to the new required height and reattach it to the cart. This wasn't going to meet Bayer's needs.

Today's labs are often used for more than one shift, and people of different heights are using the same instruments. Two people at different ends of the height spectrum could both suffer from ergonomic problems and related loss of productivity associated with the use of a fixed height work surface. Bayer found a supplier that offered a laboratory grade cart whose work surface went up and down electronically with the push of a button - *Figure 4*. Hydraulic adjustment was not acceptable for an obvious reason; no one wants a leak! Sounds simple, but someone had to ask for it before it came into being. Now researchers can easily and simply adjust a work surface to whatever height is convenient, from 28" to 40" above the floor with the push of a button. You can lower the surface to allow samples to be loaded at the top of the instrument and then raise it back up for convenient operation. With a 1,000 lb. load bearing capability, the cart can handle virtually any instrument, robotics, or other equipment that needs to be placed on it.

The Pharma facility again found an opportunity for incremental improvement. They were concerned about vibration isolation for their instruments, as well as the need to ensure a level work surface. Casters, even when locked in place, can still move slightly when bumped. The Pharma staff asked instead for their "cart" to actually be on levelers instead of casters. To move the carts, a simple, but strong dolly was developed. The dolly is wheeled under the work surface, the work surface is electronically lowered onto the dolly and then the motor keeps running to lift the feet off the floor.

Whether on a cart or on a cabinet with casters, laboratory components can now be easily moved around by the researchers themselves.

Casework

Laboratory-grade casework can be made of painted steel, wood, or high-pressure laminate. The choice is typically one of personal preference and each typically performs well if made to meet laboratory performance requirements. A good credential to look for in your casework vendors is if they are members of the Scientific Equipment and Furniture Association (SEFA). SEFA members include all of the leading manufacturers of casework, fume hoods, and related products that are used in laboratories. The SEFA 8.0 standard for casework is considered the benchmark of the design community.[6]

One lesson both Bayer and Pharma learned regarding casework is that they didn't need as much of it as before. Casework today is often used as much to hold up the work surface and what is on it as for any other reason. A movable cart meets the same need with additional benefits.

Some casework is still needed, though. One benefit of making casework mobile is that you can have an additional work surface. As instruments, computers, robotics, etc., take over the standard work surface space, there is little space left for the researcher to place note pads, notebook computers, samples, and other support items. In those cases, just roll a cabinet out from under the work surface and another work surface is now available – *Figure 5*. In some locations, additional instruments can be located on the mobile cabinet and yet under the work surface of the cart. Additional vertical space is now available.

Another benefit of mobile cabinets is that it is easier for researchers to move themselves and their support materials as they join new project teams elsewhere or just need to take materials to another part of the lab. Minor, but incremental, benefits all contribute to improved researcher productivity.

Reconfigurable by the Researcher

So, the utilities are out of the way and we have the use of movable components including casework and laboratory-grade carts. The only question left is how easy is it to connect instruments up to the overhead services? Seven feet off the floor may not seem very high, but it can be, especially if you must reach around other mobile items and instruments.

Instead of connecting directly to overhead service fittings, Pharma decided to make it simple. Quick connect service fittings were used for plumbed services in three areas. First, they were used to connect hoses to the overhead service carriers - *Figure 6*. The hoses hang almost to the floor. Next, as a cart is rolled into place, the hose is attached to another

Figure 5. Mobile casework and carts make it easy for researchers to reconfigure the lab setting at a moment's notice.

quick connect fitting located on a service manifold on the rear of the cart - *Figure 6*. Finally, instruments are quickly connected to necessary services using quick connect fittings on the front of the service manifold. All quick connect fittings are coded by shape so you don't accidentally make an incorrect connection and damage an instrument or your research. Everything is now located for maximum convenience. The quick connect fittings are capable of handling up to five nine's of purity (99.999% pure). Varying electrical services also were available through the service manifold to meet the specific needs of different instruments.

The researcher is now capable of reconfiguring the laboratory at a moment's notice.

Cost

Initial impressions are that this must cost more; surprisingly, that does not appear to be the case. Of course, you need to make a comparison of total costs to identify the total savings.

One architectural firm did its own analysis. It compared a simple laboratory design using traditional floor-mounted steel casework, epoxy resin tops, fittings for high purity gasses, etc., with the cost of the same lab in an open design. Included in both was the cost of the actual plumbing and wiring activity, not just the cost of the purchased components.

Figure 6. Quick-connect fittings are used on the overhead service carrier and the rear of the service manifold on the cart to simplify service connections when instruments are rolled into place.

The traditional floor-mounted laboratory design cost $917 per lineal foot; the open lab design only $741 per lineal foot. Much of the savings comes from making labor costs go away, such as installation of fixed casework which typically adds as much as 30-40% of the cost of the casework to the total cost. Instead of bringing in carpenters for installation, staff can just roll mobile cabinets and tables into place.

The above analysis did not include the additional benefits from pre-plumbing and wiring the overhead service carriers. It also did not take into account the cost of down time for researchers when reconfiguring a traditional fixed casework laboratory design.

Of course not all laboratories are the same or have the same needs. A simple quality assurance lab will probably never have the need for high purity gasses, much less to be reconfigured on a regular basis. Other labs will have much more of a need for just electrical and data support rather than gasses. The cost impact depends on the particular needs of the specific laboratory.

For laboratories with intense use of instrumentation, robotics and other equipment, though, and with a high likelihood of regular reconfiguration, the open lab design appears to be very cost-effective.

Results

Now, some may say the researchers have more important things to do than move their casework and instruments around, and that is true. They are there to do research. So, what do the researchers and staff have to say? Here are some comments from the staff at Pharma:

> "We love our lab. I've never worked in a lab that compares to this. The overhead distribution is so easy to use. The system is easy to change, and I like the way all the cords, hoses, and other connectors are back behind the bench, keeping the mess off the lab top. I'm actually having fun adapting my lab space to meet our needs. Being able to have a system that you can quickly change yourself makes it not only a much more productive environment, but it's fun." PhD, Scientist

> "Buildings by their very nature have barriers to science. We feel with this building we have eliminated most of those barriers." Director of Engineering

> "A big advantage is people can take charge of their space – they can control the space to enhance the science that can be performed there." Project Engineer

> "In one case, I had more bench space than I really needed, but my freezers were at a more remote location. I was able to roll out two benches and the related cabinetry and move in my freezers where I really needed them." PhD, Scientist

> "It takes less time for the researcher to reconfigure their instruments and benches themselves in these labs than it takes just to write up a change request to submit to

facilities management. Then you get the additional savings of not having to attend later meetings to explain the change request. Add to that their ability to change at once without waiting for someone else's schedule and you have a much faster process, making it possible to increase the time spent doing science. Having more time to do science is what this is all about." Laboratory Manager

"The proof is here; everyone else wants a lab that has the features of these new labs." Scientist

"The bottom line is our next expansion is planned exactly the same as this project." Research Director

As further proof of the simplicity, cost savings, and productivity associated with the Open Lab concept, it is now being used in wastewater treatment plants, teaching colleges and universities, and even in high schools to decrease the size of science classrooms without sacrificing teaching capabilities.

Conclusion

Edison had it right. If you need to reconfigure your lab, make it easy for the researcher to do it so more time can be spent on science and less time spent on justifying the need to get someone else to reconfigure the lab for the researcher.

Consideration of the Open Lab concept could end up helping your company speed up productivity and help bring products to market more quickly.

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About the Author

David Withee received his BS in management from the Massachusetts Institute of Technology and his MBA from the University of Dubuque. Withee is the National Sales and Marketing Manager for Case Systems, Inc., a leading supplier of furnishings for laboratories located in Midland, MI. In addition to serving for seven years on the Board of Directors for the Scientific Equipment and Furniture Association, Withee also served two years as the Chair of the Board. Withee also has served on the Architectural Woodwork Institute's Quality Standards Board of Review Committee. Three times in the last four years R&D magazine has invited Withee to participate as a judge in its annual Laboratory of the Year design competition. A frequent speaker on issues dealing with laboratory design and fit-out, Withee most recently has addressed the R&D Council of the International Facility Managers Association as well as the Building Owners' and Tenants' Summit on Biotech, Medical and Pharmaceutical Lab Facilities. Withee is recognized as a strong proponent of bringing cost-effective ideas and products to enhance the design and use of environmentally friendly laboratory facilities. He can be contacted by tel: 1-989/496-0451 or by email: dave.withee@casesystems.com.

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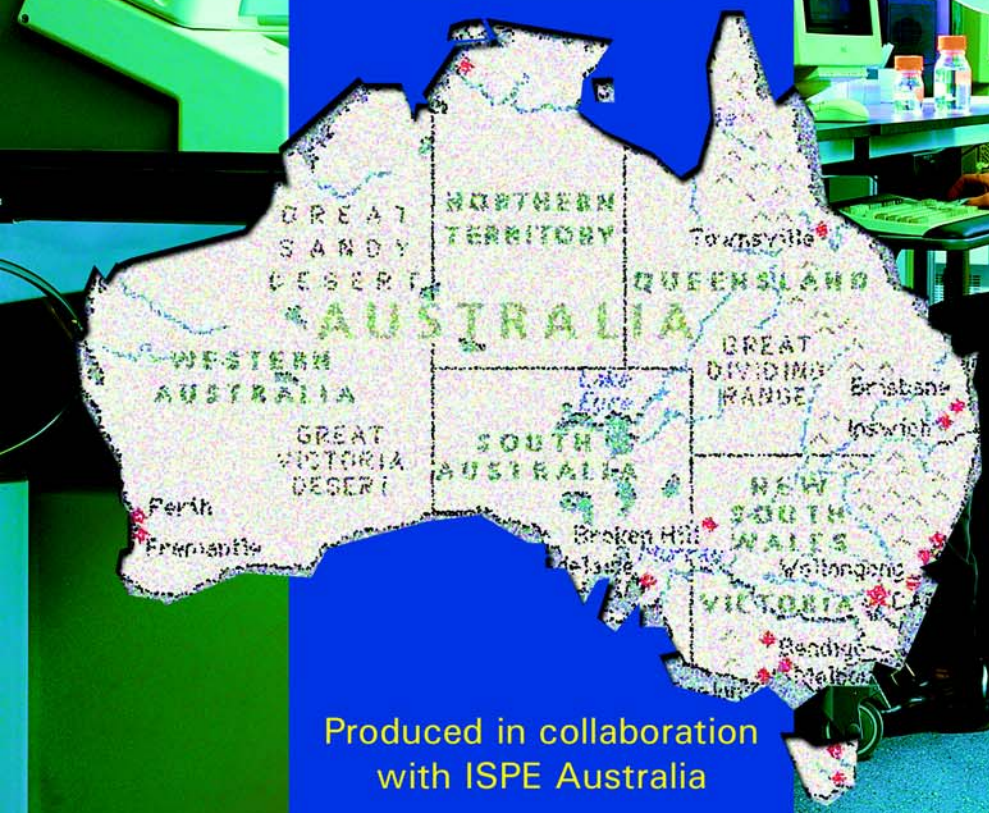
Country Profile

A look at the Pharmaceutical Industry in

AUSTRALIA



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ISPE Australia was established eight years ago and in that time, membership has increased to more than 200. Although Australia is a large country with a dispersed and relatively low population, we have representation from most state capital cities, with a number of members in New Zealand also. Chapter events are being held in Melbourne, Sydney, and Brisbane and are expanding into New Zealand.

Australia is well known as a tourist destination and its amenable climate and quality infrastructure makes it a great place to live. Australia is also a desirable place to work and do business with. This country profile includes a range of articles which reveal the unique character of our country, the depth of our local pharmaceutical industry, and the exciting opportunities ahead.

Australia is a very competitive global manufacturer with high quality and low costs. The local economy has remained robust in spite of worldwide recession. Strong growth in several key areas has seen pharmaceutical exports doubling in the five years to 2000-01 with plans to double our share of the global market over the next decade. Australian R&D and innovation is well-established and world-class, especially in the biotechnology area with a high number of biotech companies. This is sure to continue with our highly educated workforce, incredible biodiversity, and support from industry and government.

We trust that this feature on the Australian Pharmaceutical and Biotechnology Industry is of interest and increases your understanding of our dynamic and developing position in the world. We would welcome your comments and views, so please contact me to let us know what you think.

Yours truly,

Lucas Crabtree
President, ISPE Australia Affiliate

This new feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Germany/ Switzerland in the January/February issue of *Pharmaceutical Engineering*.

The Pharmaceutical Industry in Australia: A Profile

by Mark Donohoo

Introduction

Australia is a unique place of notable contrasts. Although it is the sixth largest country in the world by area, it also is the smallest continent, and with a population of 19.6 million, the most sparsely populated. The home of one of the most ancient indigenous peoples, Australia also has become the second most multicultural society in the world with migrants from more than 160 countries. While it is located in the Asia Pacific region, it has strong historical and cultural ties with the western world.

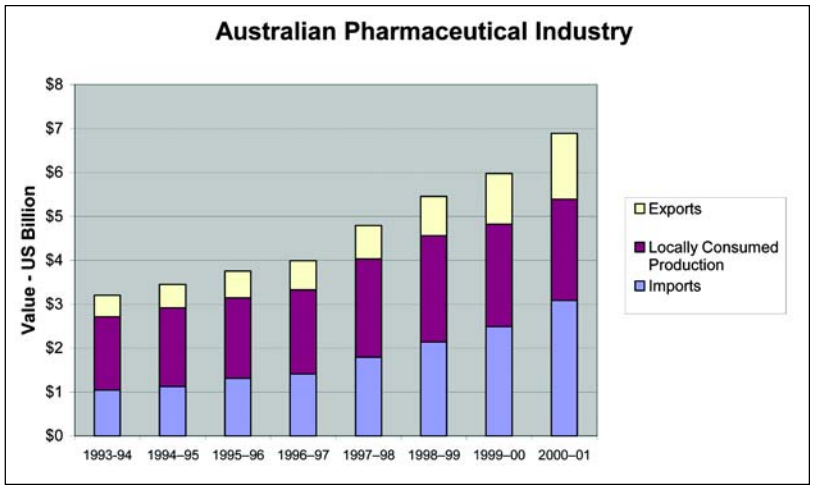

Figure 1. Growth of the Australian Pharmaceutical Industry.[3]

In relation to the pharmaceutical market, the contrasts continue. Even though Australia is the regional headquarters of many multinationals, its modern health system and health consumption patterns means the Australian pharmaceutical market is far more similar to European markets than any in Asia. In global terms, Australia's market is small yet it is also extremely well-developed. With only 0.3% of the world's population, the country still consumes around 1.25% of total global pharmaceutical output. This means that in 2000, Australia was the 18th largest pharmaceutical market by sales, while being 50th out of 187 countries ranked on population, and a little below the OECD average in terms of value of consumption.[1] The pharmaceutical manufacturing industry in Australia was worth more than $5 billion in 2000, including over the counter products.[2]

The pharmaceutical industry is important in Australia. There are around 143 companies listed as suppliers to the Australian Pharmaceuticals Benefits Scheme (PBS), employing around 16,000 people. Figure 1 illustrates the recent growth of the industry. While the value of imports has increased to more than $3 billion, local production also has continued to expand, especially in export markets. At $1.5 billion, pharmaceutical exports doubled over the five years to 2000-01 to become Australia's second largest manufactured-export category.[5]

In addition to companies involved in the manufacture of pharmaceuticals in Australia, the industry includes biomedical researchers in universities, institutes and hospitals; biotechnology companies involved in research and development; and associated service sector partners. After including statistics from these other sectors, the full size of the industry is close to $8 billion, employing 35,000 people across at least 300 firms and institutions.[3] As shown in Table A, the Australian industry has participants along the complete pharmaceutical value chain.

Research and Development

The core of basic medical research in Australia is in public universities, medical research institutes, hospitals, the Australian Nuclear Science and Technology Organization (ANSTO), the Commonwealth Scientific and Industrial Research Organization (CSIRO), the Cooperative Research Centers (CRCs), and the National Health and Medical Research Council (NHMRC).

On a global scale, Australia's performance in research and research publishing is excellent. With just 0.3% of the world's population, Australia produces 2.5% of the world's research, has four laureates of Nobel Prizes for Medicine or Physiology, two others in related fields, and recipients of many other prestigious awards.[6]

The Pharmaceutical Industry in Australia: A Profile

Among Australia's research strengths is work in immunology, reproductive medicine, hypertension, genetics, molecular biology, and oncology.[7]

One long-term feature of Australian research and development funding is the relatively high proportion of government expenditure - *Figure 2*. Much of this support is spent on basic research. Expenditure by the industry itself is around 6% of sales, which is well under the 15-20% typical of the US industry. Figure 2 also illustrates that expenditure by the Australian industry is relatively lower on basic research and higher on clinical trials and manufacturing. This is possibly because the largest Australian companies are multinationals that invest more basic research and development in home countries. (The collaboration between AstraZeneca and Griffith University to search for promising compounds from Queensland biota is a notable exception).

Investment in research and development continues to increase; one estimate is that industry expenditure is now almost double that shown in Figure 2.[8] Government expenditure has kept pace; planned funding through the NHMRC, for instance, will double between 1999 and 2004.[9] A large driver of this expenditure is the growth of leading-edge biomedical and biotechnology capabilities within Australia.

This expansion is mostly from Australia's medical research base; 70% of biomedical companies formed in 2001 were spin-offs from research institutions.[10] This is an important development which is starting to attract the interest of global pharmaceutical players. Merck, as one example, recently signed a license agreement with Amrad to develop new asthma drugs that could be worth more than $112 million. Other companies (Biota and Kinacia) have developed their own proprietary substances while Proteome Systems has produced pharmaceutical development technology.

While Australia's pre-clinical sector is not as developed as the basic medical research sector, there are some areas of strength that have achieved high levels of global recognition. Australia also has pockets of strength in pharmaceutical delivery, both in some pharmacy schools and within industry. One example is the development by Fauldings (now part of Mayne), in partnership with Glaxo Wellcome, of Kapanol, a sustained-release, morphine-based product, now available on the world market.

The largest proportion of industry expenditure (approximately 42%) on research and development is on

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Primary activity	Basic medical research; discovery research	Early development; proof of concept; Phase I; early Phase II	Development from early to later stages; Phase I, II and some Phase III	Final product development, manufacture, marketing including sales and distribution	Manufacture, marketing including sales and distribution
Secondary activity	Early proof of concept	Some discovery	Some sales, distribution; Some discovery, some proof of concept	If developed from own research: all stages. If licensed-in: later stage development, clinical trial.	Product development, formulation
Activity undertaken in Australia by	Universities, Cooperative Research Centres, Research Institutes	Biomedical start-ups, Biomedical expansion companies	Biomedical expansion companies, Multinational pharmaceutical companies	Multinational pharmaceutical companies	Generics manufacturers
Number of entities in Australia	Over 60; employing more than 14,800 researchers	150 private companies, 35 publicly listed companies; 5,700 people	20 publicly listed / private companies	50 companies; 12,000 people employed	6 companies; 1,500 people employed
Examples in Australia	Walter & Eliza Hall Institute, Monash University	Biota, Kinacia, Proteome Systems	Amrad, Thrombogenix	Eli Lilly, CSL, AstraZeneca, Merck Sharp and Dohme	Alphapharm, Mayne Health (Faulding)

Table A. The Australian industry along the pharmaceutical value chain.[3]

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clinical trial activity.[11] Studies have shown Australia has major cost advantages for conducting high quality research and development.[12] Australia has good clinical capability because of its excellent hospital infrastructure, world-class medical scientists, and a tradition of sophisticated clinical research, excellent statisticians with access to follow-up medical treatment data, and a broad base of well educated health workers to assist in clinical trials. Our regulatory system is highly regarded internationally for rigor and efficiency. We have a diverse, ethnically heterogeneous and healthy population that has not been 'saturated' by clinical trial activity. Australians are eager to participate in scientific endeavor. Recruitment for trials is relatively easy because high levels of education mean that people understand the purpose of the trials and the controls surrounding them. The country's well developed IT infrastructure and relatively low cost structure also ensures efficient and cost-effective trial management.

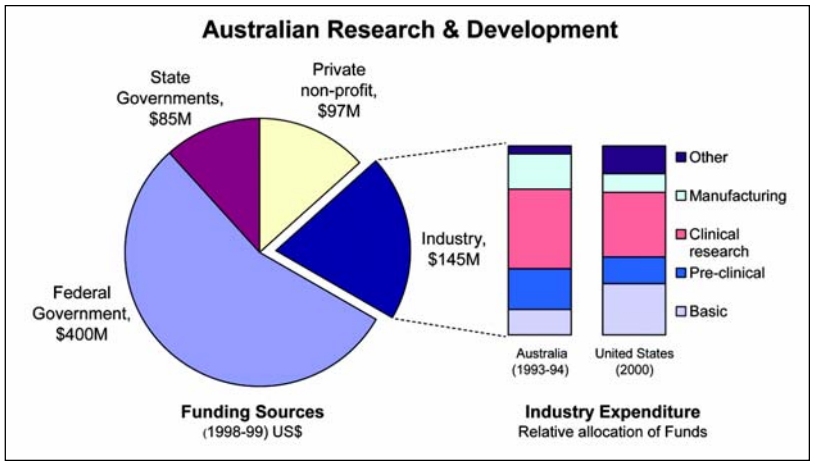

Figure 2. Australian expenditure on research and development.[1]

The infrastructure to conduct clinical trials is continuing to develop. Many public hospitals and research institutes contract regularly with pharmaceuticals companies to conduct clinical trials. A few local companies focus their business model on selected parts of the trials process. A number of multinationals have placed specialized trial activity in Australia. One example is GlaxoSmithKline and its James Lance Phase 1 facility in Sydney. Others have established centers for analyzing clinical trial data for the Asia Pacific region, for example, Eli Lilly's Clinical Outcomes and Research Institute. Increasingly, Australia also is processing more compounds developed by local research institutes who now have the expertise to initiate their own trials.[9]

Figure 2 also shows that the Australian industry appears to invest proportionally more in manufacturing and processing research and development than the US. One example of this investment is Pharmacia, the only manufacturer in the world to package oncology pharmaceuticals in plastic. This technology was researched and developed in Australia, and is deployed at Pharmacia's Bentley facility.[13]

Manufacturing

Over the last decade, some manufacturing activity in Australia has been lost due to plant closures resulting from mergers. At the same time, some new small-scale capacity has been created, some capacity has been reinforced, and in some cases, the disposal of plants by multinationals has created an opportunity for local manufacturers to take-over plants. As indicated in Figure 1, there has been a steady rise in the gross product and in exports from the manufacturing industry. The full range of manufacturing processes is undertaken in Australia though, as Figure 3 shows, the vast bulk of activity is in formulation and packaging of final form products.

Australian capacity for the manufacture of chemical actives is not large. Apart from radiopharmaceuticals manufactured by ANSTO, the largest primary manufacturing operations are for alkaloids (GlaxoSmithKline and Janssen-Cilag). Australia supplies a significant proportion of the world's medicinal opiate requirements for morphine production. The poppies are grown and processed to the straw stage and the opiates extracted. This is a classical Australian activity – adding value to an agricultural resource. The Institute of Drug Technology (IDT) is a more recent development, which has grown to become a significant FDA-approved Active Pharmaceutical Ingredient (API) development and manufacturing company. IDT has a diverse range of products, including parenteral grade cytotoxics, non-cytotoxics, antibiotics, veterinary products and biologics. Their client base lists several top 20 international pharmaceutical companies, including Pfizer and AstraZeneca.

The Pharmaceutical Industry in Australia: A Profile

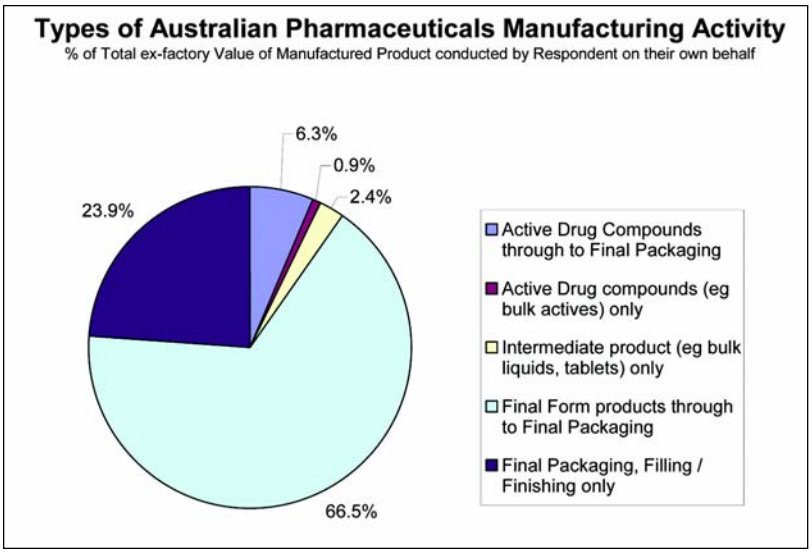

Figure 3. Types of Australian pharmaceutical manufacturing activity.[14]

Much of Australia's current specialized activity is for biological, as opposed to chemical, compounds. Australia is ranked sixth in the world for the number of biotech companies and it is estimated to have around 1% of the world's protein manufacturing capacity.[10] Australia is well positioned to take advantage of the expected increase in demand for biopharma-ceuticals due to its skills base, BSE-free source material, management capacity (especially the entrenched culture of quality assurance), and regulatory environment.

CSL, the largest biotechnology company in Australia (by capitalization), is one of its most successful and the only local vertically-integrated pharmaceutical company (active in all the value chain). Originally, a Government authority, CSL was privatized in 1994 and has now ventured internationally, using its purchase of the Swiss ZLB plant to enter the US plasma products market. It is a world leader in plasma technology and has strength in immunotherapy, immunology, protein chemistry, and protein-based novel human therapeutics to develop a number of novel products. CSL manufactures its own products as well as under license to major international corporations such as Merck, Biogen, and Schering.

As noted above, secondary manufacturing (formulation and final form production) comprises most of Australian pharmaceutical manufacturing value. Studies have shown that Australia is one of the most cost-competitive places in the world to build and operate a plant[3] and the strength of the regulatory environment and work force skills lead to high quality assurance. More than 10 companies, both local and multinational, operate at least one secondary manufacturing facility supplying local and export markets. These include GlaxoSmithKline, Pfizer, Pharmacia, Sigma, Roche, Alphapharm, Merck, AstraZeneca, Mayne, Bristol-Myers Squibb, and Schering-Plough.

Government development programs have encouraged the expansion of secondary manufacturing capabilities, especially with a focus on generating exports. For instance, the local subsidiaries of multinationals Merck (MSD) and AstraZeneca (AZA) have both invested in new state-of-the-art manufacturing plants in Sydney. AZA has spent around $100 million in infrastructure, opening their new sterile-pharmaceutical manufacturing facility in 1998. This plant is currently being expanded to more than double its original capacity, and also will serve as a regional packing center for solid-dosage forms. More than 400 people are employed in the plant where tablets, injectables, respiratory products, and fluids for inhalation are manufactured, including the use of Blow-Fill-Seal technology. Output from AZA supplies more than 17 export countries. MSD employs 850 people and has spent almost $80 million since 1993. In 2000, their factory supplied more than 1000 solid-dose presentations to 37 countries. This represents around 23% of Australia's total pharmaceutical export value and makes MSD one of Australia's top 100 exporters.

In the global manufacturing world, Australia has developed a niche expertise in packaging and formulation with many plants becoming skilled at short manufacturing runs and quick changes between products. This flexibility suits many regional export markets where orders are of smaller volumes and may become an advantage with the predicted development of 'targeted pharmaceuticals' produced for small patient populations.

Flexibility and short runs is a particular strength of generics manufacturers. Australia has a significant generics manufacturing sector, conducted by such firms as Sigma and Faulding (locally owned), Alphapharm (owned by Merck KgaA). The Australian generic medicines industry undertakes significant research and

The Pharmaceutical Industry in Australia: A Profile

development and has enjoyed substantial growth in both the Australian and export markets. This growth has been fuelled by a legislative framework that enshrines consumer choice and promotes Government cost savings. One estimate is that generic medicines have saved Australian taxpayers more than $550 million since 1995 by reducing the benchmark price of medicines.[3] (Generic export is restricted by Australian intellectual property laws which require agreement of the patent holder, while the medicine is under patent in Australia).

Faulding, started in 1845, has developed as a manufacturer of generic medicines specializing in novel delivery mechanisms. It has both research and manufacturing facilities. Sigma is another sizeable local company that manufactures both patented and generic pharmaceuticals in some cases, under contract to other companies. Arrow Pharmaceuticals has established a world center for research and development for generic medicines in Melbourne, compiling registration files for submission in Asia, Europe and the USA.

Alphapharm began in 1982 and has grown to become Australia's largest manufacturer of generic pharmaceuticals and the largest supplier (by number of prescriptions) to the Pharmaceutical Benefits Scheme, supplying more than 200 products. At its Brisbane pharmaceutical manufacturing technology base, generic products are developed, scaled up into production quantities, manufactured, and sold domestically as well as being exported to 26 international markets including Asia, Europe, and the USA.

Services

Service inputs within Australia are well developed and are typically of a high quality. Capabilities along the value chain have been developed both by dedicated suppliers who sell into the industry and within pharmaceutical companies themselves. Much of this capability is exported to the Asian region and further afield; some notable examples of services provided are:

- Research and development services - for example, Covance, Kendle, and Quintiles organize clinical trials in Australia and elsewhere; CMAX provides specialized Phase 1 trial expertise; and AstraZeneca and Griffith University provide a high speed screening service for the company's headquarters.

- Data services - for example, Eli Lilly's Clinical Outcomes and Research Institute (CORI), and its Asia-Pacific Data Management Centre, provide services for the company's clinical work in Australia and overseas.

- Training and staff development services - for example, Roche's Australian office provides staff development modules by data stream to the Asia-Pacific offices of the company; GSK operates a global center of excellence for health outcomes and exports its health economics expertise.

- Management services - several multinational companies have their Asia-Pacific regional headquarters based in Australia (for example, Bristol-Myers Squibb provides Financial Shared Services to some of the corporation's key markets in the Asia/Pacific region from its Australian base).

- Architectural and Project Management services - a number of Australian firms (such as Hooker Cockram, S2F and Bovis Lend Lease) provide design, construction, and management services all over the world.
- Process Engineering services - for example, Newpulse Systems (now Kinetics Australia) is a leading provider of complete design-build process and piping systems to biotechnology and pharmaceutical industries in Australia and Asia.

- Equipment supply - Bosspak (now part of the Romaco group) designs and manufactures tablet filling lines and developed the world's first rotary tablet counter. Bosspak has received several industry awards for design excellence and now exports 80% of its output to global markets, including Europe. Several other OEM suppliers have had both interest and success from export customers.

Sales and Marketing

The Australian market is different from the United States. For instance, there are restrictions on direct-to-consumer advertising. Most Australian marketing activity is directed to doctors since they are the decision makers because of their power to prescribe. Government regulations also restrict non-pharmacy establishments from dispensing prescriptions and scheduled OTC medicines as well as the locations and ownership of pharmacies. (Despite this obstacle, at least one major supermarket chain has plans to locate stand-alone pharmacies in its stores).

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The Australian market for prescription products is dominated by the Pharmaceutical Benefits Scheme (PBS). The purpose of the Scheme is 'to provide timely, reliable, and affordable access for the Australian community to necessary and cost effective medicines.' Drugs sold under the PBS are supplied at a government-subsidized price, with consumers making a co-payment based on their socioeconomic circumstances. In 2002, government spending accounted for 84% of the total cost of the PBS ($2.9 billion) with around 80% of this amount directed to concessional patients.[15]

Many OECD countries have similar schemes and while some governments determine prices through negotiation, Australia applies a cost effectiveness methodology, combined with reference pricing for therapeutic clusters of drugs. A committee (PBAC) advises the government on product additions (or deletions) to the PBS after assessing the clinical need, effectiveness, and cost-effectiveness in comparison with alternative treatments. The government then negotiates prices with suppliers, based on the recommendations of a pricing body (PBPA). To further constrain government costs, wholesaler mark-ups and pharmacist remuneration are controlled.

A recent study concluded that Australia pays less for drugs than most other developed countries.[16] For instance, prices in the USA are from 80% to 160% higher than in Australia, and those in UK and Sweden are around 50% higher. (The differential for innovative pharmaceuticals tends to be less than for the 'me-too' and generic categories). Despite this price difference, consumption is only slightly below the OECD average. In 1997, Australians consumed the equivalent of $213 worth of final product each, which was close to the OECD average of $245 per capita. It has therefore been argued that the PBS also provides a guaranteed market, underwriting broad access to drugs for which demand would otherwise be limited.

Cost increases in the PBS in recent years reflect a continuing trend for doctors to prescribe newer and more expensive drugs. From 1995 to 2002, the cost of the PBS more than doubled. The market is still growing although government pressure is being felt; in 2002, expenditure increased by 9.5% compared to 17.4% the previous year.[15] By contrast, the volume of prescriptions rose by less than half this rate.

During 2001-2, the largest firm by PBS sales value was Pfizer; however, it represented only 10% of the total benefit paid. The top 10 suppliers accounted for around 70% of the total PBS cost. Alphapharm was the largest supplier to the PBS by number of prescriptions. The top 10 firms again supplied around 68% of the total prescriptions written.[17] Figure 5 illustrates the distribution of PBS costs (and their relative growth) in 2002 by therapy category. The drug groups with the most increase were lipid-lowering agents, drugs for acid-related disorders, and anticancer agents.

Figure 4. An example of a locally developed identification and inspection machine.

Regulation

Responsibility for the regulation of therapeutic goods within Australia lies with the Therapeutic Goods Administration (TGA). The TGA carries out a range of assessment and monitoring activities to ensure marketed goods meet high standards and that therapeutic advances are made available to the community in a timely manner. Products covered by the TGA include pharmaceuticals, medical devices, and complementary medicines (such as herbal, vitamin and mineral products). The Australian Register of Therapeutic Goods (ARTG) lists almost 60,000 healthcare products; just under half of which are medicines.[18]

The Pharmaceutical Industry in Australia: A Profile

Overall control of the supply of medicinal drugs in Australia is exerted through three main processes: the pre-market evaluation and approval of products intended for supply in Australia; the licensing of manufacturers; and post market surveillance (including investigating reported problems, laboratory testing of products on the market, and monitoring of compliance with the legislation).

In the review and approval of drug-products, the TGA uses a 'risk-management' approach. Risk-factors considered include the strength of a product, side effects, potential harm through prolonged use, toxicity, and the seriousness of the medical condition for which the product is intended to be used. Products used to treat serious conditions, or which need to be used under a doctor's supervision, are subject to a high level of scrutiny and are evaluated for quality, safety, and efficacy. Once approved, these products are included in the ARTG as 'registered'products. Lower-risk 'listed' products, i.e., many non-prescription medicines and complementary medicines, are not generally subject to the same level of evaluation and are assessed only for quality and safety.

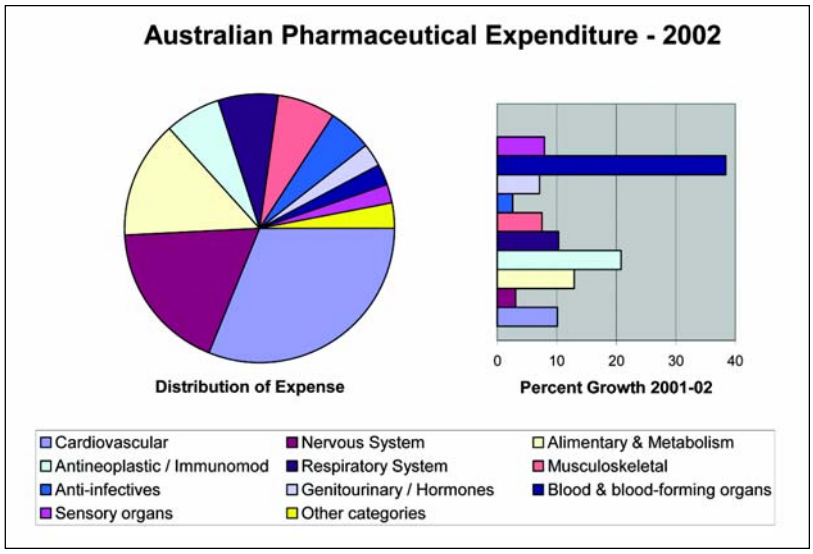

Figure 5. PBS sales value by anatomical group.[15]

TGA inspectors regularly inspect licensed Australian manufacturers to ensure compliance with the *Australian Code of Good Manufacturing Practice for Medicinal Products*. The current code, adopted in 2002, replaces a well-developed local set of documents with an entirely international standard published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S). This development is a further step in the efforts at global harmonization in which the TGA has played a committed, long term, and sometimes leading role. It also specifically increases the alignment of Australia with European Community markets (our largest trading partner) where the same code had already been mandated and assists in the licensing of overseas suppliers to our market.

The TGA is well respected world wide as a rigorous regulator. A Mutual Recognition Agreement (MRA) signed with the European Community in 1998, confirmed TGA audit and inspection processes as adequate for export to that market. Agreements with other regulators have followed, most notably including a Memorandum of Understanding with the US FDA in 2000. Plans have been confirmed for a Trans-Tasman therapeutic goods agency, in combination with New Zealand. As a center of excellence in the regulation of medicines and medical devices the TGA also regularly provides training programs and consultation with regulatory agencies and the pharmaceutical industry of countries in the region. These include China, Hong Kong, Japan, Malaysia, Indonesia, United Arab Emirates, Thailand, Vietnam, Singapore, Taiwan, Nepal, and the WHO.[18]

Industry Development and the Future

Since 1988, successive Australian governments have taken steps to give positive encouragement to the pharmaceuticals industry, and to companies willing to invest in the industry. The first of these programs, the Factor (f) Scheme, paid more than $1.1 billion over 11 years to pharmaceutical companies operating in Australia. This expenditure was intended to recognize and reward activity, including new investment, production and R&D, undertaken by companies attempting to list their products on the PBS.

In 1999 a subsequent program, the Pharmaceutical Industry Investment Program (PIIP), commenced with a budget of $195 million over five years. This assistance was provided to participating companies, in the form of higher prices for their products, in return for their making commitments to undertake certain activities in Australia, including manufacturing and R&D.

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Both programs were designed to provide partial compensation to the industry for the price suppression of medicines on the PBS resulting from the government's purchasing power and were important in addressing the sustainability of local activity. As a result of these investments, the industry has grown an export base, stimulated R&D opportunities on a world platform, embarked on major capital investment in facilities, and created employment opportunities for highly skilled people.

Since 2001, a committee has been developing a Pharmaceutical Industry Action Agenda (PIAA). The group included representatives of the Commonwealth Department of Industry, Tourism and Resources; Medicines Australia (formerly the Australian Pharmaceutical Manufacturers Association) representing most manufacturers of prescription pharmaceuticals; the Generic Medicines Industry Association and AusBiotech (formerly the Australian Biotechnology Association) which brings together companies and individuals involved in the biosciences.

The PIAA was launched in late 2002 with the aim of doubling Australia's share of the global industry by 2012, through the collaborative efforts of Industry, Government, and Research by:

- increasing investment in Australia to capture innovation and knowledge
- becoming a global hub for research, development, and commercialization
- developing Australia as a key global exporter of goods and services

The Chairman of Medicines Australia, Mr. Jeays Lilley, has said *"The PIAA can sustain pharmaceuticals as one of Australia's largest export businesses, create more jobs, keep young talented scientists in Australia and hopefully double the output of Australian research."*[19]

In support of the PIAA, the government has announced another five year R&D assistance scheme, the Pharmaceuticals Partnerships Program (P3), to commence mid-2004. It is a competitive entry program focused on developing medicines for global markets and encouraging international firms to foster partnerships with local companies.

The supporting statement by the chair of the PIAA, Mr. Graeme Blackman, represents a useful summary of this article and the future for the Australian pharmaceutical industry.

"The Australian pharmaceutical industry can double its share of the global pharmaceutical industry by 2012. Industry's vision for 10 years hence is bold and challenging. It recognizes that we have a strong base from which to grow the pharmaceutical industry. It demonstrates the commitment of all parts of the Australian pharmaceutical industry to work together, and to work with governments, to increase investment in Australia, to become a global hub for research, development and commercialization, and to develop Australia as a key global exporter."[3]

Note

Dollars shown are US dollars; exchange rate used in this article is AUD 1 = USD 0.65.

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Competitive Australia - An Advantage for the Pharmaceutical Industry

by Malcolm Tipping

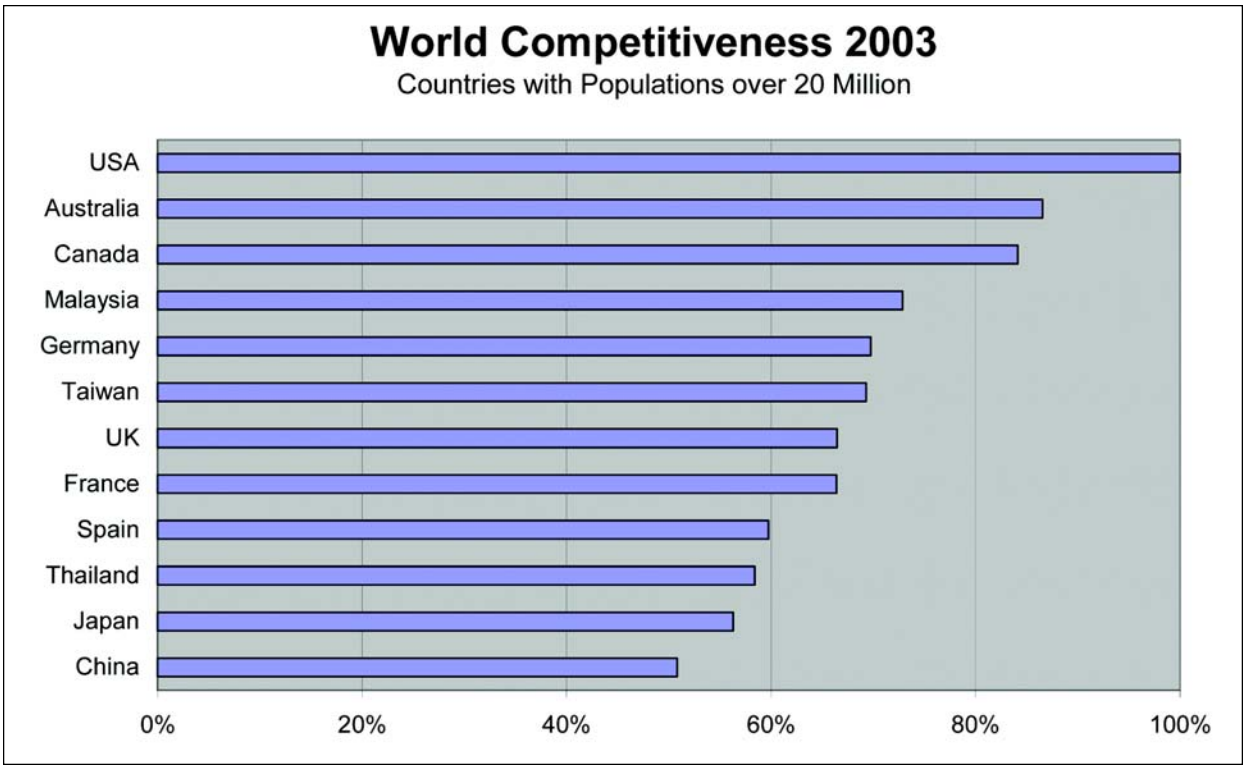
Australia has become well known globally as an ideal location to travel and has even been rated the number one place in the world where expatriate staff want to live and work.[1] Australia also is recognized as a nation who not only love sport, but also strive to excel at a wide range of artistic and technical pursuits.

What many may perhaps find surprising is that Australia is also a very attractive place to conduct business. In fact, Australia is ranked among the top performing economies in industrialized nations. Over the last five years, Australia's international competitiveness, as measured by IMD International, has been in the top three countries with populations greater than 20 million, and rose to second behind the United States in 2003.[2] As Figure 1 highlights, Australia remains ahead of many of the global economic powerhouses, including Germany, France, the United Kingdom, and Japan. IMD measures competitiveness against eight major categories – domestic economy, internationalization, government, finance, infrastructure, management, science and technology, and people. Many of the factors that underpin this result are highly relevant and useful to the development of the pharmaceutical industry.

The Australian Economy is Robust and Sophisticated

The Australian economy is the 14th largest in the world and the 11th largest in the OECD. It is the fourth largest economy in Asia, after Japan, China, and Korea.[3] It has experienced strong economic growth over the late 1990s with the trend growth rate in the four years to 1999-2000 exceeding 4% per annum, well above the OECD average. Unemployment is low and the outlook for inflation remains within the Reserve Bank target of 2-3% per annum. These factors make Australia an attractive environment for business generally.

Australia has been remarkably successful over the nineties in sustaining strong economic growth and lifting competitiveness and productivity. We have been amongst the fastest growing econo-



Competitive Australia - An Advantage...

mies in the OECD in terms of growth in overall GDP and GDP per capita. On this latter measure, Australia ranks equal to the United States.[6]

Australia moved from being one of the most highly regulated and closed economies in the '70s to one of the least regulated and more open economies from the '80s.[4] Australia now retains a record as being amongst the strongest economies with the Federal Government's Budget being one of the few in surplus, a low inflationary environment, a stable political system, and a AAA-rated Australian dollar. Low interest rates also have ensured that firms have access to low cost capital. Interest rates are forecast to remain low, at 2-3%, into 2004.[7]

As *The Economist* recently observed:
"to a visitor from the northern hemisphere, Australia is like another planet. Not only does the sun shine there much more at this time of year, but even as the economies of America, Europe and Japan appear to be stumbling for the second time in three years, Australia continues to boom. The country is now in its 12th year of uninterrupted economic expansion…"[5]

The strength of the Australian economy has seen exports (particularly for manufactured goods) grow strongly, assisted by a low and competitive Australian dollar.[4] Indeed, over the second half of the '90s, Australia's manufactured exports grew by one third, helping Australian business to capture a large share of its export markets.[4]

The pharmaceuticals industry is a significant contributor to economic growth with increasing employment, manufacturing exports, and R&D activity. Four of the top 10 Australian companies (ranked by profitability) are pharmaceutical companies.[8] Pharmaceutical exports doubled over the five years to 2000-01 and have now become Australia's second largest manufactured-export category.[4]

Basic Scientific Research in Certain Fields is Among the Best in the World

The Australian Government is committed to fostering a world-class innovation culture and R&D infrastructure. Australia's innovation policy aims to build world competitive firms and research capability; to strengthen international competitiveness; and to increase national prosperity through focus on developing medicines for global markets. Encompassed in a A$3 billion, five year strategy, Australia's innovation policy provides a number of cutting edge initiatives, including:

- substantial R&D tax concessions to encourage an increase in the amount of R&D performed by businesses in Australia
- development of a world-class Information and Communications Technology (ICT) Centre of Excellence
- establishment of a Biotechnology Centre of Excellence
- a Major National Research Facilities program that will see investment in research infrastructure of national and international significance
- tailored research and development tax rebates for small companies
- new advantageous rules for expenditure on plant and assets used for R&D

Commonwealth funding for biotechnology research alone is estimated at US$300 million a year,[9] which is roughly equivalent to the total spent by industry on research and development into human use pharmaceuticals.

Most of Australia's basic research is conducted in public universities or funded through Government mechanisms. Much of the infrastructure for clinical trials is in the public health systems, especially hospitals. Government also has established specific programs to assist in commercializing Australian research**.** State Governments continue to play significant roles in the development of the pharmaceuticals industry.

Australia has a record of first class scientific research, which is disproportionate to its size. This includes excellent capability in critical new knowledge areas and platform technologies such as genomics, bio-informatics fast screening; natural products etc. Many good drug candidates are now emerging from R&D on national biota.

Australia's innovative culture and support for R&D pave the way to the future with Australian research organizations such as the Commonwealth Scientific and Industrial Research Organization (CSIRO) ranked third in the world for environmental research.[10]

Competitive Australia - An Advantage...

Cost Competitive, High Quality Location

Cost competitiveness and commitment to quality makes Australia a highly efficient and productive location with cost structures for research and development among the lowest. Office space in Australian cities can be a fraction of the cost of comparable properties in London, New York, Tokyo, Hong Kong, and Singapore[1] and have frequent, reliable, and cost effective transport links to the rest of the world.

Australia has the highest availability of IT and finance skills of all countries, the most competitive telecommunications system in the Asia Pacific,[4] after the US the highest e-commerce usage,[11] fifth highest ranked physical infrastructure, among the lowest costs for industrial electricity and natural gas,[10] and an acceleration in labor productivity achieved through a decentralization of labor markets and the impacts of Information and Communications Technologies (ICT).[4]

Productivity

Australia has achieved one of the fastest rises in productivity, aided by the benefits of a strong labor market, microeconomic and taxation reform, and a rapid uptake of information and communication technologies.[4] Australia recorded an impressive labor productivity growth of an average of 3.0% from 1996 to 2002. This increased to 3.8% in 2002, compared with an estimated OECD average of 2.0%.[10] The US Federal Reserve has singled Australia out as one of the few economies to have improved productivity growth in recent times. In fact, it showed that Australian productivity growth rates were higher than rates recorded in the G7 countries over the last decade.[12]

Accompanied by a trend toward falling labor costs, this has provided a significant incentive for businesses to invest in Australia. Real unit labor costs have declined due to strong productivity and modest wages growth; industrial disputes are also at the lowest level in 20 years.[13] Australian oncosts are low by international standards with a high availability of low cost skilled labor (second to India).[14]

A study in 2001, by the Department of Industry Science and Resources, compared Australia with 14 other countries as an investment destination for research and development intensive activities.[15] The study modeled seven factors in setting up a 30-person research facility in a number of fields, including pharmaceuticals, clinical trials, and biotechnology research. The factors were:

- salaries, laboratory set up and running costs, rents, infrastructure and communications
- access to world-class human resources and intellectual capital
- supportive business environment such as R&D incentives and research infrastructure
- ability to engage with and benefit from local technical alliances and business networks
- regulatory issues
- communications infrastructure and time zone issues
- lifestyle, culture and language capabilities

Australia was ranked high on its knowledge base, efficiency of international communications, links to high technology manufacturing capability, access to capital and financial markets, and reliable industry intelligence about life-sciences capability. The study concluded that Australia was the lowest cost country in all fields.[15]

Australia is located conveniently to the South East Asian and Pacific regions, making it a likely candidate for a regional clinical trial base, primary or secondary manufacturing of innovative and generic products or for the distribution of finished goods to the region for either larger multinational, and specialized smaller pharmaceutical companies.

Standard of Living

A study by Ernst and Young in 2000 concluded that Australia had both the lowest cost of living and the highest quality of life.[15] Five of Australia's mainland capital cities are ranked in the top 10 livable cities in the world[2]. Australia has an excellent public health system, and is one of the top 10 spenders on healthcare as a proportion of GDP.[1]

The Workforce is Educated, Sophisticated, and English Speaking

Knowledge intensive industries require access to a skilled workforce. The pharmaceutical industry is one of the most knowledge intensive in the world and the level of skills demanded at all points along the value chain is getting higher. Australia's workforce has been a particular strength for the industry.

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The Australian labor force is multilingual, highly educated, and computer literate. Indeed, Australia has the second most skilled labor force and ranks fourth in terms of higher education enrolment.[16] Australian tertiary institutions produce a higher proportion of health and science graduates than the USA, the UK, Canada, Germany, or Singapore.[15]

Australian scientists and researchers are responsible for many advances in business and industry, and have made significant contributions in medical science. Their discoveries through the years have won prestigious international awards, including six Nobel Prizes.

Intellectual Property Protection Measures Among the Best in the World

Intellectual Property (IP) rights are respected and enforced in Australia. Australia's modern and effective IP regime is ranked more highly than countries such as the UK, Japan, Hong Kong, and Singapore,[1] having a ranking of number one in Asia and fourth internationally. Australian based firms benefit from the most comprehensive protection possible. Firms can therefore invest in R&D, transfer technology, and develop new products with confidence.

Pharmaceutical specific intellectual property protection is also strong. The *Intellectual Property Laws Amendments Act 1998* contained two amendments relevant to the pharmaceutical industry: the extension of the effective patent life by up to five years; and the introduction of 'spring boarding' for the manufacturers of generic or off-patent pharmaceuticals. The amendments attempted to balance the interests of generic and innovative manufacturers.

Laws are Effective and Enforceable

Australia's democratic society, stable system of government, and harmonious social environment can provide your business with the certainty it needs. The Australian political environment is considered one of the most stable in the world, ranked third behind only Finland and Luxembourg.[1]

Australia's strong system of checks and balances also ensures that the risk of corruption is low. Our strong and highly respected judicial and law enforcement systems provide a safety net to deter and punish corruption where appropriate.[1]

Australia's regulatory system is one of the most transparent and democratic in the world, providing predictability for business planning and operations. Unlike many countries in the region, there are no foreign exchange controls and the Australian currency is fully internationalized. In Australia, capital flows, profit remittances, capital repatriation, transfer of royalties, and trade-related payments are largely free from regulation.

Globally Respected Therapeutic Goods Regulations

Australia's excellent pharmaceutical regulatory environment is on a par with the best in North America and Europe. The FDA recently endorsed the high standard of control over Australian manufacturing exerted by the Therapeutic Goods Administration (TGA), through the signing of a memorandum of understanding between the two authorities. This signifies mutual recognition of each body's audit and inspection processes.

A Free Market for Pharmaceuticals Based on Competition and Choice

Australia has a competitive pharmaceutical market. Drivers are pricing, taxation and business costs. The Pharmaceutical Benefits Scheme (PBS) dominates the Australian market for prescription pharmaceutical products. The PBS underwrites demand; this means that for most multinationals, Australia is a reasonably sized market with an estimated $4.25 billion spent in 2000-01. This can be seen as a guaranteed market for the industry.

Conclusion

Australia is a stable, democratic society with a skilled workforce and a strong, competitive economy with the benefits of:

- understanding of and proximity to the growing Asian market (with a cost effective infrastructure for transport)
- Good Manufacturing Practice standards recognized by the USA and many Asian and European countries.
- centers for R&D in pharmaceuticals, biotechnology, medical devices, and generics
- clinical trial expertise
- infrastructure for education, training, and manufacture
- political stability

Competitive Australia - An Advantage...

- strong Intellectual Property laws
- reputation for high quality manufacture
- low cost of investment

The Australian pharmaceutical industry's vision is to double Australia's share of the global pharmaceuticals industry by 2012 through the collaborative efforts of the industry, government, and research. This will be achieved by:

- increasing investment in Australia to capture innovation and knowledge
- becoming a global hub for research, development, and commercialization
- developing Australia as a key global exporter of goods and services.

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Australia's Biodiversity - A Natural Opportunity for Drug Development

by Mark Donohoo

Introduction

The vast, ancient island continent of Australia has produced many unusual, rare, and sometimes unique examples of flora and fauna. Australia is one of only 17 mega-diverse countries with a unique proportion of botanical diversity (80%) found nowhere else in the world. The distribution of climates, topography, and soils that has produced the variation in Australian vegetation is also reflected in the distribution of animal life. Australia probably has between 200,000 and 300,000 species, about 100,000 of which have been described.[1] While this diversity presented a storehouse of healthcare goods for the original indigenous peoples, exposure to scientific analysis is a far more recent development.

In the search for new therapeutic compounds, Australia has become considered a key source. About 25% of modern drugs are derived from natural products and the wide diversity of Australian fauna and flora have been exposed to relatively minor investigation. It is estimated that the 23,000 species of vascular plants in Australia represent about 10% of the world's plant diversity. More than 85% of these are thought to be unique.[2] The rainforests of Queensland, for instance, contain an estimated 9,000 plant species – 75% of which are found only in Australia. Western Australia alone has more than 5% of the world's plant species. Only 1% of our plants have been mined for natural compounds.

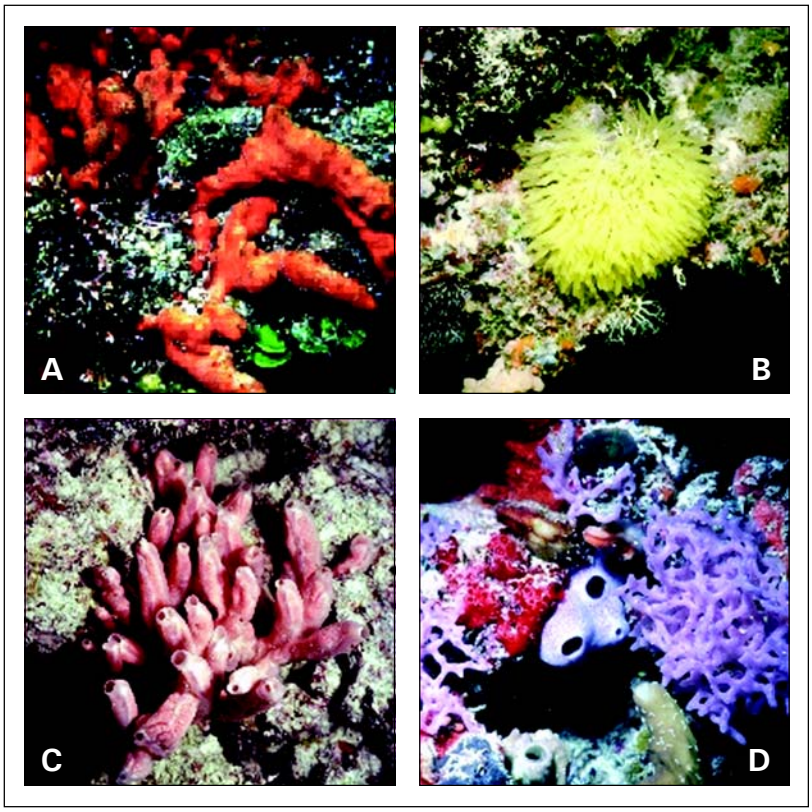

Figure 1. Marine Sponges - these new species were discovered on the Great Barrier Reef as part of NPD bio-prospecting *(all photographs J.N.A. Hooper, Queensland Museum)*.[3]

A. *Clathria (Thalysias) craspedia* - an orange-brown siliceous microcionid sponge.
B. *Sycetta n.sp.* - a yellow calcareous sponge.
C. *Echinochalina (Protophlitaspongia) isaaci* - a pale pink branching siliceous sponge.
D. *(Leucaltisn.sp.)* - A mauve calcareous sponge.

Probably the most notable Australian bio-discovery program is Natural Product Discovery (NPD), collaboration between AstraZeneca and Griffith University in Queensland. NPD (formerly AstraZeneca R&D Griffith University) was established in 1993 and is recognized as one of the top five natural product institutes in the world. The program's goal is to find potential therapeutic drugs from the biological compounds that occur in plants from Queensland's rainforests and marine organisms from the Great Barrier Reef.

Samples are extracted to form NPD's substantial extract library. Using an automated screening process, the extracts are screened for a "hit" (a substance that binds with a target protein). This high-throughput screening identifies a

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Figure 2. Funnel-Web Spider *(copyright Dr Julian White, State Toxinology Services, South Australia).*

significant number of active compounds, which are then isolated and their structure determined.

Once their structure has been understood, these natural compounds can be made synthetically in large quantities (to reduce the need to harvest large sample quantities). The scope of the project was expanded in 2000 with the addition of a Medicinal Chemistry section to undertake combinatorial chemistry on promising bioactive compounds. The addition of this section has resulted in the development of local expertise in yet another link in the drug discovery chain. As well as expertise in collection, screening, isolation and structure determination of natural products, NPD also can now boast lead optimization capabilities for commercial application.[4]

NPD has established an extensive database and has discovered more than 700 biologically active compounds.[5] Scientists collecting flora and fauna samples also have discovered and catalogued more than 60 new species of plants and 2000 new species of marine sponges. AstraZeneca has committed more than $65 million to this collaboration, and has recently confirmed its involvement to the end of 2007. The success of the program also has allowed NPD to extend its sample collection activities to Papua New Guinea, India, and China, placing this Australian research initiative at the forefront of global bio-discovery.

Some of the earliest research was necessitated by the presence of a wide range of venomous animals in Australia. These include some of the world's most poisonous snakes (the taipan, tiger snake, brown snake, and death adder) and spiders (red back spider and funnel web spider), as well as a number of marine stingers (the box jellyfish, stonefish, and sea snake). All of these are dangerous to humans and have caused deaths. Research and development of antivenoms began in 1928 with collaboration between scientists at the Walter and Eliza Hall Institute and the Commonwealth Serum Laboratories (CSL).[6] Although antidotes for all snakebites had been developed by 1962, it was not until 1980 that one became available for the funnel web spider. When CSL was privatized in 1994, the investigation work was transferred to Melbourne University and the Australian Venom Research Unit.[7] CSL has gone on to become Australia's largest biotechnology company and continues to manufacture and supply antivenoms to hospitals.[8]

In a major contrast to the early work by CSL, one Australian company is looking for drugs in venomous animals, using the latest in genome to drug technologies. Xenome, a spin-off from the University of Queensland, has leading edge expertise in the characterization of venom genomes and has an exclusive worldwide royalty free license to a large portfolio of novel venom peptide compounds, including those from coneshells, spiders, snakes, scorpions, and centipedes. Among Xenome's important drug leads are several coneshell peptides targeted at pain modulation. Over the course of 2002, Xenome signed agreements with companies from Europe, the UK, and the US to use this knowledge base in the development of a range of therapeutics and pharmaceuticals.[9]

Other bio-prospecting programs are developing from research bodies with government funding. These may lead to partnerships with pharmaceutical and biotech companies, or to spin-off commercialization ventures.

The Commonwealth Scientific and Industrial Research Organization (CSIRO) is involved in a project to collect samples of insects and develop a library of extracts. More than 1000 species of insects have been collected and extractions, validation and chemical profiling are well underway.[9] Work to date has yielded several anti-microbial and potential anti-cancer actives.[10] This activity has led to the recent formation of Entocosm, as a spin-off from CSIRO. Entocosm use a technology platform licensed from the CSIRO with the intention of exploiting insect biological and chemical diversity for a range of therapeutic applications. Entocosm also are collaborating with experts in infectious diseases and natural products chemistry from Canberra Hospital, and the Australian National University (ANU).

Cooperative Research Centers (CRCs) are another government funded program set up in 1990 to establish formal strategic long-term agreements between industry, research, and government to support R&D and education objec-

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tives. The CRC for Bioproducts was established in 1999 to focus on developing commercially valuable materials produced by plants and other living organisms, for various uses including complementary medicines, nutraceuticals, and pharmaceutical intermediaries.[12]

Another initiative is the CRC for Discovery of Genes for Common Human Diseases.[13] Cerylid Biosciences is the industry partner for this CRC and are integrating genomics and natural product screening to discover and develop drugs to treat common human diseases. Cerylid's internal screening program is focused on the identification of new anti-cancer drugs from its Natural Products Library. It also has two ongoing gene discovery projects for endometriosis and type-1 diabetes.

Biota specimens are sourced from Australia, and South East Asia as well as Antarctica. From these regions, Cerylid Biosciences has generated extensive and proprietary libraries of about 600,000 natural product samples.[14] The libraries are deployed in collaborative drug discovery partnerships with leading pharmaceutical and biotechnology companies, such as Aventis.

Cerylid also has access to the Tasmanian human population for genetic studies through an exclusive relationship with the Menzies Research Institute in Tasmania.

Bioprospect Limited is a company that provides nature derived chemicals for various discovery programs, from nutraceuticals to front-line pharmaceuticals. Collections are expanding its extensive extracts library by around 2000 species per year. With a landmark license from the state government of Washington, Bioprospect is the broker of unique and largely unexplored biota. The company has signed a number of agreements with US based companies. An alliance with Apath LLC is intended to develop potential treatments for the Hepatitis C virus and other viral pathogens.[15]

Australia's rich biodiversity means companies have the benefit of one of the world's most diverse ecosystems at their doorstep. In combination with local access to leading-edge research expertise and technology, the bio-prospecting industry has grown rapidly in Australia and is likely to remain the subject of strategic investment.

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This article presents the issues that need to be addressed when developing and operating a Calibration Management Program with emphasis on European regulations.

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Calibration Management - A European Perspective

by Brendan Barry and Nigel de Haas

Introduction

The accuracy of measuring instruments and measuring systems that are used in pharmaceutical manufacturing to control or record Good Manufacturing Practice (GMP) process parameters need to be maintained within appropriate specified limits while they are in service to satisfy the quality requirements of the process or product.

In addition to GMP measurements, manufacturing plants are likely to have a number of environmental and safety instruments, that while having no bearing on product quality, have a direct impact on the site environmental operating license and on health and safety requirements respectively.

Within the European Union, the national authority (in Ireland, the Irish Medicines Board) conducts inspections under the overall control of the European Medicines Evaluation Agency which regulates all pharmaceutical manufacturing facilities. The requirements for calibration are specified in Volume 4 of "The Rules Governing Medicinal Products in the European Union - Good Manufacturing Practices[1]" (known as the EU GMPs).

Section 3.40 of the EU GMPs requires that "Balances and measuring equipment of an appropriate range and precision should be available for production and control operations" and Section 3.41 requires that "Measuring, weighing, recording, and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained."

This article presents the issues that need to be addressed when developing or operating a calibration management system in a pharmaceutical manufacturing facility with particular emphasis on requirements of the European regulatory organizations governing the integrity of measurements.

Managing Calibration

Calibration is defined internationally[2] as the "set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards."

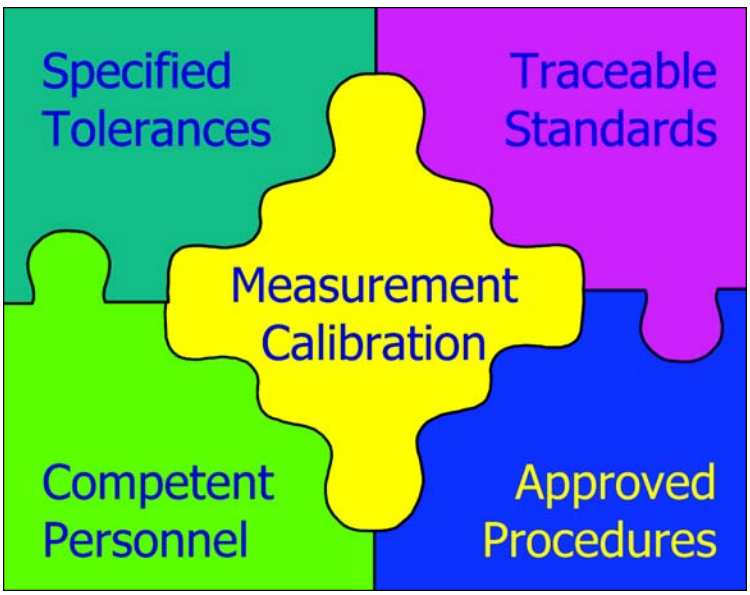

Figure 1. Calibration cornerstones.

It is important to note that calibration is a comparison, not an adjustment. It is simply a record of the differences found at the time the calibration was performed between the actual working or plant instrument, and a reference stan-

dard against which it was compared. The act of calibration does not in itself demonstrate that the instrument is within any particular limits if the results are not compared with a tolerance specification that defines such limits.

For this reason, it is necessary to systematically manage the four basic cornerstones of calibration, namely measurement tolerance specifications, reference standard traceability, personnel competence, and calibration methods to enable unsatisfactory results to be identified, and acted upon - *Figure 1*.

The set of operations required to ensure that an item of measuring equipment is in a state of compliance with requirements for its intended use is referred to as "Metrological Confirmation"[3] by some authorities, and include calibration, adjustment where necessary, calibration status labeling and recording.

Unique Identification

Every measurement function in the facility needs to be assigned a unique identity or tag number to facilitate completely unambiguous reference to the measurement in production, maintenance, and calibration Standard Operating Procedures (SOPs) and records.

Difficulty can be experienced if the serial number of a physical instrument forms all or part of the identification, as the physical instrument may be replaced in time whereas the measurement function remains.

The measurement function may be filled by a single discrete instrument such as a pressure gauge or a balance, or may be a measurement system comprising of a series of functionally interconnected instruments that make up the measurement chain from the sensor to the point of use. The functional interconnections may be in the form of electrical connections, or realized in software where instruments are networked.

A clear, documented specification of the individual instruments in the measurement system and the manner of their interconnection is fundamental to understanding its accuracy capability and dynamic response. The serial number of each physical instrument in the measurement system, together with its date of installation (and removal where applicable), forms part of the documented history of the measurement function.

Criticality Assessment

Once all measurement functions in the facility have been uniquely identified, they should be entered on a master schedule to enable their measurement range, calibration points, and accuracy tolerance to be determined and reviewed by the competent authorities. The GAMP Good Practice Guide: *Calibration Mangement*[4] suggests that the schedule should be listed on a plant equipment or system basis, and that a minimum of the Process Owner, Engineering, and Quality Assurance should be represented on the Criticality Assessment Team.

The ultimate responsibility has of course to lie with the Process Owner (Production Area Manager) as the user of the equipment. The role of Engineering is to ensure that resources are in place to carry out calibrations at the defined interval, while Quality Assurance verifies that GMP requirements are met.

It is important to note that it is the measurement function that is being assessed, and not the capability of the physical measuring instruments. Clearly, the sum of the manufacturer's tolerances of the individual instruments in a measuring system should be better or at least equal to the required measurement function tolerance, or they will not be capable of remaining in tolerance over the calibration interval.

The criticality categories assigned to measurement functions are usually "GMP Critical" where the measurement has a direct effect on product quality, "Environment Critical" for measurements associated with environmental monitoring and "Safety Critical" where the health and safety of persons are at risk when the measurement accuracy exceeds tolerance limits.

Two further categories are commonly used for the remainder of measurement functions. "Non Critical" usually denotes measurements that are calibrated as part of the routine calibration program, but which do not give rise to deviation reports if the measurement accuracy is found to exceed tolerance limits. "Engineering" applies to the non-essential utility type of instruments used by Engineering for fault-finding that are only calibrated on request.

Installing Adequate Instrumentation

The point was made in the previous section that the installed instruments should have a measurement accuracy capability that is better than or equal to the measurement function accuracy tolerance determined by the Criticality Assessment Team.

This illustrates the importance of documenting the instrument master schedule for a new project and carrying out the criticality assessment prior to specifying the instruments in order to avoid installing inadequate instrumentation.

The calibration interval is directly linked to the long-term stability and measurement accuracy of the installed instruments. If these have a low rate of drift, the calibration interval can be longer with a low risk of an out-of-tolerance condition arising. However, where the tolerance is small or where the impact on product authorization is severe, it is prudent to calibrate at shorter intervals to reduce the risk further.

Competence and Training of Personnel

All staff conducting calibrations should be technically competent by virtue of education and experience to carry out calibrations of the measurement functions assigned to them, and should be trained to carry out calibration in accordance with the approved facility SOPs at all times. Most manufacturing facilities now assess employee competence rather than simply recording training, as was the case in the past. This is also in line with the requirements in the 2000 version of ISO9001.[5]

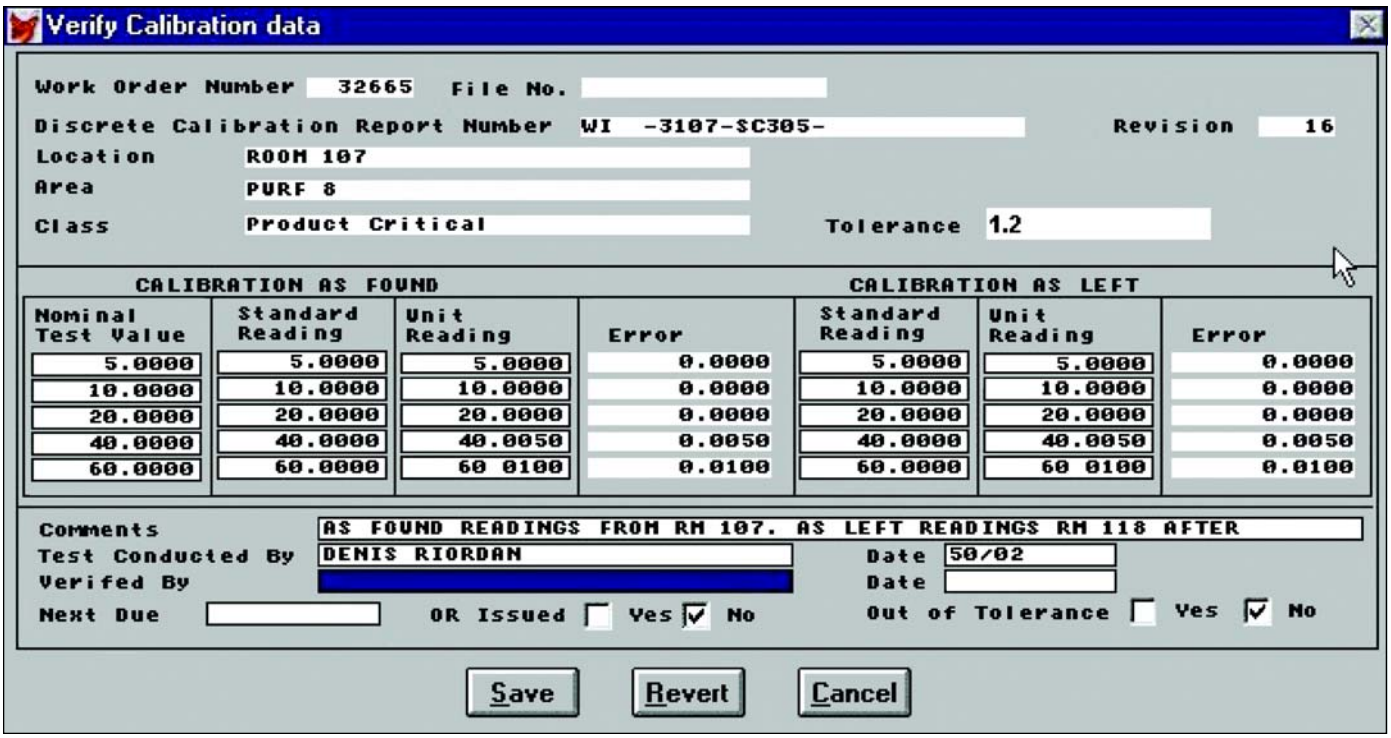

Figure 2. Calibration results entry screen.

Calibration Procedures

Documented SOPs defining the method of conducting calibration for each type of measurement parameter contained on the instrument schedules are central to the integrity of calibration results. The ability of calibration SOPs to achieve scientifically correct results should be validated by test studies prior to approval.

Since calibration is the act of comparing the measured value of the instrument under calibration with a reference standard, in most cases, it is not necessary to use the engineering level adjustment functions on the instrument to carry out the calibration. Where the measurement error of the instrument is found to exceed its limits at one or more of the designated calibration points ("As Found"), it will need to be adjusted in accordance with the manufacturer's instructions, and a second ("As Left") calibration then carried out to verify that it meets its return to service tolerance limit.

A common mistake is to document calibration SOPs that are related to a particular instrument make and model, rather than related to the measurement parameter. For example, the authors have noted instances of calibration SOPs detailing the steps to be followed when accessing engineering functions in a chart recorder, rather than focusing on the requirements to achieve the narrowest possible thermal gradient between the recorder's temperature sensor and the reference standard.

A core GMP concept is that the organization must be in control of its processes, and implicit in this is that no instrument can be used outside its calibration due date without written authorization from the Production Area Manager.

The question of whether or not status labels showing the "Next Calibration Due" date should be attached to instruments depends on where the organization places responsibility for verifying that instruments are within their calibration interval before use. If the responsibility in production SOPs lies with the operator, then a means such as status labels needs to be used to enable the operator to carry out the verification.

Alternatively, if the responsibility is moved to the Production Area Manager to take active steps to remove all invalid instruments from availability for use, it may be an option to use the calibration management system as the mechanism for verifying that instruments are within their calibration interval. If this approach is adopted, particular care should be taken to ensure that portable instruments such as temperature indicators and pressure gauges on mobile equipment are captured.

Out-of-Tolerance Instruments

Where a measuring system is found to have an error at one or more of its calibration points that exceeds the accuracy tolerance assigned to it by the Criticality Assessment Team, doubt exists for all measurements made by the system since its previous calibration (when it was returned to service within tolerance).

The action taken will be determined by the criticality category of the measuring system. If it is "GMP-Critical," a deviation report must be completed and the Area Manager and Quality Assurance immediately notified to enable an impact assessment to be carried out. Similar actions will be followed using appropriate channels for out-of-tolerance "Environment-Critical" and "Safety-Critical" measurement systems.

To minimize the impact of out of tolerance conditions on

high importance "GMP-Critical" measurements, dual monitoring of the process parameter can provide an extra degree of confidence in the measurement accuracy. The disadvantage of the necessity to complete two calibrations for one measurement can far outweigh the difficulties of completing a thorough assessment of the impact of an error that may have existed for some period of time. A further advantage of dual monitoring is that it can serve to highlight drift.

Planning and Recording Calibration

It would be unusual today to find a pharmaceutical manufacturing facility that did not use a computerized calibration management system as a tool for planning calibration activities and printing calibration work orders. Where differences exist is whether the hand written calibration results are entered into the computerized system prior to review, or whether the review is carried out on the hand written calibration report and the review result alone is entered.

The key objective of calibration, which is to verify whether the measurement function was within its specified tolerance for the previous period of service, is satisfied in both cases. The benefit of entering the calibration results is that the drift characteristic of the measuring system can be analyzed over time; the price paid for this is the time taken to enter the results into the computerized system, and the time taken for a second person to verify that they have been entered correctly.

If the results are not entered, the calibration record is the combination of the filed calibration report with hand written results together with the review result entered into the computerized system. Where calibration results also are entered (Figure 2), the printed complete calibration report together with the hand written original are filed, and these together with the electronically stored data constitute the calibration record.

A number of reference standard vendors offer multifunction instruments with communicating capability, while several computerized calibration management system vendors offer hand-held computing devices as a tool for recording calibration results. These have the advantage of reducing the possibility of transcription errors, and eliminating the need for second person verification of entered results.

The computerized calibration management system is a GMP system and must be validated to meet regulatory requirements. In earlier days when the choice and capability of standard computerized calibration management systems was very limited, some organizations developed bespoke systems to meet their exact needs. However, fears of Year 2000 issues, the advent of electronic record regulations, and the absence of a migration path have caused most organizations to convert to a standard vendor package.

Impact of New Technologies

In hazardous areas such as reactor rooms, it is not possible to perform process measurement loop calibrations using non Intrinsically Safe (IS) reference equipment without first purging the area of potentially explosive gases and certifying it safe for use of equipment that can provide a source of ignition.

This has meant that some calibrations are conducted by simulation, instead of full application of process conditions. This is particularly true in the case of temperature calibrations, which would typically require an electrically heated dry block or liquid bath as a thermal medium for the sensor and the reference standard to complete a loop calibration. In many industries, most calibrations like this tend to be carried out by resistance substitution at the transmitter to avoid the need to use non-IS equipment.

A number of new fieldbus technologies are based on smart transmitters with individual node addresses that continually broadcast the process variable as a digital word on the fieldbus network. This eliminates the traditional hard wired measurement loop and enables the transmitter complete with its sensor to be removed from the hazardous area for a full system calibration in the workshop, without compromising the integrity of the measurement loop.

Many smart instruments that monitor their internal electronics have the potential to report diagnostic and drift information if a suitable software application is installed on the network to interact with the instruments. While this functionality does not replace the need to calibrate the instrument against a reference standard, it does provide predictive warning of the need to calibrate the instrument in the near future.

Developments in the area of smart self-diagnosing instrumentation, coupled with improved sensor and transmitter stability, has led to a situation where many manufacturers claim that extended calibration intervals can be applied (up to five years, in some cases). However as mentioned earlier, the use of extended calibration intervals should be tempered against the potential impact of out of tolerance conditions on product quality.

Tamperproofing Instrument Settings

The hardware or software settings that can affect the calibration of each of the instruments in a measurement system must be protected against tampering. In the case of hardware adjusters, simple tamperproof adhesive labels covering the adjustment point are an option, provided that the distribution of these can be shown to be under positive control.

Protection of software configurable instruments against tampering is far more complex. Configuration of this category of instrument falls into three distinct categories:

- by using keys on the instrument itself
- by using a hand-held configuration tool, or a laptop computer running configuration software
- from a networked computer running configuration software or asset management system software

The issue common to each of these categories is that the instrument configuration should be documented and validated, access to engineering functions should be denied to the operator, and calibration personnel should only be permitted

to change adjustment parameters (not the base configuration that has been validated). In all cases, this requires formal password administration in accordance with the organization's access policies, and at least two and possibly three hierarchical levels of access control.

Control of Reference Standards

It is essential that the reference standard against which a measuring system is calibrated has a negligible tolerance in comparison to the system under calibration, and that the calibration of the reference standard is traceable.

The traceability of a reference standard calibration is the establishment of a known, valid relationship to a nationally or internationally recognized standard in accordance with International Laboratory Accreditation[6] (ILAC) requirements as defined in Figure 1 "Calibration Hierarchy" of ILAC-G2:1994 Traceability of Measurements" - *Figure 3*.

Traceability is authenticated by accreditation of a calibration laboratory for the particular measurement by its national accreditation authority, which authorizes the laboratory for measurements within its published scope of accreditation. Accreditation verifies that the laboratory complies with ISO/IEC17025[7] for all of its accredited calibrations.

Within Europe, these authorities enter into multilateral recognition agreements under the umbrella of the European Accreditation[8] (EA), which in turn enters into bilateral recognition agreements with calibration accreditation organizations such as American Assocation for Laboratory Accreditation (A2LA)[9] in the US and the Standards Council of Canada (SCC)[10].

Accreditation authorities require participating laboratories to satisfy the ILAC traceability criteria which include:

- an unbroken chain of comparisons to a national or international standard
- a statement of measurement uncertainty that takes each step of the chain into account
- evidence of the technical competence of the laboratory, e.g. by demonstrating that they are accredited

Using Contractors for Calibration

In the current climate of headcount minimization, it is not always possible to use in-house resources to carry out calibration, and calibration contractors are then required. Since calibration is a GMP activity, it follows that the contract personnel must meet the same levels of competence as the existing facility staff that they are supplementing.

A key decision is whether to permit the use of reference standards provided by the calibration contractor, or to use the contractor solely as a supplier of competent personnel, restricting reference standards to those controlled by the facility. In the latter case, qualification of the contractor is limited to verifying that all proposed calibration personnel are competent, and ensuring that they are fully trained on the facility's GMP and calibration SOPs prior to commencing work.

Where the contractor is engaged to provide both personnel and reference standards, the contractor's quality management system should be audited in advance of calibrations to verify that the integrity of the contractor's reference standards is under positive control, and that the contractor can demonstrate that affected customers are immediately notified when a reference standard that has been used in their facility is subsequently found to be out-of-tolerance.

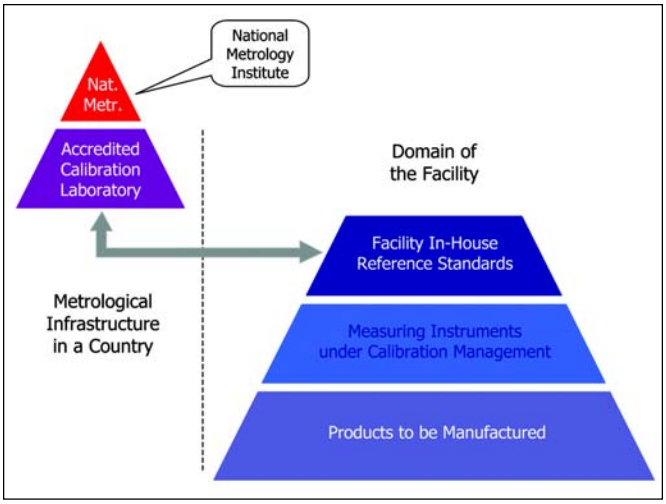

Figure 3. Traceability of product measurements.

The quality management system operated by the contractor should be in full compliance with ISO9001[5] at a minimum, and the expectation within Ireland is that this is certified by an accredited authority.[8] This demonstrates that the contractor has an auditable system in place, but does not remove the need for the pharmaceutical manufacturer to audit the contractor to satisfy themselves that the system is operated to a level commensurate with the requirements of the proposed work.

Continuous Improvement

To ensure that the effectiveness of calibration at a facility is maintained and where feasible improved, two primary Key Performance Indicators (KPIs) in the management of a calibration program are:

- the percentage of calibrations completed on schedule
- the percentage of calibrations found to be within tolerance

Ongoing analysis and review of these KPIs provides the driver for continuous improvement, as the organization strives toward 100% compliance in each of these. Coordinating calibration activities with availability of production equipment is not easy. Extension of calibration intervals to accommodate overruns on scheduled calibrations, increases the risk of out-of-tolerance instruments and should require written authorization from the production Area Manager.

It is desirable to operate calibration intervals that are as long as possible without increasing the risk of out-of-tolerance instruments in order to minimize the disruption to production caused by scheduled calibrations. These objectives can only be realized by systematic analysis of calibration management information.

Review of calibration intervals is a risk assessment activity, which balances the cost of potential deviations over a prolonged period against the cost of frequent calibrations. While some organizations will systematically increase the calibration interval after a number of consecutive successful calibrations, i.e., calibration where no adjustment is required, it is the authors' experience that the extension of calibration intervals is best achieved by groupings of similar instruments, e.g., HVAC temperatures, room pressures etc.

This enables a thorough review of the performance of instruments and calibration for that grouping to be conducted; where the results indicate small amounts of calibration drift and very infrequent out of tolerance situations, the interval can justifiably be extended for the entire instrument grouping.

While the overall objective is maximization of the calibration interval, the results of the review may in some cases require a reduced interval. This can be indicative of deficiencies in equipment, personnel, or methodologies and highlights the need for remedial action to be taken.

Summary

The European approach as required by European regulators is essentially science-based with measurement tolerances related to product quality requirements and calibration SOPs designed and validated to provide an appropriate uncertainty of measurement in each instance.

While simulation of measurement variables forms the basis of some calibrations in the Active Pharmaceutical Ingredient (API) manufacturing area where potentially explosive atmospheres may be present, this is not the practice in Finished Pharmaceutical manufacturing where full system calibrations are always performed.

Calibration management is the activity that underpins the integrity of GMP, environmental, and safety measurements. Competent, trained personnel using traceable reference standards and following sound calibration practices to verify specified measurement tolerances are key elements of an effective system.

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