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A Practical Guide to Construction, Commissioning and Qualification Documentation – and its Critical Role in Achieving Compliance

by Wael Allan and Andrew D. Skibo

This article focuses on construction contractors who can deliver qualified facilities and presents the advantages of using a construction contractor who can perform Commissioning and Qualification.

Good documentation is essential for pharmaceutical and biotech manufacturing facilities to achieve regulatory compliance. As defined by the Food and Drug Administration (FDA), "Validation is a *documented* program providing a high degree of assurance that a process/system consistently meets pre-determined specifications." The clear presumption is that if the required activities have not been properly documented, then they have not been performed.

Naturally, the initial focus must be on the proper construction and start-up of the facility. Yet, a well-constructed facility that is on time, within budget, and whose every system is performing to specifications is of no value to the operating company if the associated documentation does not effectively support the qualification process – it is a classic case of failing to see the forest through trees. In fact, the construction contractor must appreciate the significance of documentation, and make it an integral part of the construction planning, implementation, and commissioning process from day one.

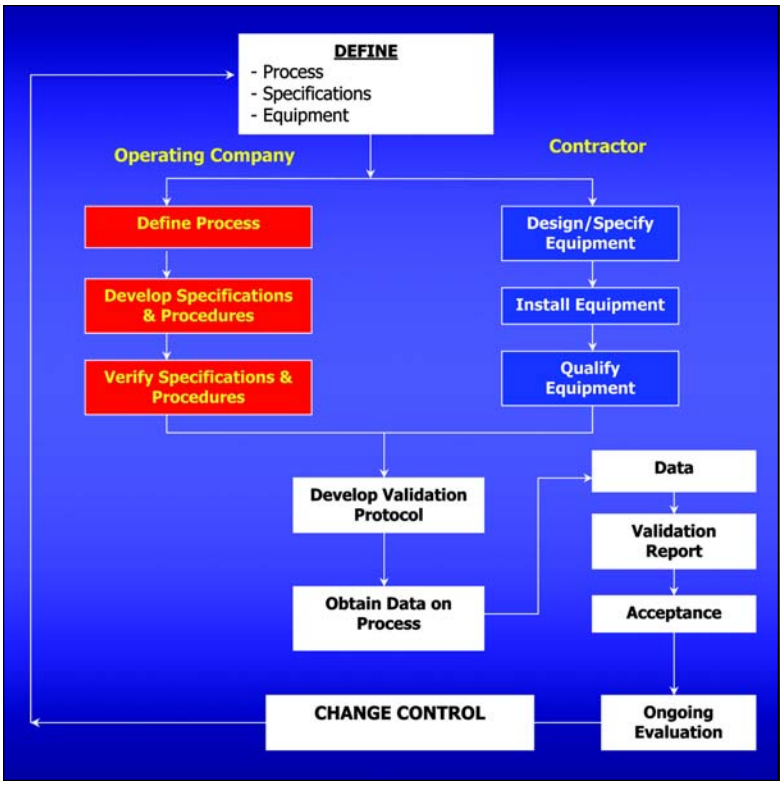

Figure 1. Validation life cycle.

Note: the term "Construction Contractor" is used to indicate a third party company responsible for construction, commissioning and qualification. This article focuses on construction contractors who can deliver qualified facilities. It also presents the advantages of using a construction contractor who can perform C&Q, as well as construction led rather than design led projects. A "full service provider" could provide all of these activities. These activities could be provided in

part by a Construction Management (CM) contractor, a commissioning contractor, a qualification contractor and the operating company.

Turn Over Package (TOP): Laying the Foundation

Good documentation is an essential part of the Quality Assurance (QA) system. For new and renovated facilities, Commissioning and Qualification (C&Q) are key aspects of cost and schedule. Therefore, documentation – in the form of the TOP, C&Q protocols, and other required documents – plays a pivotal role in ensuring a compliant facility. Every operating company has specific standards and methodologies for C&Q. The construction contractor's job is to make sure that the TOP enables the operating company to effectively carry out its QA strategy. Therefore, the TOP must be well-organized, meet the operating company's expectations, and provide the proper level of documentation quality.

To be successful, an integrated documentation process must start very early in the project in conjunction with the planning of C&Q. It must involve engineering, construction, and qualification/validation. Moreover, project documentation requirements, and the roles and responsibilities for the operating company, construction contractors, and vendors alike, must be clearly defined.

Too often, documentation work is delayed until the later stages of the project, or the effort required to do it successfully is underestimated. For example, on an 18-month project, the QA/documentation officer should be involved by the first quarter of the project – during the planning phase — to begin to organize the TOP to meet the operating company's needs and expectations. It is well worth the small investment to bring that individual on board early to avoid problems during the qualification process, and ultimately, reduce time to market. This approach eliminates duplication of effort by leveraging documentation from commissioning into Installation Qualification (IQ). IQ is approximately 30% of the qualification effort; by leveraging commissioning documentation, a savings of approximately 50% of IQ effort could be made, resulting in an overall saving of 15% of qualification time.

The Validation Life Cycle

Just as good documentation is required to achieve regulatory compliance, clear user specifications that are fully understood by the construction contractor are required to meet the operating company's unique needs and expectations. If the constructor fails to understand these from the outset, the TOP is likely to be inadequate. Therefore, for every step taken by the operating company, engineers and construction contractor, a high level of integration is required to ensure that the resulting documentation is appropriate, compliant, and structured in a meaningful manner - *Figure 1*. The diagram

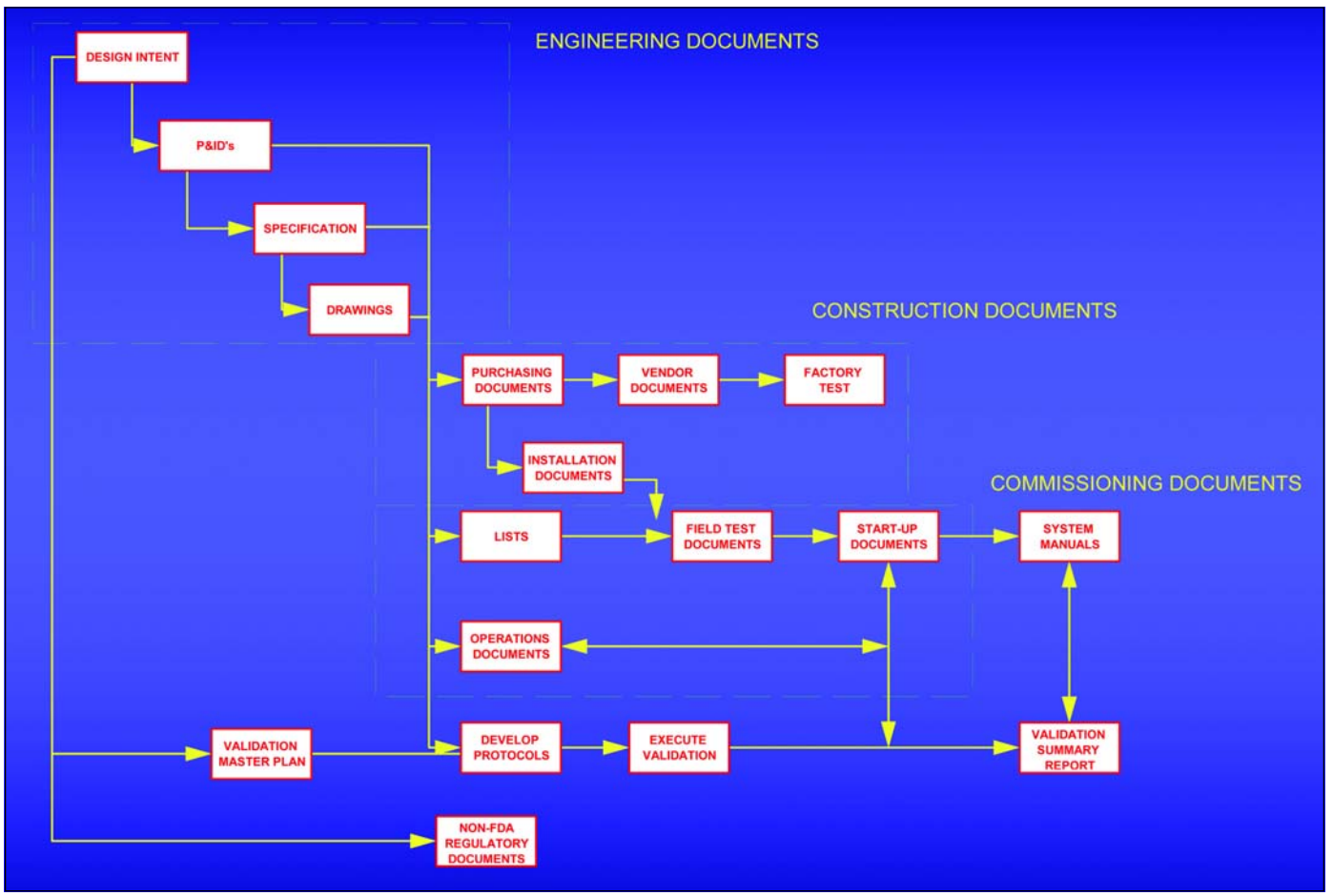

Figure 2. Document hierarchy.

illustrates the importance of the "definition" stage for both the operating company and the contractor. In all aspects of the life cycle, documentation/data is a very critical element.

The operating company's definitions of specifications and process requirements drive the whole project. Specifically, the operating company defines the process, develops procedures and specifications, and verifies these. In turn, the construction contractor specifies and installs equipment, and tests and qualifies making systems ready for validation and operation. This process requires that the construction contractor accurately "translate" the operating company's definitions and expectations into systems, bricks, and mortar. Otherwise, the succeeding steps – development of the validation protocol through change control – will be fraught with problems, delaying time to market.

A Practical Guide to Project Planning

Effective project planning is the key to a successful and cost-effective documentation effort. More importantly, is the integration of construction with C&Q. Operating companies have different preferences: some would award construction and commissioning to the same construction contractor; others would go further and award construction and C&Q to the same construction contractor, ensuring a successful, seamless integration and quality documentation, resulting in the handover of a qualified facility rather than a merely mechanically completed one. (There are additional variations and operating company contracting preferences, which are outside the scope of this article.) The construction contractor's role in a C&Q project can be broken down into three steps:

- develop and agree upon the scope of work and responsibilities
- agree upon a methodology and develop the project execution plan and quality manual
- develop a project management plan incorporating document management

Each of these steps has components with a significant impact on documentation; therefore, the construction contractor should fully integrate these steps into project planning. The following is a practical guide to each step and its essential components.

Step 1: Develop and Agree Upon the Scope of Work and Responsibilities

At the start of a project, it is essential for the operating company and construction contractor to agree on the scope of work, perform a risk analysis to identify critical and non-critical systems, and identify who is responsible for the various project deliverables, including documentation; the construction contractor also must identify systems and boundaries.

Identify Systems and Boundaries

Working from the operating company's definitions and engineers' drawings, the construction contractor must graphically delineate each system and its boundaries. This has significance for the organization of the TOP, for example, if it is to be organized by system; it also identifies which subcontractor and/or vendor has responsibility for what element.

PHASE	DOCUMENT TYPE	ALL SYSTEMS Good Engineering Practice	CRITICAL SYSTEMS Enhance Documentation
Engineering	Design Intent	B	V
	P&IDs	C	V
	Specifications	B	B
	Drawings	C*	V
Construction	Purchasing	B	B
	Vendor	B	C
	Installation	C	C
Commissioning	Lists	B	B
	Factory Testing	B	B
	Field Testing	B	V
	Start-up Forms	B	V
Operating	Training	B	V
	Maintenance	C	V
	Procedures	B	V
Regulatory	Applicable Codes	B	C
	Inspection Certificates	C*	C
	Permit Documents	B	B
Validation	Validation Master Plan	---	V
	Validation Protocols	---	V
	Validation Summary Report	---	V

B: BASELINE DOCUMENT - These documents are created and retained in project records with appropriate project approvals.

C: CONTROLLED DOCUMENT - These documents are created "as built" retained in project files with appropriate project approvals and maintained after commissioning. (Note C* means that only some of the documents in this category require document maintenance)

V: VALIDATION DOCUMENT - These documents are treated as controlled documents, but with the added approvals required for validation programs. Additional approvals usually are limited to Quality Assurance and operations. Document maintenance is a formal change control process.

Table A. Documentation requirements.

Perform Risk Analysis

The risk analysis is an extremely important activity involving the operating company and construction contractor. The result will capture operating company expectations by classifying systems into critical and/or direct impact systems and non-critical and/or indirect impact systems. This is significant because critical systems, such as fermentation, require a higher level of documentation. Thus, the risk analysis culminates in establishing the project documentation requirements - *Table A*. Documents should be categorized into *baseline* documents, *controlled* documents, and *validation* documents. For non-critical and/or indirect impact systems, Good Engineering Practice (GEP) is considered sufficient while critical/direct impact systems are earmarked for compilation of enhanced documentation packages.

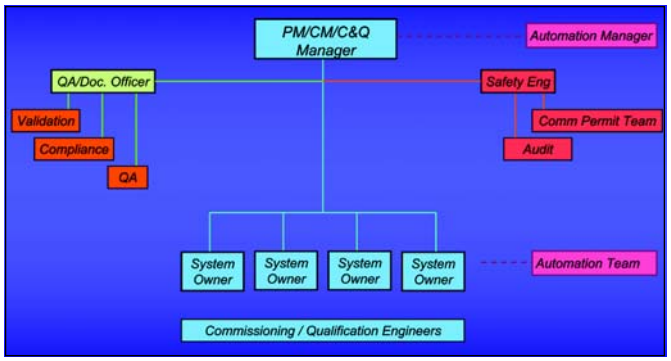

Figure 3. Role of QA/documentation officer.

Name Responsible Parties/Individuals for Specific Activities/Deliverables

With respect to documentation, a hierarchy from "design intent" through to "validation summary reporting" should be established based on the delineation of systems and boundaries - Figure 2. Responsibility for specific documents is assigned to various firms and individuals. Moreover, certain deliverables must be completed before others can start, requiring that these individuals clearly understand their responsibilities, integrate their activities, and effectively communicate with one another. A critical project also benefits from a graphic diagram of the project document hierarchy, which is distributed to each team member. Otherwise, false assumptions might be made and critical documents could "fall through the cracks." This aspect of Step 1 culminates in two sets of documents: non-FDA regulatory documents (i.e., for reference, archiving, etc.) and regulatory documents.

Identify the Project QA/Documentation Officer

The project QA/documentation officer is a key resource with respect to documentation and must be carefully selected. That is, the project QA/documentation officer's capabilities must far exceed organizing and distributing documents – he or she must fully understand the regulatory requirements for documentation - *Figure 3*.

The QA/documentation officer should report to the construction or overall project manager and/or the C&Q manager (either as a member of construction staff or under subcontract if C&Q is performed by a party other than the construction firm) and liaise with the operating company's validation, regulatory compliance, and QA groups. This individual is charged with ensuring that the operating company's requirements, policies, and expectations are transferred to all parties involved; confirming that all parties know which documents to produce, and when; and ensuring all the documents are consistent with one another and fulfil the regulatory requirements of compliance, validation, and QA. The QA/documentation officer audits all documentation, including the TOP, ensuring that it can be leveraged to help the operating company streamline qualification.

In essence, the QA/documentation officer must effectively align the contractual expectations of the operating company and construction contractor. While some operating companies prefer to hire a third party, the advantages of hiring a construction contractor with this in-house capability are greater consistency, compliance, and speed.

Step 2: Agree Upon a Methodology, and Develop the Project Execution Plan and Quality Manual

Well before design is completed, the construction contractor and operating company should agree upon a qualification methodology. Based on this, the construction contractor will identify standard operating procedures; develop a schedule, commissioning plan and validation master plan; and also agree on the level of leverage from commissioning into qualification. These, among other strategies, will be used to determine the organization of the TOP. Leveraging can be defined as the utilization of properly documented activities carried out during construction and commissioning which can be used in support of qualification (IQ and OQ) resulting in the avoidance of unnecessary repetitions hence reducing qualification time.

Identify Standard Operating Procedures (SOPs)

The construction contractor must identify and define all SOPs, including protocol formats, numbering systems, and the review and approval process. This ensures that proper procedures are in place to document all systems and components for the TOP. The construction contractor must maintain consistency among numbering systems used by the various suppliers and align these with the operating company's requirements for the project. Ultimately this important component of the methodology and project execution plan ensures a smooth compilation of the documentation and TOP.

Develop a Project Schedule Capturing Commissioning, Qualification, and Validation

Development of a project timeline by the construction contractor identifies the required resources and critical timings for data or documentation that are required for subsequent activities to proceed. This is critical to streamlining the process.

Develop Commissioning Plan

An important component of the project methodology is the commissioning plan, which identifies the level of documentation appropriate for commissioning, level of quality, and required signatories based on the operating company's qualification strategy. For example, some operating companies use an Integrated Commissioning Qualification (ICQ) strategy, in which much of the commissioning documents will be leveraged into the qualification effort, thereby reducing time to market - *Figure 4*.

Develop Validation Master Plan

The validation master plan, including computer systems validation, must be aligned with the commissioning plan and operating company's qualification strategy.

Determine Organization of TOP

Based on the strategies of C&Q, the construction contractor must determine the proper organization of the TOP and what level of documentation is required from the various parties. The organization of the TOP is critical to the success of the qualification process – that is, it must be organized in such a way that the operating company is able to leverage the documentation and data into qualification. In effect, the TOP aligns the contractual responsibilities of the operating company and construction contractor. The TOP signifies the end of an important phase and a handover to the operating company. In some cases, the TOP could signify the end of mechanical completion, where design and construction data is turned over to the operating company; in others, it signifies the completion of commissioning and qualification - Figure 5.

The TOP consists of specifications, manuals, drawings, and other documentation that fully characterizes each system or piece of equipment installed in the facility. The construction contractor should prepare a TOP matrix for each system, which defines the documentation required for all its components. Compiled in a formal and organized package, the TOP serves as part of the basis for Installation Qualification (IQ), which verifies that the physical components of the system have been installed according to design specifications. As the final major component and system quality audit prior to Operation Qualification (OQ), the IQ is a critical step that lays the foundation for compliance and testing of the facility.

In fact, the TOP is critical throughout all phases of the project – from design and procurement to handover at mechanical completion, commissioning, or qualification. Thus, each of the following activities must be carried out to ensure documentation of compliance:

- **Design and Procurement Phase:** the construction contractor's team must review the design of the project for system boundary demarcation, regulatory requirements, commissionability, Good Automated Manufacturing Practice (GAMP), and Code of Federal Regulations (CFR) 21 Part 11 compliance, and to develop the templates for commissioning, Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), and qualification documents. The commissioning plan and validation master plan are developed and delivered in this phase. Members of the team responsible for commissioning must review Piping and Instrumentation Diagrams (P&IDs) and 3D design models for safety and the inclusion of commissioning requirements. They also will attend Hazard and Operability (HAZOP) and constructability reviews, as well as design specifications and procurement documentation to assure that the requirements of the operating company are included and delivered.

- **FAT:** during the procurement phase, the construction contractor should ensure that a determination is made as to which equipment will undergo formal FAT. Items which

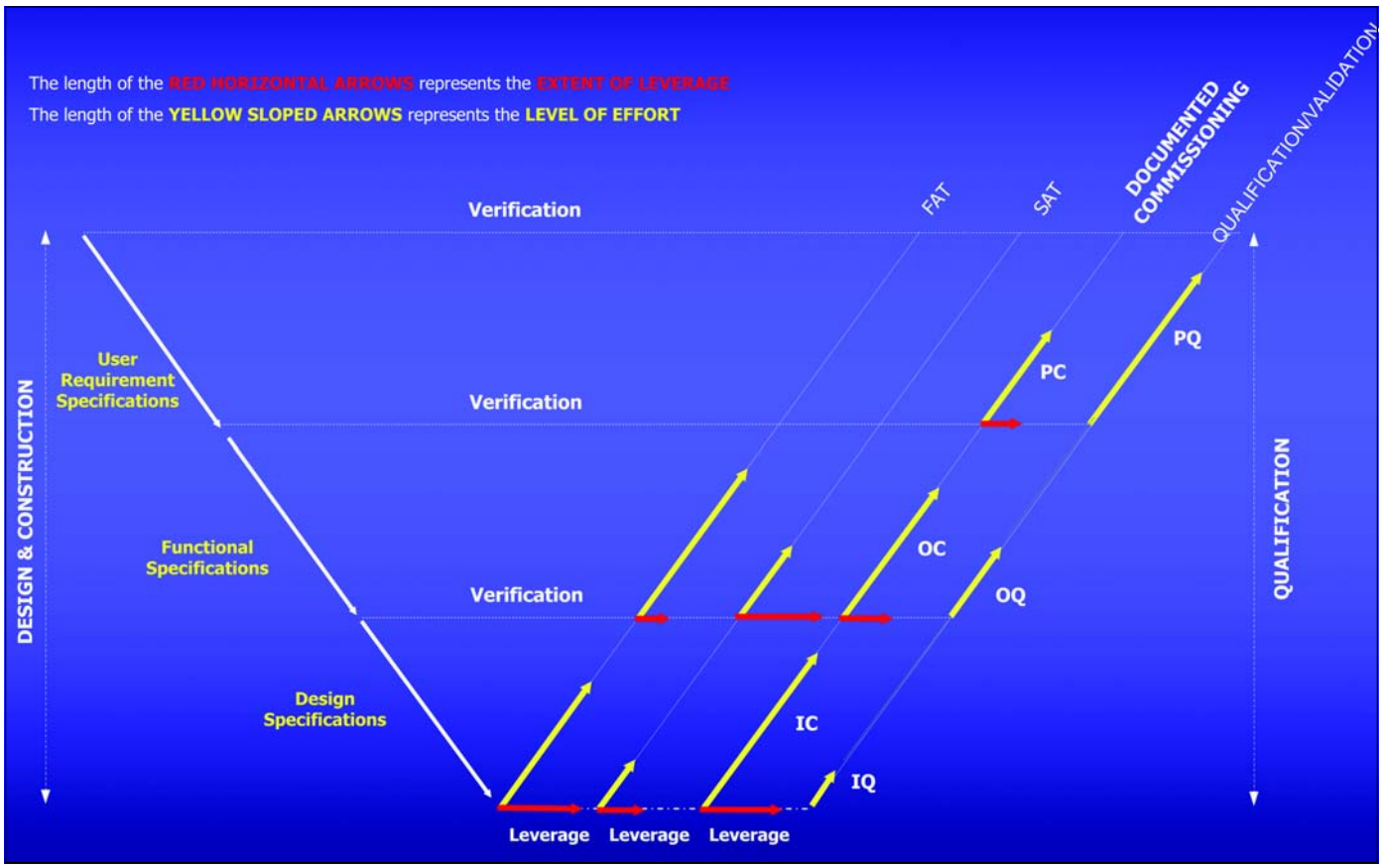

Figure 4. Leveraging commissioning into qualification.

cannot undergo "FAT" should be subjected to a "document and component verification." For the selected items, the construction contractor must develop and issue FAT test protocols. The construction contractor's FAT team, led by the individual who is responsible for commissioning, will execute the FAT in the vendor's facility. The commissioning head must verify that the equipment complies with the User Requirement Specifications (URS) and design specification, and that all documentation for operation, maintenance, and qualification are complete and available. Functional testing is generally undertaken for information and engineering verification purposes only. Programmable Logic Controller (PLC) functionality must be verified, as well as the data communications to the plant supervisory systems to ensure their compatibility and transmission. Finally, documentation, controls hardware, and the component schedule must be formally verified because these will be subsequently used to leverage the IQ.

- **Construction:** during construction, the project team will audit construction of each system and witness primary construction activities, such as loop testing, pressure testing, and flushing. The team also coordinates vendor installation checks and verification of SAT readiness. In addition, the bulk of the commission and qualification documents are generated and issued for approval during the construction phase. A number of construction activities must be documented, as well as witnessed, to meet Good Manufacturing Practice (GMP) requirements (e.g., welding of sterile piping and verification of slopes) and will be used to leverage the IQ. By working closely together, the QA/documentation officer, supporting staff, and construction team can expedite the handover from construction to commissioning – speeding time to market.

- **SAT:** the construction contractor typically splits the SAT into two phases – an installation and documentation verification phase and a functional testing phase. An audit of the FAT documentation and schedule checks is performed to verify that no changes have occurred since the FAT (i.e., the FAT data is still valid for the IQ). During functional testing, the system is tested, coupled with the actual site utilities, and linked to the site supervisory system for full data transmission functionality.

- **Commissioning:** in the pre-commissioning phase, the construction contractor performs final hot-loop checks and instrument calibrations, as well as motor and device run-in tests. The construction contractor is responsible for the

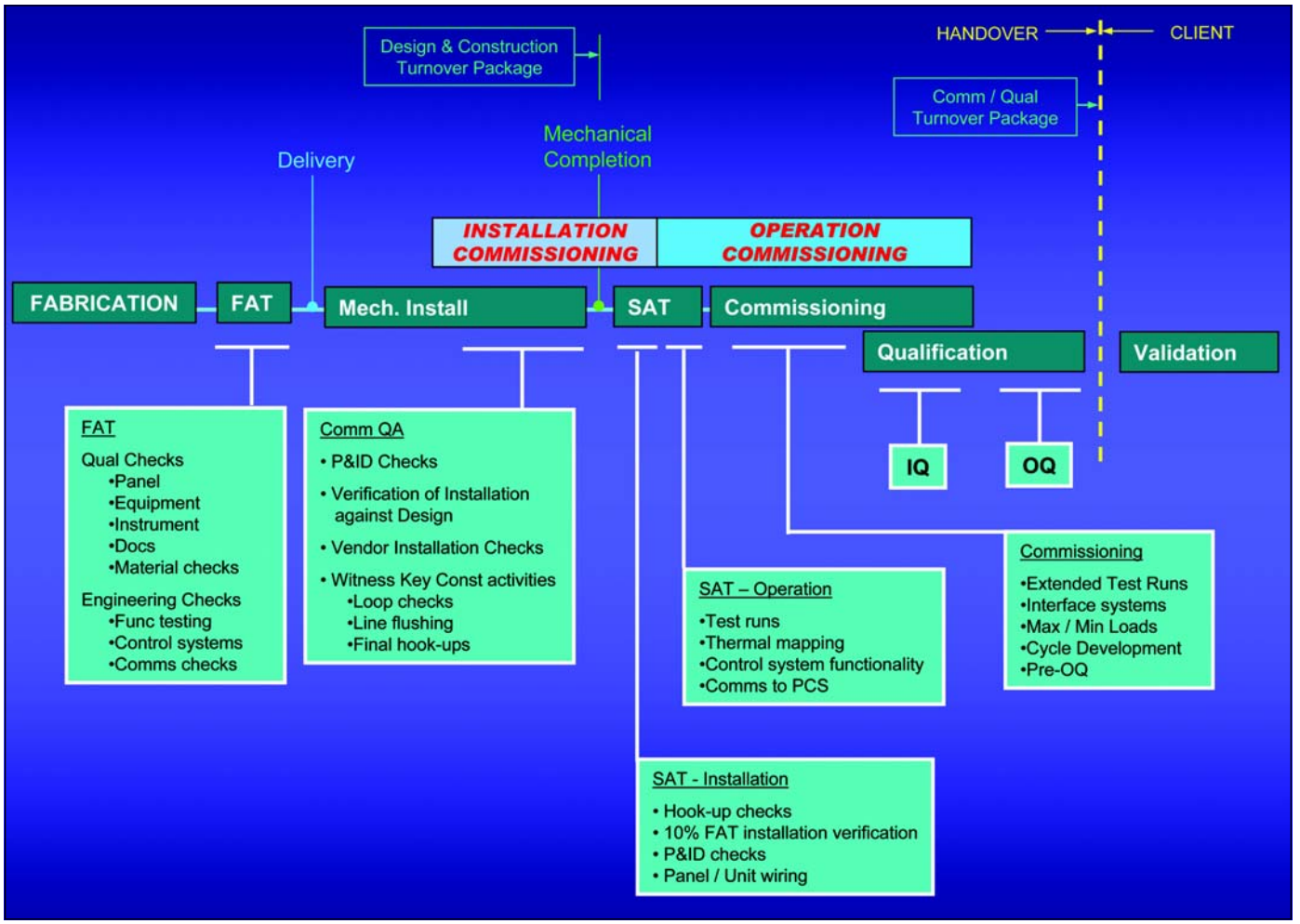

Figure 5. TOP's critical role in all project phases.

execution of the commissioning procedure and IQ protocol. During commissioning, each system is tested in conjunction with other interface systems for the functionality as required by the URS and specifications. Toward the end of the commissioning phase, the construction contractor performs a pre-run of the OQ testing to "de-bug" and provide assurance of a successful OQ execution. During commissioning, the construction contractor may perform an expanded level of testing of system functionality (i.e., in excess of the OQ requirements) to test the limits of system capabilities. It is important to note that not all of these tests will necessarily need to be documented – the construction contractor and operating company should discuss and agree upon the extent of documentation required as part of the commissioning plan and its documentation requirements.

- **IQ:** following the SAT and pre-commissioning, the construction contractor performs system IQ. Much of the verification data from FAT, construction, SAT, and pre-commissioning can be leveraged into the IQ if it has been effectively documented, which saves the operating company valuable time - *Figure 6.* The QA/documentation officer is responsible for the verification of the IQ support documentation files from the various project phases.
- **OQ:** a separate standalone OQ should be performed to enable the commissioning procedure to be segregated from the formal qualification files. A pre-run of OQ testing in the commissioning phase ensures a successful OQ, which will reduce deviations and streamline the OQ process and its documentation.

Plan for Integration of Construction, Commissioning, Qualification and Validation

The construction contractor normally is focused on getting the facility built and started up. However, the construction contractor's overriding goal must be the integration of *all* field activities with respect to documentation – the success of the qualification and validation process ultimately depends on the quality of documentation at each step. Typically, documentation is divided into two categories — project files and qualification files - *Figure 6*.

The project files are handed over to the operating company for reference and archiving; they will not compose part of the qualification package. The qualification files are controlled documents, which fall under the change control procedure; therefore, these must reflect greater attention to the URS, specs, vendor audit, validation master plan, and project plan. From a regulatory perspective, if the engineer, construction contractor, or operating company makes any changes to the

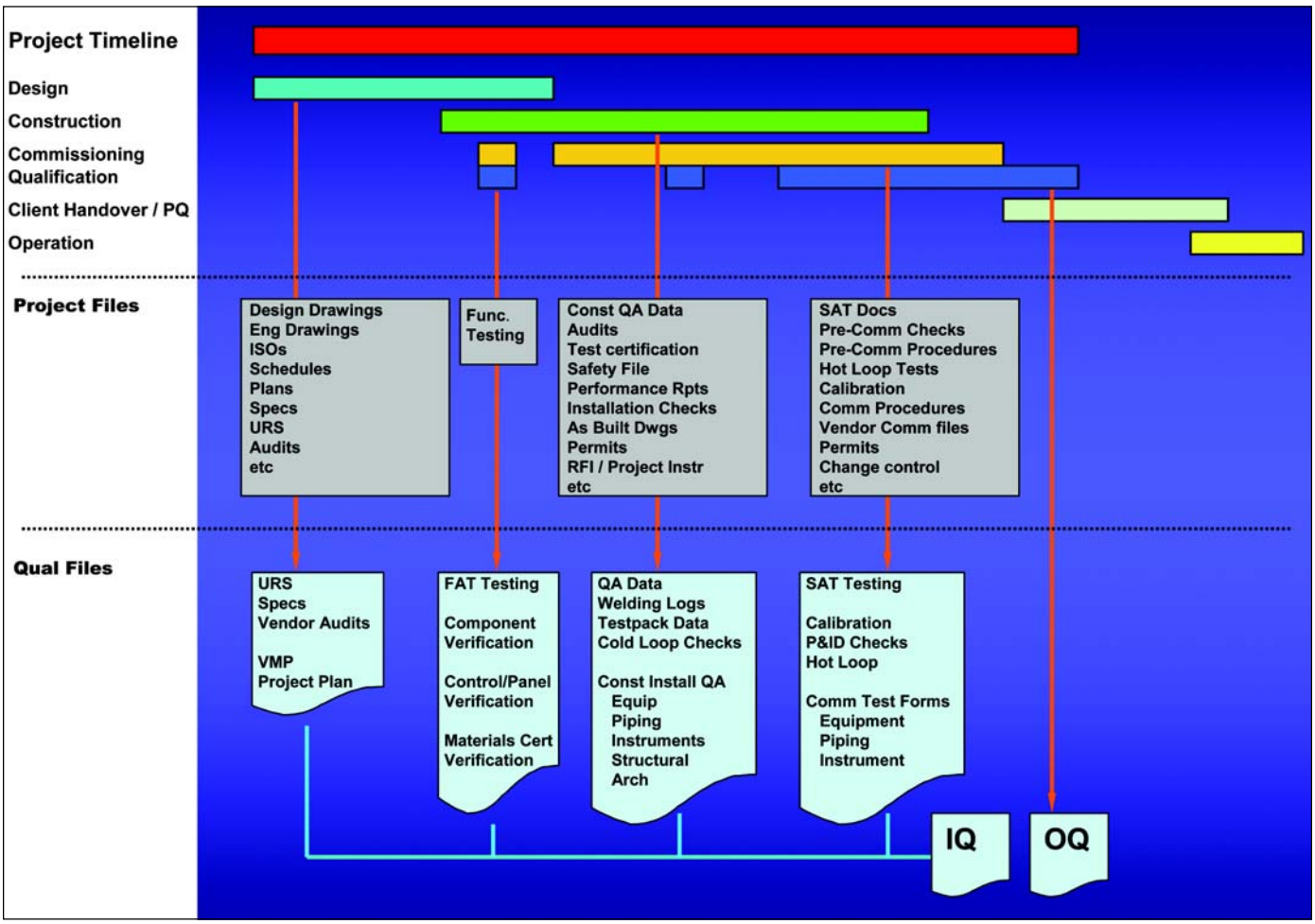

Figure 6. Integrated documentation (project and qualification files).

systems, the qualification files must be updated so that they reflect the validated standards of the operating company's facility. Associated with the handover of documents to the operating company, the construction contractor should set up operations and maintenance training for the operating company's key personnel, as well as document training for the entire project team. The construction contractor also should be involved in change control and deviation management.

Step 3: Develop a Project Management Plan Incorporating Document Management

Considering the voluminous documentation gathered and developed during the course of constructing, commissioning, qualifying and validating a modern pharmaceutical or biotech manufacturing facility, the control, tracking, and data storage mechanisms employed to amass these materials have become indispensable tools for efficient and successful project management.

Document Control, Review Cycles, and Approvals

In a successful project, document control is not the sole responsibility of a single individual. Instead, it is a team effort that requires early involvement of all the participants – engineers, project managers, vendors and sub-construction contractors, commissioning, qualification and validation groups, including their technology leads. Policies, practices, and procedures developed by this team must be rigorously adhered to by all parties throughout the project. The construction contractor's role cannot be understated — even procurement documents gathered in the early stages of the effort will become an important part of the TOP that will support the licensure and regulatory approval process.

If the operating company already has established document practices, procedures, and change control policies in place, the construction contractor should establish document methods for distribution, review cycles, version control, numbering, and approvals that mesh with these practices. The construction contractor may use an electronic document control platform to create distribution groups for recipients of various types of documents and control different versions of documents as they are developed, recording all relevant comments and the names of their originators.

Data Security

The operating company should ensure that the construction contractor is prepared to physically secure and store critical original hard-copy documents in fireproof cabinets, and ensure that electronic versions of these documents are backed up regularly on two systems in two separate locations. Often, the construction contractor's project managers will ensure that copies of critical project documents are maintained at three locations.

Reducing Time to Market

High-quality documentation is essential to achieve regulatory compliance. The construction contractor must appreciate the significance of documentation, and make it an integral part of the construction planning, implementation, and commissioning process from the inception of the project. The construction contractor's goal is not only to build a facility on time and within budget with systems that perform to specifications – it is also to develop a TOP that is well organized, meets the operating company's unique needs and expectations, and provides the proper level of documentation quality. When the construction contractor effectively manages the construction and commissioning documentation process, the operating company can leverage the resulting documentation for the qualification process, reducing time to market.

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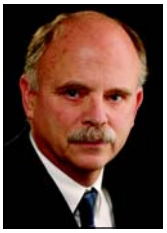

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This article describes the development, implementation, and results of an expert elicitation survey about risks associated with pharmaceutical manufacturing processes, and discusses potential application of this data collection methodology to a broader range of experts.

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Elicitation of Expert Knowledge about Risks Associated with Pharmaceutical Manufacturing Processes

by Dr. Nga L. Tran, Brian Hasselbalch, Dr. Kara Morgan, and Dr. Gregg Claycamp

Introduction

Recently, the FDA-Center for Drug Evaluation and Research (CDER) conducted a survey to elicit expert knowledge about risks associated with the manufacturing processes of a number of pharmaceutical product types. This survey was carried out as part of the Center's ongoing effort to develop and implement a systematic approach to prioritize sites for routine cGMP inspection.

The International Conference on Harmonization (ICH) in the current draft of ICH document Q9, Quality of Risk Management, defines risk as a combination of the probability of the occurrence of harm and the severity of that harm. As an ICH participant, CDER recognizes this definition of risk.

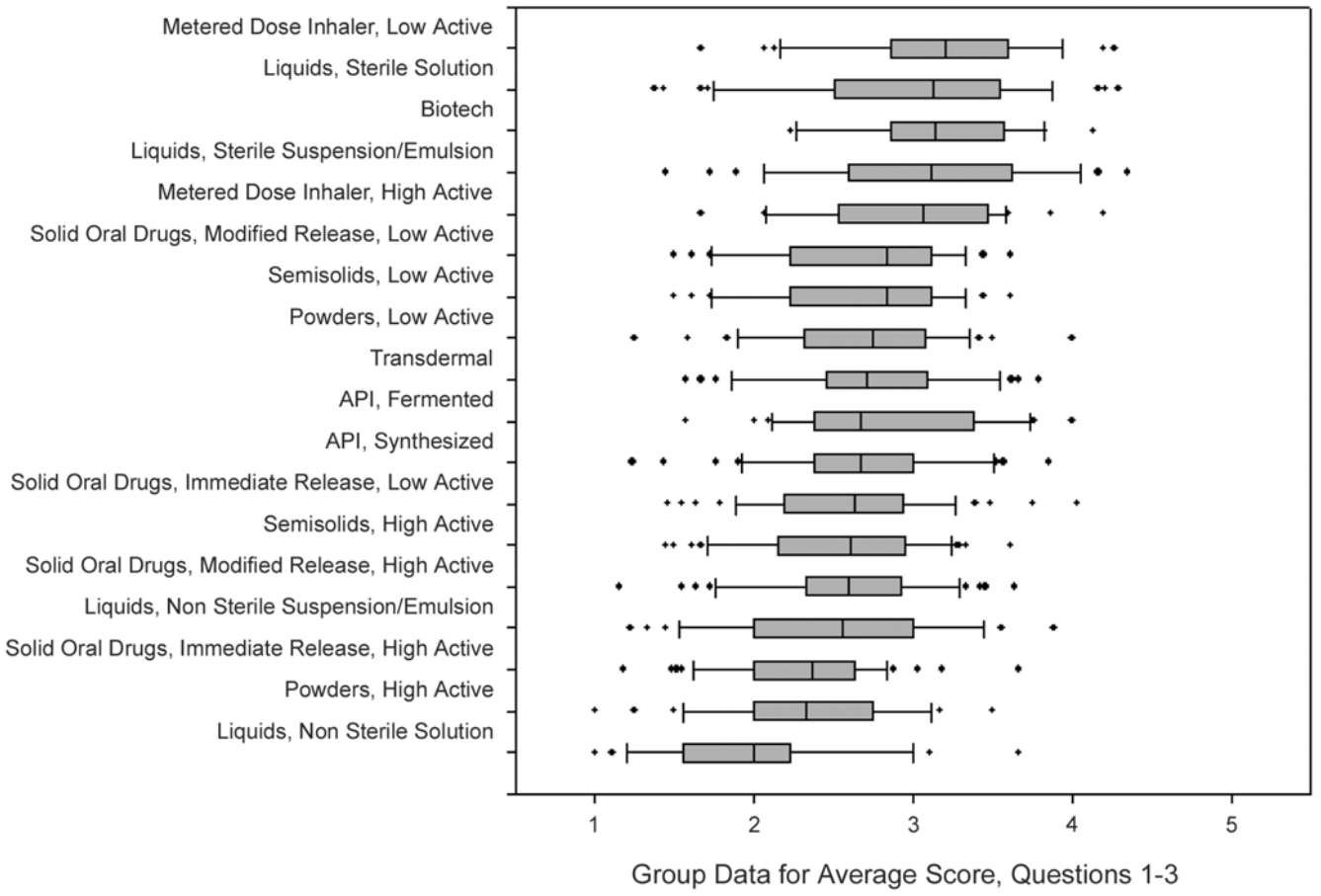
Prioritizing sites for inspection has been a long-standing challenge for Agency managers. Historically, FDA district offices have identified sites for annual inspection based on a variety of informally applied factors, including, for example, a district manager's knowledge of the inspectional history and corporate culture of the district as well as the perceived risk to the public health of manufacturing errors. More recently, under the cGMP Initiative, FDA-CDER has implemented a systematic approach to prioritize sites for inspection in order to ensure that FDA inspectional resources and oversight achieve the maximum public health impact. This effort thus far has led to a risk ranking framework that is based on three principal components: *Product, Process,* and *Facility-Table A*. A more detailed description of the CDER-risk-ranking model has been described in a white paper published by the Agency.[1]

To implement this risk-ranking framework, a risk estimate, rank, or weight must be assigned to the factor associated with each top-level component (Product, Process, and Facility). Such weight assignments ultimately determined the final site score, which would be used to rank and select site for inspection. As such, whenever possible, the weight assignment would be objectively based on empirical data. In order to estimate the relative contribution to risk for the product and facility scores, we used the available information on product recall, inspection, and compliance histories to operationalize these aspects of the risk-ranking framework. However, such data do not exist for factors relating to the process component.

The key issues in the implementation of the process factor of the risk-ranking model involve questions concerning the relevant inherent process risk factors, the relevant process control

Table A. Top-level components for the site selection model.[1]

Factor Category	Description	Example(s)
Product	Factors pertaining to the intrinsic properties of drug products such that quality deficiencies could potentially and adversely impact public health.	Dosage form; intrinsic chemical properties
Facility	Factors relating to characteristics of a manufacturing site believed to be predictive of potential quality risks, such as the lack of effective quality systems.	Poor CGMP compliance history
Process	Factors pertaining to aspects of drug manufacturing operations that may predict potential difficulties with process control and/or vulnerability to various forms of contamination.	Measuring; mixing; compression; filling



Notes: The solid, vertical line in the side box marks the 50th percentile (median.) The right and left of the box represent the first and third quartiles (25th and 75th percentile,) respectively. The values at the end of the whiskers and lines that extend from the box are 2 standard deviation of the mean (95%CI.) All data points outside of the whiskers are plotted individually as *

Figure 1. Box plots of product rankings based on potential for a loss of state of control.

and risk mitigation factors, and how to weight the importance or rank them. Although the Agency does not have the information needed to answer these questions, the Agency does have a large number of staff with expertise in this area. An expert elicitation survey was developed by an Agency-wide working group to systematically capture this body of knowledge, and formulate the key process-related factors and weights for inclusion in the current risk-ranking model.

Although it is preferred that data used in decision-making are empirically derived, it is widely recognized that the needed data are sometimes not available or, if available, are incomplete, unreliable, or only indirectly applicable. In such cases, expert judgment is the only way to complete the required knowledge. Expert data obtained under rigorous methodological rules are increasingly being recognized as a valuable asset in numerous scientific fields, including chemistry, nuclear sciences, seismic, and civil applications.

Methods

Expert Elicitation Survey Development

An FDA working group that included expertise in pharmaceutical manufacturing sciences, chemistry, risk analyses, and expert elicitation was established to develop the expert elicitation survey. The working group was initially confronted with several broad questions including:

- What are the relevant process-related risk factors?
- What are the sources of variability and poor quality?
- What, if any, units of operation and/or products are more liable to a loss of control or at risk to contamination?

Working group members agreed that answers to these challenging questions would depend on the type of products involved. However, it also was acknowledged that given the large number of potential products, it would not be feasible to conduct a survey that would elicit answers for every possible combination of product and manufacturing step (or unit of operation). To facilitate the survey, we recognized the need to identify "mutually exclusive" categories of products and units of operation and were encouraged by ISPE's approach published in its Baseline® Guide on Oral Solid Dosage Forms.[4] In this Guide, ISPE characterizes levels of effort and difficulty

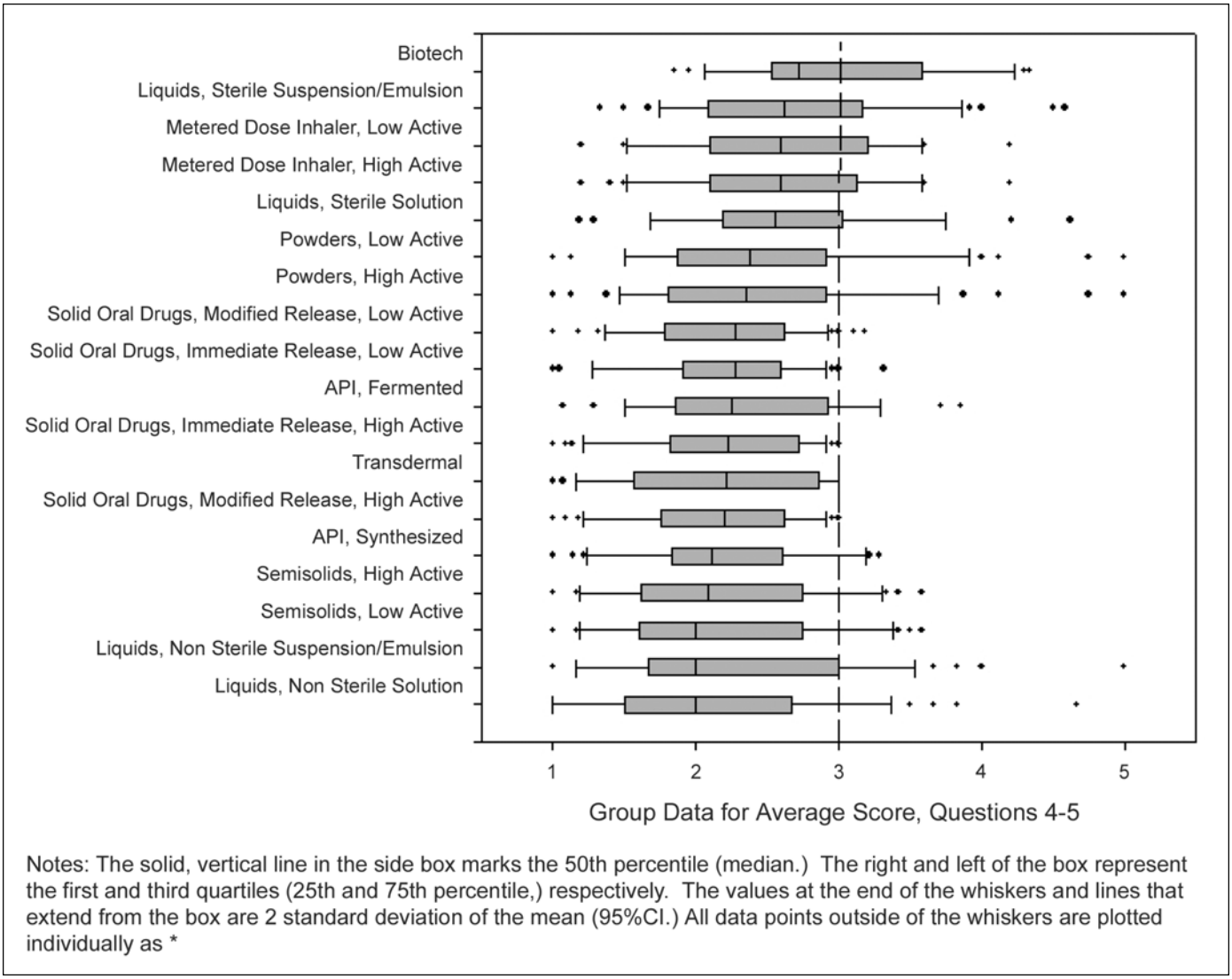


Figure 2. Box plots of product rankings based on potential for contamination.

across a variety of areas of consideration in constructing a new production facility broadly by unit operation and equipment level.

In general, the survey we used was designed to elicit from respondent a relative ranking of the likelihood of a loss of a state of control and of the vulnerability of the process to contamination for a product category and for each individual processing operation associated with that product category. Experts were asked to rate the manufacturing steps according to the commonly employed manufacturing operations (e.g., measuring, mixing, compression, and filling) and for a variety of product categories (e.g., immediate and modified release solid-oral drugs, sterile liquids, metered dose inhalers, and active ingredients by chemical and fermentation processes).

Subsequent to the initial discussion, the Working Group met on several occasions to discuss and identify variables that would be used to evaluate the risk to product failure and variability, "mutually exclusive" categories of products and key units of operation typically associated with these product groups. The following sections describe these steps.

Step 1: Identifying Variables of Interest and Developing Survey Questions

A list of potential variables that could be used to evaluate risk of product failures and variability were first generated by the Working Group members. Among the initial list were: contamination (product to product and environment to product), protecting operators (if operators could be harmed by exposure to material under process, it could result in less control or attentiveness to quality), yield, changeover, cleanability, validation/qualification (validation to be defined as inclusive of qualification), and maintenance. From this initial list of variables, the Working Group identified two broad types of process-related factors:

- factors associated with maintaining process control, i.e. process control variables
- factors associated with potential vulnerability to product or environmental contamination, i.e., contamination variables

1.	API Fermentation
2.	API Synthesized
3.	Biotech
4.	Liquids, Non-Sterile, Solution
5.	Liquids, Non-Sterile, Suspension/Emulsion
6.	Liquids, Sterile, Solution
7.	Liquids, Sterile, Suspension/Emulsion
8.	Metered Dose Inhaler (MDI), High Active
9.	Metered Dose Inhaler (MDI), Low Active
10.	Powders, High Active
11.	Powders, Low Active
12.	Semisolid (Ointment/Cream), High Active
13.	Semisolid (Ointment/Cream), Low Active
14.	Solid Oral Drugs, Immediate Release, High Active
15.	Solid Oral Drugs, Immediate Release, Low Active
16.	Solid Oral Drugs, Modified Release, High Active
17.	Solid Oral Drugs, Modified Release, Low Active
18.	Transdermal

Table B. Product categories in process elicitation survey.

As these two main factors were crystallized as the central focus of the expert elicitation survey, questions were developed to capture the important concepts underlying each of these factors. The following three questions were constructed to capture the experts' input on the three mutually exclusive elements of risk to loss of control deemed to be critical by the Working Group. Response options are shown after each question.

1. To what degree does this unit of operation contribute to variability in quality of the final product?
   1. minimal; 2. minimal to moderate; 3. moderate to high; 4. high to very high; 5. very high

2. How difficult is it to maintain this unit of operation in a state of control?
   1. slightly; 2. slightly to moderately; 3. moderately; 4. moderately to very; 5. very

3. If a problem does occur, how reliable are the current detection methods?
   1. very; 2. very to moderately; 3. moderately; 4. moderately to slightly; 5. slightly

And the next two questions were developed to capture the expert judgment on the two mutually exclusive elements deemed critical by the Working Group regarding contamination:

4. Is this unit of operation more or less vulnerable to contamination from previous product?
   1. slightly; 2. slightly to moderately; 3. moderately; 4. moderately to very; 5. very

5. Is this unit of operation more or less vulnerable to contamination from the environment?
   1. slightly vulnerable; 2. slightly to moderately vulnerable; 3. moderately vulnerable; 4. moderately to very vulnerable; 5. very vulnerable

Step 2: Identifying Product Categories and Units of Operation

Because the manufacturing of pharmaceutical products closely track product dosage form, products were categorized by dosage form, i.e., tablets, liquids, and metered dose inhalers. For each dosage form, additional distinction would be made if it was determined by the Working Group that such distinction would lead to a different answer to the questions listed in Step 1. For example, higher and lower active weight content was used to further categorize similar dosage forms since the Working Group members believed that the responders would need to make these distinctions in order to be able to accurately answer the posed questions. Using this approach, the Working Group identified 18 mutually exclusive product categories to be included in the expert elicitation survey. Table B lists these product categories.

To identify the manufacturing steps that are typically associated with the majority of the above product categories, the Working Group relied on its own expertise as well as the following references:

- Remington: Pharmaceutical Sciences, 18th edition[5]
- Modern Pharmaceutics, 3rd edition[6]
- Pharmaceutical Process Validation, 3rd edition[7]
- ISPE Baseline® Pharmaceutical Engineering Guide, Vol. 2, Oral Solid Dosage Forms, 1st edition[4]

Expert Selection and Survey Delivery

Prior to the full implementation of the survey, a pilot survey was conducted in December 2003 through in-person interviews with five FDA experts. Feedback on the clarity of the survey instructions, questions, options for answering the questions, product categories, and units of operation were obtained from the pilot survey. In general, the pilot survey showed that the survey was clear and questions were answerable. Based on comments received from the pilot survey, minor refinements were made and the survey was finalized prior to final delivery to a full panel of experts.

The panel of FDA experts to whom the survey was delivered was selected from the following groups: 1) reviewers from CDER, 2) senior CDER staff in the Office of Compliance, and 3) senior Office of Regulatory Affairs (ORA) field staff. Fifty experts were selected for the survey, based on the expertise needed and the level of experience of the individuals. The overall response rate was 100%. The survey was conducted in May 2004. The survey was sent to the experts via email, and the experts were instructed to print and complete the survey by hand. Data from the completed and returned surveys were entered by the Office of Compliance staff. Data quality assurance was conducted by the staff of the Office of Compliance.

Analyses and Results

Average Summary of Responses

Ranking responses on a 5-point scale (from 1 as the lowest to 5 as the highest rank) as elicited from the survey for questions

Product Category	Potential for a Loss of Control		Potential for Contamination		Percent Response
	Average Ranking (Questions 1, 2, &3)	Standard Deviation	Average Ranking (Questions 4 & 5)	Standard Deviation	
Biotech	3.1	0.5	3.0	0.7	48%
Liquids, Sterile, Solution	3.0	0.8	2.7	0.8	92%
Liquids, Sterile, Suspension/Emulsion	3.1	0.7	2.7	0.8	100%
Metered Dose Inhaler, High Active	3.0	0.6	2.6	0.7	62%
Metered Dose Inhaler, Low Active	3.2	0.6	2.6	0.7	62%
Liquids, Non-Sterile, solution	2.0	0.6	2.1	0.9	94%
Powders, High Active	2.3	0.6	2.4	0.9	92%
Solid Oral Drugs, Immediate Release, High Active	2.3	0.5	2.1	0.6	94%
Liquids, Non-Sterile, Suspension/Emulsion	2.5	0.7	2.3	0.9	100%
Semisolid (Ointment/Cream), High Active	2.5	0.5	2.2	0.7	84%
API, Synthesized	2.6	0.6	2.2	0.6	100%
Solid Oral Dose, Immediate Release, Low Active	2.6	0.5	2.2	0.6	94%
Solid Oral Drugs, Modified Release, High Active	2.6	0.5	2.1	0.6	92%
Powders, Low Active	2.7	0.6	2.5	0.9	92%
Semisolid (Ointment/Cream), Low Active	2.7	0.6	2.2	0.7	82%
API, Fermentation	2.8	0.6	2.3	0.7	100%
Solid Oral Drugs, Modified Release, Low Active	2.8	0.5	2.2	0.6	92%
Transdermal	2.8	0.6	2.2	0.7	66%

Table C. Average ranking and response rate for each product category.

1, 2, and 3 were averaged together to represent average rating of risk for the potential loss of control. Then, they were averaged across units of operation and respondents to determine the average risk ranking for potential loss of state of control for each product category. Similarly, responses to questions 4 and 5 were averaged across units of operation and respondents to determine the average rank of potential for contamination for each product category. Table C summarizes the average ranks and standard deviations for potential loss of state of control and potential for contamination for each product category. Biotech, MDI (both high and low active), and sterile liquid (both solution and suspension/emulsions) product categories have the highest average ranking for both potential for loss of a state of control and potential for contamination.

Experiences with product categories were not equal among the surveyed experts. As such, not all respondents provided answers to all product categories included in the survey. Biotech, MDI, and Transdermal product categories have the lowest response rates, 48%, 62%, and 66%, respectively. Response rate for each product category also is summarized in Table C.

Box-plots of the ranking responses for questions 1, 2, and 3, which were averaged together and across units of operations to represent average rating of potential for a loss of control for each product category are shown in Figure 1. Similarly, box plots of responses for questions 4 and 5 to represent potential risk of contamination for each product category are shown in Figure 2. Biotech, MDI (both high and low active), and sterile liquid (both solution and suspension/emulsions) product categories remain the top ranked product categories based on median scores.

Cluster Analyses of Responses on Combinations of Product Categories and Units of Operation

In addition to averaging the responses, multivariate K-Mean clustering analyses of responses to the combinations of product category and unit of operation also were carried out using S-Plus.[8] Responses to questions 1, 2, and 3 for the product category and unit of operation combinations were clustered into five groups. Each cluster was assigned a ranking based on the rank-order of the clusters' centers, i.e., cluster with the highest center was given the highest rank of five and cluster with the lowest center is given the lowest rank of one. A product category and unit of operation combination belonging to a cluster would assume its cluster rank. A similar clustering approach also was applied to questions 4 and 5. As in previous averaging analysis, the cluster ranks based on questions 1, 2, and 3 provide ranking of potential risk of loss of state of control, and the cluster ranks based on questions 4 and 5 provide the ranking of potential risk of contamination.

Ranking of Potential for Loss of a State of Control

The cluster ranking of the combinations of product categories and units of operation resulted in the same top five ranked product categories (biotech, liquid sterile solution, liquid sterile suspension/emulsion, MDI low active, and MDI high active) as those ranked based on averaging responses. Within each product category, ranking varied between units of operation. While most of the processing steps associated with the top five ranked product categories also are ranked high, the measuring step is typically ranked lower. For product categories with overall low ranking, such as the solid oral

Product Categories	Product Category Ranking	Units of Operation	Unit of Operation Rankings
Biotech	5	Bioreaction, Seed; Bioreaction, Production; Cell Bank Maintenance; Isolation Recovery; Pasteurization; Purification; Viral Clearance	5
		Filling; Formulation	4
		Measuring	3
Liquid, Sterile, Suspension/Emulsion	5	Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Aseptic Filling-Traditional Method; Mixing Blending; Terminal Sterilization	5
		Measuring	3
Liquid, Sterile, Solution	5	Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Aseptic Filling-Traditional Method; Filtration; Lyophilization; Terminal Sterilization	5
		Measuring	3
		Mixing Blending	2
Metered Dose Inhaler (MDI), Low Active	5	Assembly; Filling; Micronization of components; Mixing Blending	5
		Measuring	4
Metered Dose Inhaler (MDI), High Active	5	Assembly; Filling; Micronization of components; Mixing Blending	5
		Measuring	3
API Fermentation	4	Fermentation; Inactivation; Isolation; Purification	5
		Processing	4
		Primary Packaging; Weighing	2
API Synthesized	4	Isolation; Purification; Reaction	5
		Processing; Workup	4
		Weighing	3
		Primary Packaging	2
Powders, Low Active	4	Mixing Blending	5
		Milling	4
		Measuring	3
		Primary Packaging	2
Semisolids (Ointment/ Cream), Low Active	4	Emulsification; Mixing Blending	5
		Deaeration; Heating Cooling	4
		Measuring	3
		Primary Packaging	2
Solid Oral, Modified Release, Low Active	4	Coating; Pelleting	5
		Compression (tablet); Drying; Encapsulation (hard gel); Granulation (dry and wet); Milling; Mixing Blending	4
		Measuring	3
		Primary Packaging	2
Transdermal	4	Active Deposition, Coating; Extrusion	5
		Cutting; Drying; Mixing Blending; Primary Packaging	4
		Measuring	3
Liquid, Non-Sterile, Suspension/ Emulsion	3	Emulsification; Mixing Blending	5
		Measuring	3
		Primary Packaging	1
Semisolids (Ointment/ Cream), High Active	3	Emulsification	5
		Deaeration; Heating Cooling; Mixing Blending	4
		Measuring	3
		Primary Packaging	2
Solid Oral, Immediate Release, Low Active	3	Mixing Blending; Granulation (dry and wet)	5
		Coating; Compression (tablet); Drying; Encapsulation (hard gel); Milling; Pelleting	4
		Measuring	3
		Primary Packaging	2
Solid Oral, Modified Release, High Active	3	Coating; Pelleting	5
		Compression (tablet); Drying; Encapsulation (hard gel); Granulation (dry and wet); Milling; Mixing Blending	4
		Measuring	3
		Primary Packaging	2
Solid Oral, Immediate Release, High Active	2	Compression (tablet); Granulation (dry and wet); Mixing Blending; Pelleting	4
		Measuring	3
		Coating; Drying; Encapsulation (hard gel); Milling; Primary Packaging	2
Powders, High Active	2	Milling; Mixing Blending	4
		Measuring	3
		Primary Packaging	2
Liquid, Non-Sterile, Solution	1	Measuring	3
		Mixing Blending	2
		Primary Packaging	2

Table D. Cluster ranking of product categories and units of operation for potential loss of a state of control.

immediate release high active category, most processing steps are ranked low; however, there are several processing steps that are ranked high, such as compression (tablet), wet and dry granulation, mixing-blending, and pelleting. Product and unit of operation rankings for potential loss of a state of control based on K-mean cluster analysis are summarized in Table D.

Potential for Contamination

Cluster ranking of contamination risks for the combinations of product categories and units of operation also resulted in biotech, liquid sterile solution, liquid sterile suspension/emulsion, MDI low active, and MDI high active as the top ranked product categories. Ranking also varied between units of operation within each product category. Product and unit of operation rankings of contamination risks based on K-mean cluster analysis are summarized in Table E.

Discussion and Recommendations

Survey Protocol

Formal methods for obtaining the judgments of experts have been evolving since their inception after World War II. Despite its long history of application, standardized protocols for the selection, preparation, and elicitation of experts do not and should not exist.[9] Analysts in the field of expert elicitation have consistently argued that rather than standardized procedures, protocols should be crafted to suit the particular problem under investigation.[3,10,11] In accordance with conventional practice, an FDA team developed a protocol, in a form of a survey and detailed instructions, to elicit expert judgments about the potential for a pharmaceutical manufacturing process to be subject to loss of process controls or contamination. As such, it should be noted that the scope of the elicitation is limited to obtaining expert judgments about the likelihood relating to the manufacturing processes such that if a product category is judged to involve more risky manufacturing steps it would then have a higher potential for poor quality. This protocol does not extend to judgments about risk to public health.

Experts

Expert judgment studies make use of a panel of experts who bring in different information, arising from different interpretations, different analytical methods, and/or different experiences.[2] Fifty-five experienced FDA officials were chosen to participate in this survey and 50 responses were received. Nearly half of the participants were senior drug program investigators from the Office of Regulatory Affairs with the remaining being senior review and drug cGMP compliance officials in the Centers for Drug Evaluation and Research and Veterinary Medicine. Review staff represented disciplines such as chemistry, engineering, biochemistry, microbiology, pharmacology, and pharmacy. Nearly all responders reported having 10 or more years combined experience in FDA and the drug industry.

Utility

Information obtained from the survey has been of great utility in the implementation of the risk ranking model to prioritize pharmaceutical sites for cGMP inspection. To implement this risk-ranking framework, a risk ranking (or weight) is first assigned to the factors associated with each top-level component (Product, Process, and Facility) and subsequently, the combination of these factor-ranks (weights) would determine the site overall potential risk scores, which would be used to rank and target inspection. As previously indicated, the Agency has systematically compiled product and facility related information such as product recall, inspection, and compliance histories that could be used to operationalize these aspects of the risk ranking framework. However, such data do not exist for factors relating to the process component. The expert elicitation survey provides a systematic means of gathering knowledge and an objective approach to assign ranks to the factors associated with the process component of the risk-ranking model. Ranking results also provide a basis for investigators to better focus their product quality inspection. For example, once a site has been chosen for inspection based on overall site risk score, variability in the ranking of units of operation within each product category (Tables D and E) could help the inspector to focus on units of operation that have been ranked as more vulnerable to potential loss of process controls or contamination.

The results from this formal and systematic approach of collating judgments from a broad range of experts also could provide the pharmaceutical industry with benchmark data, which can be used to examine a company's risk assessment practices. If a company's assessment leads to conclusions that are different from the experts' norm then additional evaluation can be carried out to determine reasons for differences.

Limitations

There are a number of limitations associated with this survey. First and foremost, since the expert elicitation survey was only delivered to FDA experts, the results reported in this article do not capture the broad range of expertise that exists outside of FDA. The response rate to the surveys for the Biotech Product Category was only 48% (only 24 responded out of 50 surveyed experts). While the expert elicitation was not a random survey and statistical validity is not at issue, the low response rate presents some concern with regard to the potential lack of expertise in the biotech area among the pool of experts included in this survey. An additional consideration is the fact that the survey was designed to elicit judgments about the manufacturing risks associated with very broad product categories (Table B) and not specific product. As such, experts were forced to average their answers across a broad range of products that fall into such product category. While broad aggregation of products helped to facilitate the delivering of the survey i.e., reduce respondent's time spent on the survey and fatigue, the consequence could be a loss of a significant amount of information.

Question 3 in the survey ("If a problem does occur, how reliable are the current detection methods?) would require experts to account for the average rate of firms implementing expected process controls. As such, the results from this survey do not reflect risk associated with firms that are performing below average expectation or standard industry practices, i.e. not implementing minimal in-process controls; nor do results reflect firms exceeding expectations, e.g., firms with Process Analytical Technologies (PATs). Nevertheless, for the purpose of selecting a site for cGMP inspection, such deviation from average/expected practices would be captured during the actual inspection. As such, using the results from this survey for the site-selection model does not preclude the inspector's ability to differentiate between firms with enhanced controls from those performing below averages.

Recommendations

In light of the limitations described above, the following recommendations are provided to improve the expert elicitation survey:

- Expand the expert panel to include expertise outside of FDA such as ISPE working members.

  ISPE has a broad range of members who would have current working knowledge of the robustness and capabilities for a variety of products. They are likely to be familiar with units of operation that require frequent attention and in-process monitoring and maintenance. Hence, inclusion of expert judgments from this group would greatly enhance knowledge about risk associated with various pharmaceutical manufacturing processes.

- Future revision of the survey protocol should consider further differentiation of the existing product categories and units of operation.

Product Categories	Product Category Ranking	Units of Operation	Unit of Operation Rankings
Biotech	5	Bioreaction, Production; Bioreaction, Seed; Filling; Formulation; Isolation Recovery; Purification; Viral Clearance	4
		Cell Bank Maintenance; Measuring; Pasteurization	3
Liquid, Sterile, Solution	4	Aseptic Filling-Traditional Method	5
		Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Filtration; Lyophilization; Measuring; Mixing Blending	3
		Terminal Sterilization	1
Liquid, Sterile, Suspension/Emulsion	4	Aseptic Filling-Traditional Method	5
		Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Measuring; Mixing Blending	3
		Terminal Sterilization	1
Metered Dose Inhaler (MDI), High and Low Active	3	Micronization of components	4
		Filling; Measuring; Mixing Blending	3
		Assembly	1
Powders, High and Low Active	2	Milling; Mixing Blending	2
		Measuring; Primary Packaging	1
API Fermentation	2	Fermentation	3
		Inactivation; Isolation; Processing; Purification	2
		Primary Packaging; Weighing	1
API Synthesized	1	Processing; Purification	2
		Isolation; Primary Packaging; Reaction; Weighing; Workup	1
Liquid, Non-Sterile, Solution	1	Mixing Blending	2
		Measuring; Primary Packaging	1
Liquid, Non-Sterile, Suspension/Emulsion	1	Mixing Blending Emulsification	2
		Measuring; Primary Packaging	1
Semisolids (Ointment/ Cream), High and Low Active	1	Emulsification; Mixing Blending	2
		Deaeration; Heating Cooling; Measuring; Primary Packaging	1
Solid Oral, Immediate Release, High and Low Active	1	Granulation (dry and wet) Milling; Mixing Blending	2
		Coating; Compression (tablet); Drying; Encapsulation (hard gel); Measuring; Pelleting; Primary Packaging	1
Solid Oral, Modified Release, Low Active	1	Compression (tablet); Granulation (dry and wet); Milling; Measuring; Mixing Blending	2
		Coating; Drying; Encapsulation (hard gel); Pelleting; Primary Packaging	1
Solid Oral, Modified Release, High Active	1	Granulation (dry and wet); Milling; Mixing Blending	2
		Compression (tablet); Coating; Drying; Encapsulation (hard gel); Measuring; Pelleting; Primary Packaging	1
Transdermal	1	Active deposition, coating	3
		Extrusion; Mixing Blending	2
		Cutting; Drying; Measuring; Primary Packaging	1

Table E. Cluster ranking of product categories and units of operation for contamination risks.

In the current survey, products are categorized based on broad dosage forms. These broad dosage forms could be further differentiated. For example, the oral solid dosage form could be differentiated into several product groupings, including hard and soft capsules and tablets. Further, for products with additional processing steps that are not captured in the current survey, these additional steps should be identified and included in future revision of the survey. Differentiations should be made where experts believe there are true differences.

- Uncertainty

Expert knowledge is not a certainty, but it is entertained with an implicit level of confidence or degree of belief.[2] Survey methods that allow the experts to express their degree of confidence in their responses will also permit a determination of the level of confidence in models that use these data. As such, future surveys should allow experts to express uncertainties in their responses.

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Disclaimer

The views expressed herein do not represent official FDA or US government policy. No official support or endorsement by the FDA is intended or should be inferred.

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A Precedent for Risk-Based Regulation?

by Jonathan Coburn, Stanley H. Levinson, PhD, PE, and Greg Weddle

This article compares "risk-based" regulation as a new concept in the pharmaceutical industry against 30 years of experience in the nuclear power industry.

Introduction

The life sciences industry has impressive capabilities for identifying and analyzing risk. Yet, the industry's application of this knowledge and expertise is skewed. The industry's risk assessment capability is unsurpassed when it comes to assessing the risks drug compounds pose to humans; however it has not applied this risk assessment expertise to the process of making those drugs. Instead, drug manufacturing is governed by the "deterministic" cGMP regulations of 21 CFR 210/211. However, the FDA intends to change this. It recently published "Pharmaceutical cGMPS for the 21st Century – A Risk-Based Approach,"[1] which stated "the FDA is implementing a risk-based approach to regulating pharmaceutical manufacturing." As FDA and the industry embark upon this initiative, it might be interesting to consider, on a general basis, how regulation of production might transition from a deterministic to a risk-based approach. Here's one possible scenario.

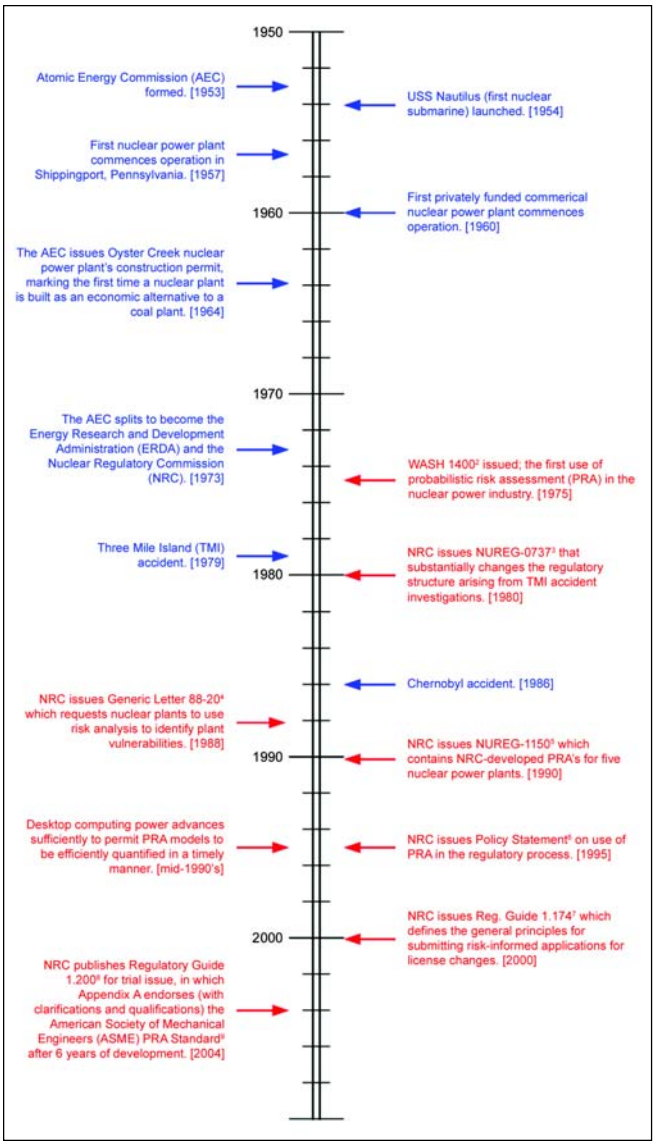

Figure 1. Nuclear timeline.

A Risk Story

Consider an industry whose activities are deemed to be "risky," and is therefore regulated by a government agency whose mission is to protect the health and safety of the public. Historically, the regulator has achieved its mission by using a deterministic regulatory approach based on good engineering practices, safety factors, and experience.

Industry events, economic forces, and changing technology drive the regulator to consider risk-assessment techniques as a way to improve the regulatory structure. While suitable techniques exist, the industry has only slowly gained experience in using them, and new technological advancements now allow them to be broadly applied. So the regulator

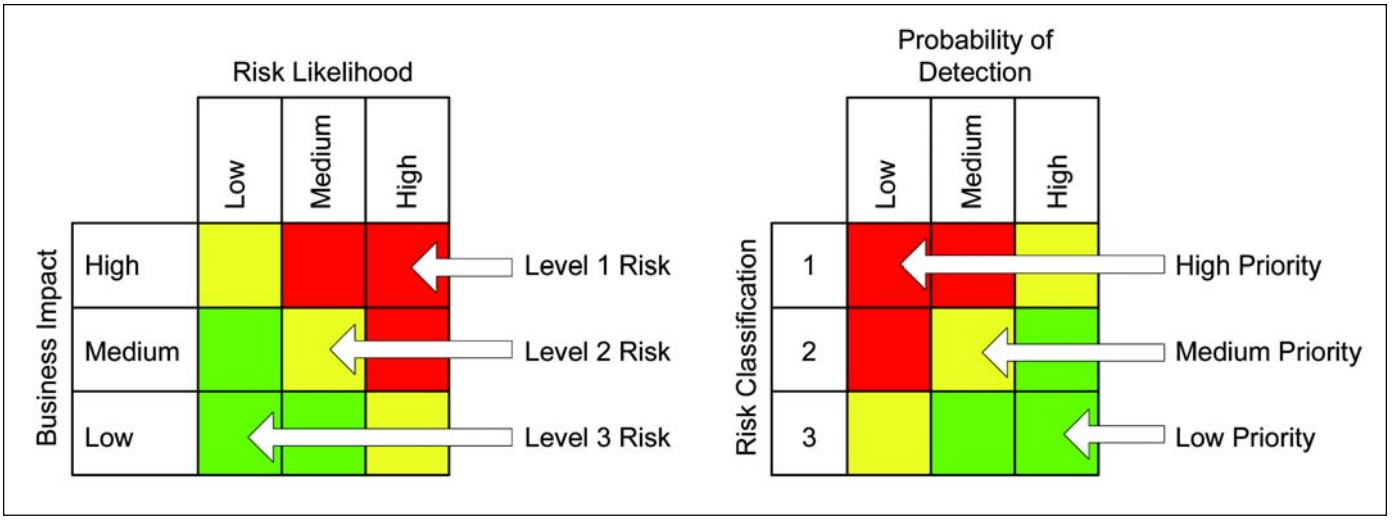

Figure 2. GAMP risk assessment approach.

states its intention to move toward a risk-based regulatory structure.

The industry perception that risk-based regulation might substantially ease regulatory burden, coupled with the openness of the regulator to explicitly focus on risk, cause a flurry of risk-based experimentation. The industry begins to apply various risk assessment techniques in creative ways across the entire regulatory spectrum. But soon the regulator faces some tough, fundamental issues.

Explicit consideration of risk shatters the black/white, safe/unsafe paradigm of deterministic regulation. The regulator knows there is no such thing as zero risk, even though its mission statement promises to "ensure" the health and safety of the public. But can anything really be "ensured" in a risk-based world? The regulatory paradigm now changes from safe/unsafe to safe enough. The new paradigm has potentially far reaching public relations, political, and legal ramifications. The regulator and industry are faced with many new questions, such as:

- How will risk-based regulation be viewed from outside the industry?
- Is this a new way of regulating or a different slant on what we have always done?
- Will risk-based regulation replace existing regulation or create a second "layer" of regulation?
- How should risk-based regulation be presented to the public?
- How safe is "safe enough?"

The industry faces considerable economic pressures, including a high regulatory compliance cost burden. The industry sees risk-based regulation as a potential way to reduce compliance costs by eliminating existing deterministic regulations that impose costs without a commensurate contribution to safety, or by identifying alternatives to existing regulatory requirements that are both less costly and less risky. The risk assessments show that it is possible to both improve safety and lower costs, a clear win-win-win proposition for the industry, the regulator, and the public.

But all this activity gives the regulator concern. First, there is a credibility problem. For decades, the regulator has told the public the deterministic regulatory approach was "safe," but now this new risk-based approach seemingly challenges the basis on which safe operation is based. And there are other issues. Regulators are conservative by nature, and the thought of a complete regulatory change is unsettling. And the regulator knows that conservatism in regulation is not a bad thing. The existing deterministic regulatory structure has generally served the public well, and simply abandoning it for the promise of a better way imposes risk in and of itself. Now the regulator must ask:

- What will the new regulatory structure look like? Will it be entirely risk-based, entirely deterministic, or a mixture of both?
- How rapidly should the industry adopt risk-based techniques in making changes to a regulatory structure that has, in the main, served the public well?

A Broader Industry Risk Comparison

The life sciences industry is unsurpassed in its ability to determine design risk; that is, in assessing the risk to the public of "designing" and introducing a new drug. The nuclear power industry, through sophisticated risk assessment techniques like PRA, is unsurpassed in its ability to assess production risk. In contrast, PRA was not used to a great extent in the design of the nuclear power plants operating today (though it is being used in new designs), and the application of risk assessment techniques to pharmaceutical production is just beginning. Thus, each industry is strong where the other is weak.

This article focuses on production risk in light of the FDA's intention to pursue risk-based cGMPs. However, a broader comparison of design vs. production and the associated risks and regulatory approaches is instructive. Table A offers a brief comparison of these issues.

NUCLEAR	LIFE SCIENCES
Risk Profile A nuclear reactor accident is a low probability, high consequence event. Risk, defined as the product of probability and consequences, may be similar to that of pharmaceutical industry. The NRC, through the safety goal policy, has established Quantitative Health Objectives (QHOs) to try to address the question: how safe is safe enough? The QHOs state, in part, that the risk of death from nuclear power will not exceed 0.1% of chance of dying from other risks to which the public is exposed. In practice, the NRC uses risk thresholds for risk-informed applications based on surrogate risk metrics (such as core damage frequency) at which they are confident the QHOs are met. The public views nuclear power risk in a general sense rather than an individual sense. The observable risk from nuclear power is low. Like commercial aviation, there is risk to individuals in a statistical sense, but everyone thinks that they will never be involved in a crash. The public has no personal experience base of nuclear power risk.	Drug failures have higher probabilities but lower consequences than a nuclear accident. Some consequences (e.g., adverse side effects) are expected for every drug, so the pharmaceutical industry has a higher observable risk than the nuclear industry. Also, drug effects on the population develop more slowly than could be the case for a nuclear accident, providing time for the consequences to be mitigated. Pharmaceuticals face an inherent dilemma regarding risk. Drugs are approved considering their risk to the public in a statistical sense. But drug risk is considered in a personal sense by the millions of individuals who take prescription drugs every day. The public has a near zero risk threshold on an individual basis, but the approval threshold is not so stringent. The public has been exposed to the warnings and possibilities of "side effects" and relies, perhaps somewhat skeptically, on drug companies and physicians to help them weigh the personal risk of use. In this there is an inherent understanding that the individual has some control over drug risk.
Design Process Nuclear power is produced in the U.S. in only two ways; the processes and science behind them are well understood. Nuclear power plants are not designed by the power producers, but rather by a small group of large, global engineering companies. Patent protection does not play a prominent role; a design type (e.g., pressurized water reactor) cannot be patented in its entirety like a new drug compound, although the design companies possess numerous patents for various design aspects of the plants themselves.	Drugs are "designed" in an R&D process undertaken by the drug producers themselves, or by smaller companies with intellectual property or who specialize in drug discovery. Innovation in the form of drug discovery is an important driver of competitive advantage. Designs (i.e., drug compounds) are patented, and patent protection plays a very prominent role in shaping the competitive dynamics of the industry. The risk and impact of deploying a new medicine to the public must be evaluated at each new drug application. Benefit versus adverse reaction, ability to diagnose, target, and exclude will be weighed against benefit. The impact to the GMP process, changes to standards, or in some cases, new production methods will be introduced. The impact of these new processes to the overall risk is a new consideration.
Design Risk Nuclear power plants are designed to withstand specific design basis accidents. Design risk exists to the extent that the design basis accidents do not adequately envelope the entire range of risks actually experienced during operations, and by uncertainties in the analysis of the effects of these events. As this paper discusses, events at nuclear plants have revealed gaps in the design bases, and plant modifications and other corrective measures have been taken. By quantifying actual operational risk, PRAs have identified and mitigated much of the nuclear design risk. Design risk has historically been addressed through deterministic General Design Criteria. Existing plants were designed using only deterministic risk considerations, though extensive modifications driven by risk insights have subsequently been made. New reactor designs incorporate risk-informed insights.	Drugs pose inherent risk to the people who take them, and some level of adverse effects on the public is expected for every drug. Drug approval depends on whether these risks are outweighed by the potential benefit of the drug. Much of the legal exposure of the industry arises from individuals or groups of individuals who have been harmed by a drug. Both anticipated and unanticipated adverse health effects on the public reflect drug design risks. That is, these risks arise from the inherent nature of the drug, even if they are produced exactly as intended.
Production Process Safe production of nuclear energy is the responsibility of an operating company (utility) that selects a design, applies for and receives a license, builds a power plant, and then operates the plant. Nuclear power production is heavily regulated through a number of mechanisms; day-to-day operation is governed by a set of Technical Specifications that define acceptable operating parameters and conditions for the plant. Detailed Operating Procedures are developed for all aspects of operation, driven by the Technical Specifications and plant design. Nuclear plants have pervasive quality programs with extremely high quality standards. A "risk-informed" regulatory approach is used for nuclear plant operation in which risk assessment techniques (PRA) can be used extensively to improve the safety impact of operations, as well as to provide economic benefits (e.g., shorter outages, on-line maintenance).	Drugs are produced in regulated production (GMP) facilities. GMP regulations are very general compared to the regulations that govern nuclear power plant operation. These high-level regulations are used by the manufacturers to develop plant SOPs and quality programs in a manner similar to the nuclear industry, but drug producers have significantly more latitude in applying the regulations to their own production processes. Today, they use historical best practices and subject matter experts in a deterministic approach to production. Risk-based regulatory approaches to drug production are in their infancy, and current risk assessment techniques are strictly qualitative.
Production Risk The public safety risk of nuclear power production consists of radiation exposure due to an accident. As this article discusses, the industry and the regulator use very sophisticated risk analysis techniques to scrutinize how the plant is operated. The results of risk assessments find their way into plant Technical Specifications, SOPs and maintenance programs such that production risk is mitigated as much as possible.	The public safety risk of production basically comes down to not shipping defective product from the site. This is managed in two ways. First, stringent measures are taken to ensure that drugs are produced in accordance with the appropriate regulatory and process standards. Second, if some defective product is produced, it must be detected before being shipped off the site for sale. The industry currently relies heavily on post-production testing to ensure safe products are distributed. Risk-based approaches to managing production risk are in their infancy.
Regulatory Review Regulation is focused on mitigating and/or preventing nuclear accidents. Each nuclear power plant has a license that can be revoked. Regulation pervades all aspects of operations, and inspections are constant. The NRC maintains Resident Inspectors at all nuclear power plants. Additional inspection intensity is focused on plants or their parent companies with a sub-par history of safe operation.	Regulation aims to ensure that a drug is reasonably safe before it can be sold to the public and that it is produced consistently. Some harm to the public is expected from every drug; the FDA must weigh those costs against the benefits of the drug. The FDA does not have the resources to oversee all production and R&D facilities. The FDA must rely on data provided by the drug companies for drug approvals. It performs spot inspections of production facilities. A company's history will reflect on FDA's inspection regime and frequency.

Table A. Broader industry risk comparison.

After considering all the issues, the regulator issues a policy statement regarding the use of risk-assessments in regulatory activities. Unwilling to completely abandon the existing body of deterministic regulations, the regulator states that risk assessments will augment, rather than replace, this existing regulatory structure. To denote this shift in emphasis, the regulator stops referring to "risk-based" regulation in favor of a new term: "risk-informed" regulation.

A policy is easily stated at a high level, but the policy must be implemented at the working level. Moreover, it must be implemented in such a way that the regulator has sufficient confidence in the results of the risk analyses to rely on them when public safety is involved. So the following questions arise regarding applicability, consistency, and technical adequacy/quality of risk assessments.

- What are the attributes of acceptable risk analysis techniques?
- How deeply will a regulator become involved in the details of risk assessment techniques when they are used for regulatory compliance?
- How important will it be to apply risk assessment techniques consistently across the industry? Will consistency be audited? If so, how?

What is a Probabilistic Risk Assessment in the Nuclear Power Industry?

A Probabilistic Risk Assessment (PRA) is a structured analysis using a combination of probabilistic and deterministic techniques to estimate the risk associated with nuclear power plant design, operation, and maintenance. The three risk metrics generally used are core damage frequency (Level 1 PRA), radioactive material release (Level 2 PRA), and health effects on the public (Level 3 PRA).[9]

A PRA systematically analyzes potential sequences of events (called accident sequences) to determine their contribution to one or more of the risk metrics. Each sequence starts with an initiating event (e.g., a reactor trip). Specific systems are designed to actuate to mitigate the consequences of an initiating event so that safety is ensured; relays trip, pumps start, valves open, etc. Each of these events in a sequence has a probability of success or failure that can be quantified from historical experience and failure data sources.

In a Level 1 PRA, system models are used to depict the combination of system successes and failures that constitute accident sequences. Although there are many different modeling techniques, event tree analysis and fault tree analysis are used almost exclusively in PRAs.[12]

An event tree model traces accident sequences in terms of the functional or system successes or failures that make up those sequences. An event tree model provides end-to-end traceability from the accident initiating event to the accident sequence outcome.

Figure 3 is an example of an event tree with four mitigative systems labeled A, B, C, and D. The event tree starts at the left with an initiating event and ends at the right with an outcome related to a risk metric. After the initiating event, each mitigative system either succeeds (i.e., operates as designed) or fails. (throughout the event tree, system successes take the upper branch and system failures take the lower branch). The logic of the event tree, the various permutations of system success and failure, depend on how the systems are designed and configured to work together. One permutation shown in the event tree reveals that if both systems A and B fail, systems C and D cannot prevent core damage. Other permutations show that successful response of systems C and D will prevent core damage if either system A or system B fails, but the outcome varies if one of systems A and B fails and one of systems C and D also fails.

Fault tree analysis is performed to identify the potential events or combinations of events that can make the plant safety system unavailable to respond to initiating events. The system fault trees can be quantified to obtain estimates of the probability of system unavailability. Using these system unavailability probabilities as inputs to the event tree models, the probabilities of the various accident sequences can be estimated. These probabilities can be combined to estimate the core damage frequency of the plant, which will depend on the design of the plant, how it is operated, and how it is maintained.

A simple system of two pumps and two valves is shown in Figure 4. Assume that for a given accident sequence, success for this system is defined as providing flow from both of the pumps. Therefore, success requires that both pumps start and their associated valves open. A corresponding fault tree is shown in Figure 5.

Developing and running PRA models can provide risk insights that might otherwise be missed. For example, system redundancy can reduce risk, but also it adds complexity so that more failures must be considered. What is the tradeoff? Using event tree and fault tree models, a PRA can assess how various systems and components work together to mitigate risk across system/human performance boundaries. PRA also facilitates risk ranking of systems, components, and human actions. The importance indicates which items, if they fail, would have the most significant impact on plant risk. This allows plant operators and regulators to focus on the equipment and systems with the most risk impact.

- What will the role of industry groups be?
- Should risk-assessment standards be developed? If so, what should their scope be and who should develop them?

To deal with issues of consistency and technical adequacy, the regulator suggests risk assessment requirements. Practitioners who perform risk analyses must be adequately trained. Risk assessment techniques must accurately consider all relevant risk variables for the regulatory applications for which they are used. Risk models must be consistently applied. Professional and industry organizations can help by developing standards and conducting independent audits and peer reviews.

After a long (25-year) evolutionary process, the regulator and industry settle into a consistent and predictable risk-informed regulatory process. The regulator relies on both deterministic and risk considerations to make changes to the existing regulatory structure. The regulator approves the use of risk assessments for situations where it deems them sufficiently robust, and has confidence when industry uses these techniques because the models adhere to certain standards.

Not Just a Story

Of course, this is not just a story. It is a very broad description of what transpired when the Nuclear Regulatory Commission (NRC) and the commercial nuclear power industry transitioned from a deterministic to a "risk-informed" regulatory approach. Figure 1 presents a nuclear industry timeline that includes major industry events (in blue) and major events related to the use of risk analysis in the industry (in red).

This article contends that ***any*** industry that attempts to incorporate risk into an existing deterministic regulatory structure will face fundamental questions similar to those presented above for the NRC and the nuclear power industry. All regulators are conservative and will find it hard to shift their regulatory paradigm. All regulators must use an approach in which they have confidence and that is defendable to the public. All regulators want to apply regulations consistently. Because the ***regulatory dynamics*** are similar, it would be wise to consider what lessons the FDA and the life sciences industry can take from the nuclear industry experience.

This article examines the nuclear experience and identifies seven themes that are likely to be of importance for a risk-based/risk-informed regulatory structure for production in the life sciences industry. A full comparison of all the risk issues faced by these industries is beyond the scope of this article, though some ideas are presented in the sidebar ("A Broader Industry Risk Comparison") for interest. It is not the purpose of this article to predict exactly how the transition will occur, nor is it to make a case that this transition will exactly mirror the nuclear industry experience. Rather, this article attempts to help structure the risk-based cGMP debate in terms of fundamental regulatory issues. Hopefully this article will help the life sciences industry more rapidly develop common expectations for the transition to risk-based cGMPs.

A Brief Note about Risk Analysis Terminology

Before proceeding with the seven themes, a brief note is needed regarding the terminology of risk assessment in the nuclear industry. The primary risk assessment technique used in the nuclear industry is a Probabilistic Risk Assessment (PRA). Please refer to the sidebar for a brief overview of PRA. This article quotes from several NRC publications that include the term "PRA," both in generic and specific risk assessment contexts. Substituting "risk assessment" for "PRA" provides the proper context for this discussion. This article argues that quantitative risk assessment techniques will become necessary within any risk-based/risk-informed regulatory framework, but it does not argue for wholesale adoption of PRA techniques per se.

Seven Themes of Risk-Based Regulation

Making Risk Explicit

Considering risk in a regulatory structure is not new. The purpose of regulatory agencies like the NRC and the FDA is to protect the health and safety of the public. In other words, they exist to manage risk. They protect the public from the potentially severe adverse consequences from beneficial, but risky, societal activities such as making drugs and operating nuclear power plants.

If regulatory agencies exist to manage risk, why isn't "risk-based" regulation already the preferred approach for regulating? While both the FDA and NRC have traditionally relied upon "deterministic" regulations to ensure safety, deterministic regulations have always been based on implicit considerations of risk. For example, cGMP regulations exist for manufacturing space because that is where the risk is; the FDA does not regulate how a pharmaceutical company operates its corporate headquarters facility. Similarly, the activities governed within the cGMP regulations are those that could affect product quality, i.e., that are risky. By extension, one can easily conclude that ***all public safety regulation implicitly considers risk***.

If it is accepted that there is an implicit risk-based foundation underlying the existing deterministic regulatory framework, then taking a "risk-based approach to regulating pharmaceutical manufacturing" does not appear to be a fundamental philosophical change. Rather, it becomes a matter of making the existing implicit risk assumptions explicit, examining them in the light of new processes, analytical tools, and technology, and using the insights gained to improve safety. If there is a concurrent economic benefit, so much the better.

But making risk explicit can give the impression that new risk elements are being injected into the regulatory framework that were previously overlooked. Many risk elements are not new and have already been considered implicitly, but some new risk insights are likely to be found by using risk assessment techniques (this is discussed below under "Unforeseen Risk Drivers.") This is a credibility trap for the regulator. How can these new risk insights be considered without casting doubt on the adequacy of the entire existing regulatory structure? To minimize the effects of the credibility trap, the FDA will need a well-considered, defendable approach to risk-based regulation and a corresponding strategy to communicate it consistently and effectively.

Risk-Informed, Not Risk-Based

Imagine a motorist driving down a street late at night. Authorities have placed a red light at an intersection in the motorist's path, and deterministic traffic regulations say the driver must stop regardless of the presence of other traffic or the actual risk that running the light might pose to the driver or others. In a purely risk-based world, there would be no traffic light. Each driver would evaluate the probability and consequences of operating a vehicle in various situations, and would continue at speed through the light if the situation is "safe enough" or stop if the risk is too high. The driver's actions are based on the perceived risk compared to an acceptable threshold, whether set by the authorities or determined individually by each driver. In a "risk-informed" regulatory approach, the authorities recognize the intersection as a risky situation that calls for additional caution so they have installed a flashing yellow light. A driver approaching the intersection must slow down and check for traffic in all directions. The driver stops if necessary, or continues through the light at a safe speed if the "coast is clear." The driver's actions are a consequence of considering actual real-time risk (is traffic coming?) and following deterministic regulations, i.e., the traffic laws governing driver behavior at a flashing yellow light.

In a risk-informed approach, risk considerations comple-

ment a deterministic regulatory framework. Deciding whether a risk-informed regulatory framework will replace or complement an existing deterministic framework is a fundamental question of policy. The NRC adopted the risk-informed approach in the 1995 NRC Policy Statement[6] regarding the use of PRA.

> *...the Commission believes that the use of PRA technology in NRC regulatory activities should be increased to the extent supported by the state-of-the-art in PRA methods and data and in a manner that complements the NRC's deterministic approach.*

What path will the FDA take? What the FDA means by the term "risk-based" is open to some interpretation. What is the difference between a new "risk-based" approach and an approach that makes informed decisions about risk and imparts them in a deterministic regulatory structure? It can be argued that the FDA's approach[1] is risk-informed, and it is hard to argue that any regulatory agency would opt for anything other than the risk-informed approach. To choose otherwise would go against both precedent and the conservative nature of regulation itself, and would put the agency's political capital at risk.

Evolution, Not Revolution

Figure 1 shows that the first use of PRA in the nuclear industry was WASH-1400[2] in 1975. The NRC presented general principles for using risk assessments in a regulatory context when it published Regulatory Guide 1.174[7] in 2000. This is a span of 25 years. Truly, the nuclear industry saw an evolutionary, not a revolutionary, transition to a risk-informed regulatory structure. Evolutionary change is in keeping with the risk-informed approach, which takes as a premise the retention of some form of deterministic structure and a controlled transition.

The lag in computer technology was certainly a factor contributing to the length of the evolutionary transition in the nuclear industry. Even though it was not until the mid-1990s that computer capabilities advanced sufficiently to allow use of risk assessment techniques on a wide scale basis, much of the delay should be attributed to the nature of regulation itself. The evolutionary pace of change allowed the industry and the NRC to identify, investigate, and confidently address standards, validation, training, education, public perception, and the many other issues associated with the change in regulatory approach. The need to treat these issues right the first time in the life sciences industry argues strongly for the FDA to adopt an evolutionary approach.

There should be no such technological barrier to widespread application of quantitative risk assessment techniques in the life sciences industry. However, the FDA faces challenges of both scale and scope as compared to their NRC counterparts. There are 103 commercial nuclear power plants

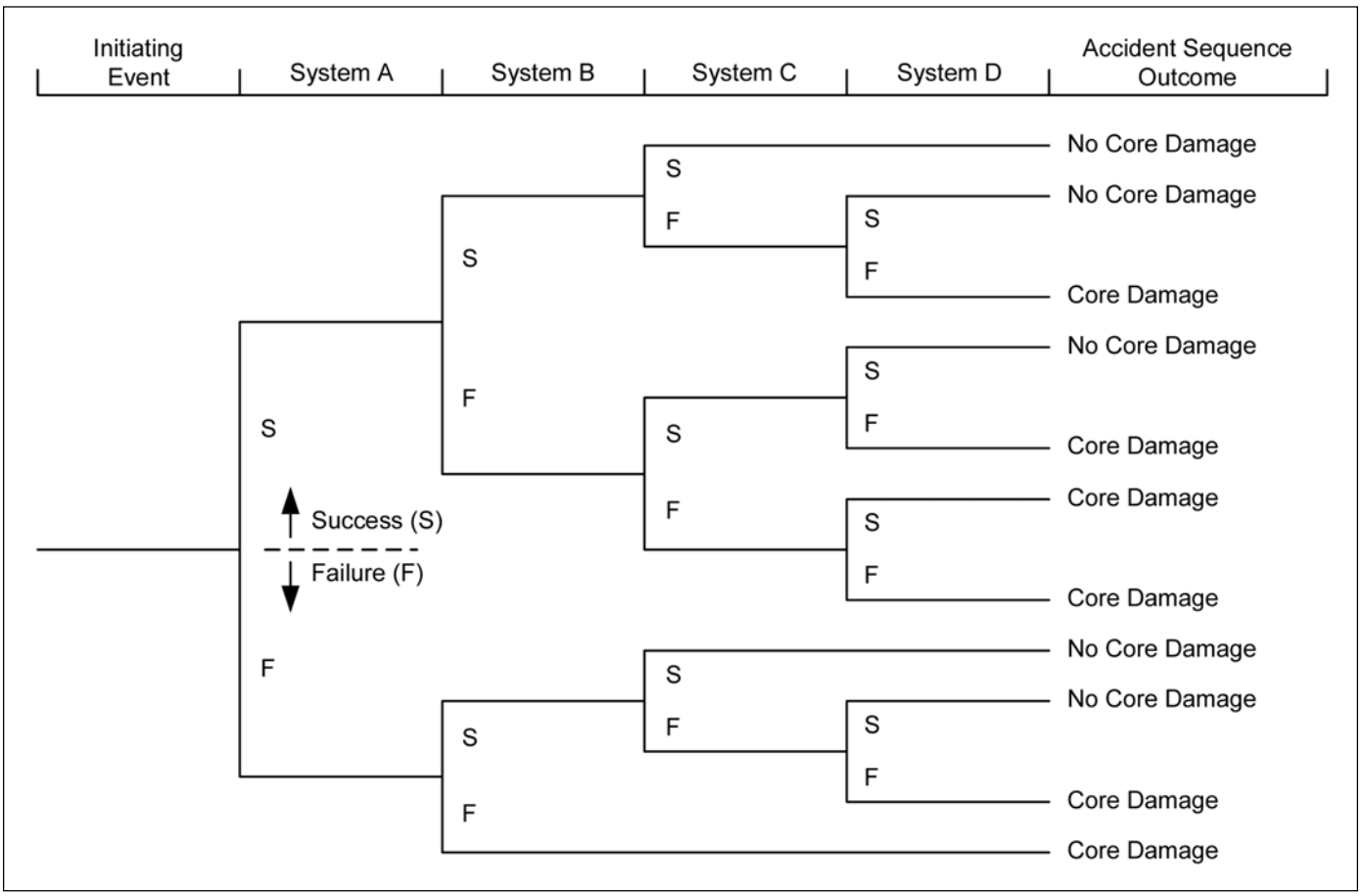

Figure 3. Example of an event tree.

operating in the United States; the number of cGMP facilities is many times greater. There are only two basic commercial nuclear power plant designs in the U.S. (pressurized water reactors and boiling water reactors); the regulator understands them very well. In the life sciences industry, there are many processes for which there are varying degrees of understanding. How to frame a workable risk-informed structure to govern all this activity without a larger use of resources will be a substantial challenge for the FDA.

Unforeseen Risk Drivers

The accident at Three Mile Island (TMI) in 1979 overturned some of the basic assumptions about risks associated with nuclear power plant operation. The most severe accident postulated for nuclear power plants prior to the accident, and the one on which much of the safety design of the plants was originally based, was the large break loss of coolant accident (LOCA). This was thought to be the limiting accident because it results in the most rapid conceivable loss of cooling water from the reactor cooling system, and thus, the greatest potential for melting the reactor core. But extensive risk analyses after TMI showed that a small break LOCA was potentially more severe than a large break LOCA. The small break LOCA depressurizes the core less rapidly; the higher pressure limits the ability of the plant safety systems to pump emergency cooling water into the reactor core. The lesson to be learned is that formal risk analysis can provide counterintuitive insights that disprove conventional wisdom about risk embedded in deterministic regulatory structures.

It is also interesting to note that risk analysis found significant risk associated with seemingly benign engineering support systems. For example, an instrument air system might actuate a valve that, because of unintended system dependencies due to common cause failure, may have an important effect on safety.

It is quite likely that taking a risk-informed approach in the life sciences industry will reveal risk components that are currently underemphasized or simply not present in traditional cGMP space. Bringing science into the cGMPs through robust risk analysis will require reconsideration of the conventional wisdom about where risk exists.

Quantification, Consistency, and Adequacy

Risk assessment technologies used in the nuclear power industry use both quantitative and qualitative methods. Because qualitative methods tend to involve potentially greater uncertainties and inconsistencies, quantitative methods are heavily relied on in risk-informed nuclear regulation. Most risk-informed applications in the nuclear power industry rely on the ability to estimate (at least) core damage frequency quantitatively. In contrast, risk assessment techniques applied to GMP space, such as the GAMP approach (outlined below) have so far been entirely qualitative. If regulatory (i.e., safety) decisions are going to be made and defended to the public based on risk assessments, there will be irresistible pressure to develop and use consistent quantitative risk assessment methods.

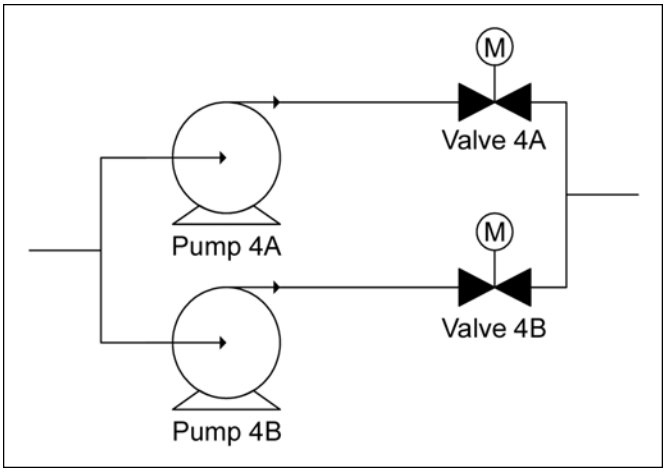

Figure 4. Example system.

Making risk explicit has broken the safe/unsafe paradigm. How does a regulatory agency provide "adequate" protection of public health and safety within the new paradigm? The answer, of course, depends on what "adequate" means. The use of qualitative, risk-informed approaches helps to determine adequacy. For example, consider the general GAMP risk assessment approach in which potential hazards and/or risk events are postulated and then assessed using a two-step qualitative approach as shown in Figure 2.

1. Plot Severity (low-moderate-high) against Probability (low-moderate-high) to obtain a Risk Class (1-2-3) for each event

2. Plot Risk Class (1-2-3) vs. Detectability (low-moderate-high) to obtain a Risk Priority (high-medium-low) for each event.

The outcome of this process is a risk priority of low, medium, or high assigned to the hazard/event. Different technical or administrative controls are put in place to mitigate the risk based on the assigned risk priority.

There is considerable fuzziness associated with this approach simply because it is qualitative and reasonably involved (it has 27 combinations and two sorting/binning processes to achieve three possible outcomes). Despite the fuzziness, qualitative risk assessments such as the GAMP approach can be very useful in the context of guides or best practices. They are a simple and logical first step to making risk explicit.

But fuzziness can be harder to defend when it is used, not merely as a guide or best practice, but as a basis for a new regulatory framework that will continue to "adequately ensure" public health and safety. Then the FDA might be concerned with questions such as the following:

- What exactly determines the boundaries between low, medium, and high business impact/risk likelihood/probability of detection?

- What if Pharmaceutical Company A deems the risk likelihood of one event to be low and Pharmaceutical Company B deems the risk likelihood of the same event to be high? In such cases, does the FDA have a duty to investigate the discrepancy? What if two different sites operated by the same company show similar discrepancies?

- Do the outcomes of these assessments increase or decrease risk compared to the existing deterministic regulatory structure? Are these changes small enough that the regulator can continue to "adequately ensure" safety? Is there a risk threshold below which the risk level is always acceptable? If so, how does one know when this threshold is crossed?

- What is the cumulative effect of conducting multiple, independent, qualitative risk assessments across a broad spectrum of applications within a pharmaceutical manufacturing facility? Would there be a danger of missing system and process interdependencies that would bring total risk to an unacceptably high level?

These questions can be answered in terms of ***quantification, consistency,*** and ***adequacy***.

Quantification can be desirable in so far as it makes risk priorities less fuzzy, and therefore more defensible, both in technical and regulatory space. It may be in the best interest of both the FDA and the industry to establish quantitative techniques to avoid the resource drain and scrutiny that could be involved with answering questions like those presented above for every qualitative analysis.

Although risk-informed regulation in the pharmaceutical industry is relatively new, the pressure for greater risk quantification is already evident. It is interesting that the entirely qualitative GAMP framework was one of the first approaches to explicitly consider risk in the industry. The first stage of quantification might be a risk-weighting approach in which numerical values are assigned to the different outcomes in a qualitative risk assessment process to yield numerical risk results. Risk thresholds can then be defined for different risk rankings. The FDA has published a risk-weighting approach similar to this to prioritize inspections.[10] The next stage of quantification might involve assessing the risk associated with production processes, such as risk-based applications of Process Analytical Technology (PAT). It will be hard to keep these applications qualitative because they are inherently quantitative; they are measured and controlled using numerical (quantitative) information that lends itself well to statistical analysis of risk. So, as the FDA tries to bring the science into the regulatory structure, risk quantification is likely to expand.

There also are issues of consistency, scope, and technical adequacy. The NRC looks at the issues this way.

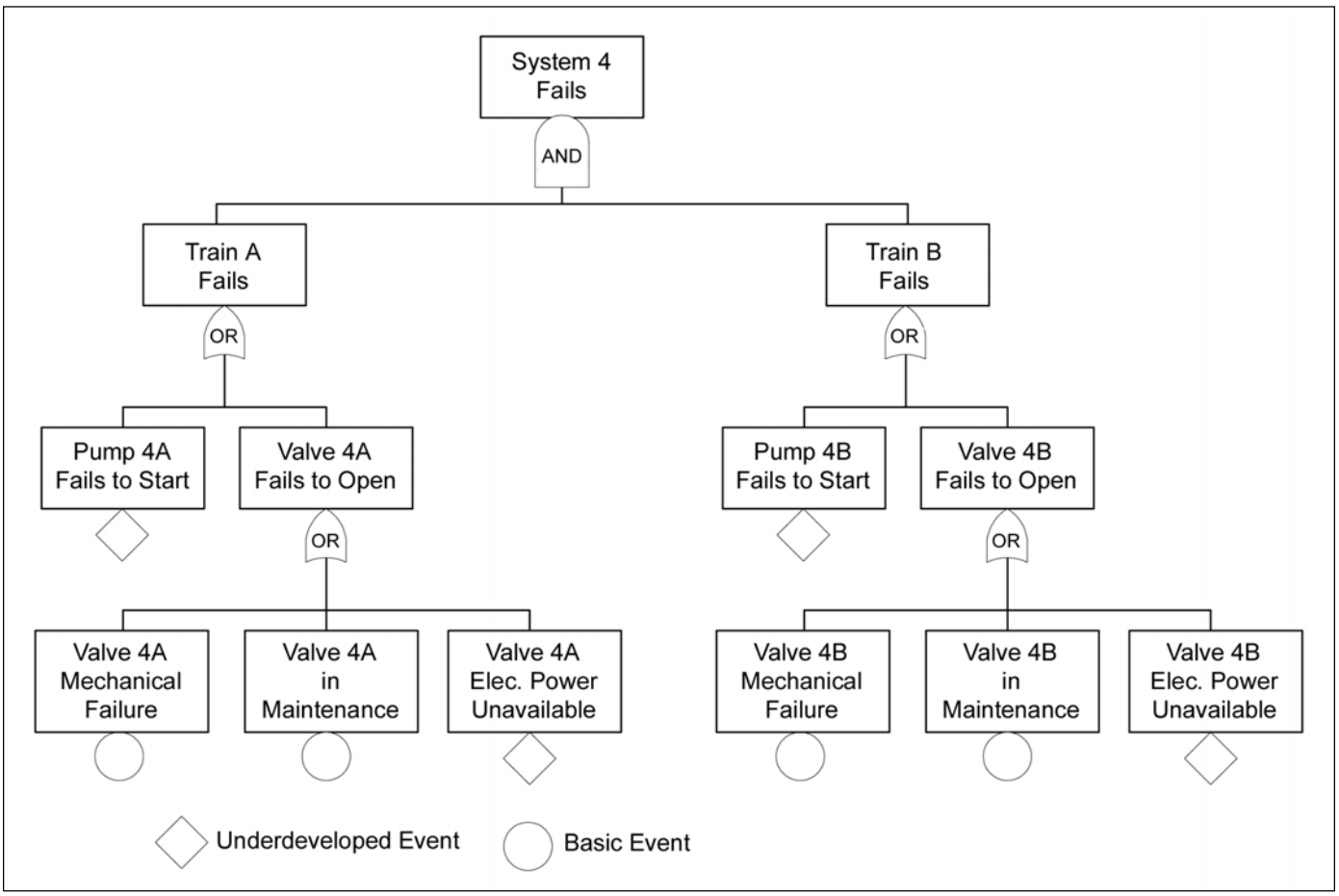

Figure 5. Example system fault tree.

> *In any regulatory decision, the goal is to make a sound safety decision based on technically defensible information. Therefore, for a regulatory decision relying upon risk insights as one source of information, there needs to be confidence in the PRA results from which the insights are derived. Consequently, the PRA needs to have the proper scope and technical attributes to give an appropriate level of confidence in the results used in the regulatory decision-making.*[11]

If risk assessments are to be included as part of a formal, stable regulatory structure, the regulator must have confidence in the results of those assessments. It would be betrayal of its public trust for the FDA to simply rubberstamp every attempt at regulatory change that calls itself risk-based or risk-informed. So the FDA will eventually have to set some standards for risk assessments. The FDA is likely to become involved in certifying the methodologies, insisting on the use of consistent data sets, setting training and proficiency requirements for those who conduct the analyses, etc. Following standards will go a long way in establishing consistency among the many risk assessment practitioners within the industry and the FDA. Professional groups could play a major role by helping to establish consistency within the industry.

Risk Thresholds vs. Incremental Changes

If risk is quantified through consistent, robust risk-analysis methodologies, the next logical step might be to set a quantitative threshold that represents an acceptable level of risk. Conceptually, a quantitative risk model for a pharmaceutical manufacturing site could drive a "risk meter" that indicates the current risk state of the operation. If the overall risk is at an acceptable level, is it necessary to individually regulate each activity that supports the process? Should cumulative risk be tracked? If so, is there a limit to the maximum accumulated risk? Or, if a process change can be shown to impose no additional risk, should the change be subject to regulatory scrutiny?

The nuclear experience is described above. The NRC refused to abandon its traditional approach for an exclusively quantitative, risk-based approach. Accordingly, the NRC has not set an absolute risk threshold. However, relative risk thresholds and incremental risk thresholds are commonly used in the nuclear industry's risk-informed regulatory approach.

But implementation difficulties are lessened when quantitative risk techniques are used to improve the regulatory structure incrementally, on the margin. This minimizes the concern over bias in the risk models by relating changes in risk to an initial state that everyone agrees is "safe." One need not know an absolutely accurate absolute risk value to assess changes in risk from a given initial state. Quantitative risk analyses can be used to assess the incremental benefits of new and existing regulations (the amount of risk the regulations reduce) against the associated compliance costs. Without robust, quantitative risk analysis techniques, it is difficult to know how much the industry gains in terms of risk reduction for each dollar spent on compliance. The FDA does not want to expend resources to enforce regulations that have little marginal risk impact, and the industry does not want to spend money on compliance that does not result in appreciably lower risk. Quantitative analysis provides a framework for discussion between the industry and the FDA to strike the right balance between cost and risk.

Establish General Principle

Twenty-five years of experience with risk assessments in the nuclear industry culminated with the publication of Regulatory Guide 1.174[7] containing five general principles to govern applications of risk assessments within the nuclear power industry regulatory framework. These five principles are paraphrased below.

A risk-informed application:

1. ***Cannot be used as an avenue to violate existing regulations.*** That is not to say that regulations can not be changed through a formal rulemaking process that takes risk principles into account, but industry must comply with all regulations currently in force, seek a specific exemption, or change the regulation.

2. ***Must consider defense-in-depth.*** Defense-in-depth is a regulatory philosophy the NRC has used since the beginning of nuclear power regulation. It holds that multiple means to accomplish safety functions must be provided, i.e., no one measure should be relied upon completely to ensure safety.

3. ***Must maintain sufficient safety margin***.

4. ***Can be implemented only if the change in risk is small.*** The regulatory guideline contains guidance on what constitutes a small change in risk.

5. ***Must be monitored as part of an overall program to assess the aggregate risk impact of (potentially) many minor risk changes.*** The concern is that many small changes in risk, each individually assessed, might lead to an unacceptable total risk increase, especially when common cause failure mechanisms are considered.

Of these specific principles, one could quite easily see something similar to numbers 1, 4, and 5 adopted in the life sciences industry. This points to common regulatory dynamics inherent to public safety regulation that this article has taken pains to illustrate. But the larger point is to recognize that general principles will evolve, which fit with both general regulatory dynamics and the specific challenges of life sciences regulation. The ultimate intent of the discussion in the life sciences industry should be to establish these basic principles. The sooner this is done, the sooner a stable and predictable risk-informed regulatory framework can be established.

Conclusions

This article presents a very high-level overview of the experience of the nuclear power industry in moving away from a strictly deterministic regulatory approach to production to one that involves explicit considerations of risk. The regulatory dynamics inherent to public safety regulation argue that the nuclear power industry experience should be considered closely when considering a similar transition for the life sciences industry and the FDA.

The nuclear power industry experience suggests that explicit risk-informed regulation will complement, rather than replace, existing (risk-implicit) deterministic regulations. There will be pressure to use quantitative risk assessment techniques that are applied consistently throughout the industry and adhere to common standards. Regulatory change will accelerate as general principles of risk-informed regulation are established, as risk analysis techniques used in the industry become more robust, and as the FDA becomes more confident in the accuracy of their results. These changes will be evolutionary, not revolutionary, and will include both changes to existing regulations and implementation of new regulations.

Perhaps the evolution of risk-informed regulation of pharmaceutical production can be streamlined by considering experience from the nuclear power industry. This experience shows that improved safety, lower costs, and better quality are not mutually exclusive in a risk-informed world. These outcomes can be achieved most rapidly by recognizing the pressures exerted by regulatory dynamics on both the regulator and industry, and how these are likely to play out. Working cooperatively within these constraints will reduce the uncertainty over what "risk-based regulation" will bring. If nothing else, answering the questions that confronted the nuclear power industry can provide a strategic framework for regulatory changes and help identify the logical next steps in the regulatory evolution.

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This article presents a practical model for design qualification under a pre-established strategy framework.

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Design Qualification in Practice – from Strategy to Report

by Yossi Chvaicer

Introduction

Much work has been written enhancing the advantages of good interface between mechanical completion, automation implementation, and validation activities. Project managers are encouraged to follow ingenious flowcharts, V-models,[1] W-models,[2] and project life-cycle strategies aiming to accomplish overall quality, cost-benefit achievements, and time-to-market reductions. This truth reflects two exceptional facts in the pharmaceutical industry. The first is the vast amount of thought put into the Engineering Commissioning efforts. The second is that Installation, Operation, and Performance Qualification (IQ/OQ/PQ) are not only common practice, but also spread knowledge in this industry today.

In spite of the benefits introduced by these modern approaches, they lack a clear and useful methodology for the preceding Design Qualification (DQ) work. For instance, what exactly must a validation engineer write down in his/her DQ reports to provide successful evidence of achievement for these advanced models? What should be verified, and to what extent in the design, when a plant capacity and layout update occur six months after the HVAC system design has been completed? How will that be incorporated under design control? Similarly, what happens when the contact surface finishing of a new vessel is downgraded by procurement personnel due to sudden project budget cut-backs? What traceability level is desired? How can all these changes be reasonably supported during an inspection focused on design?

Eventually, qualifying the design of a new

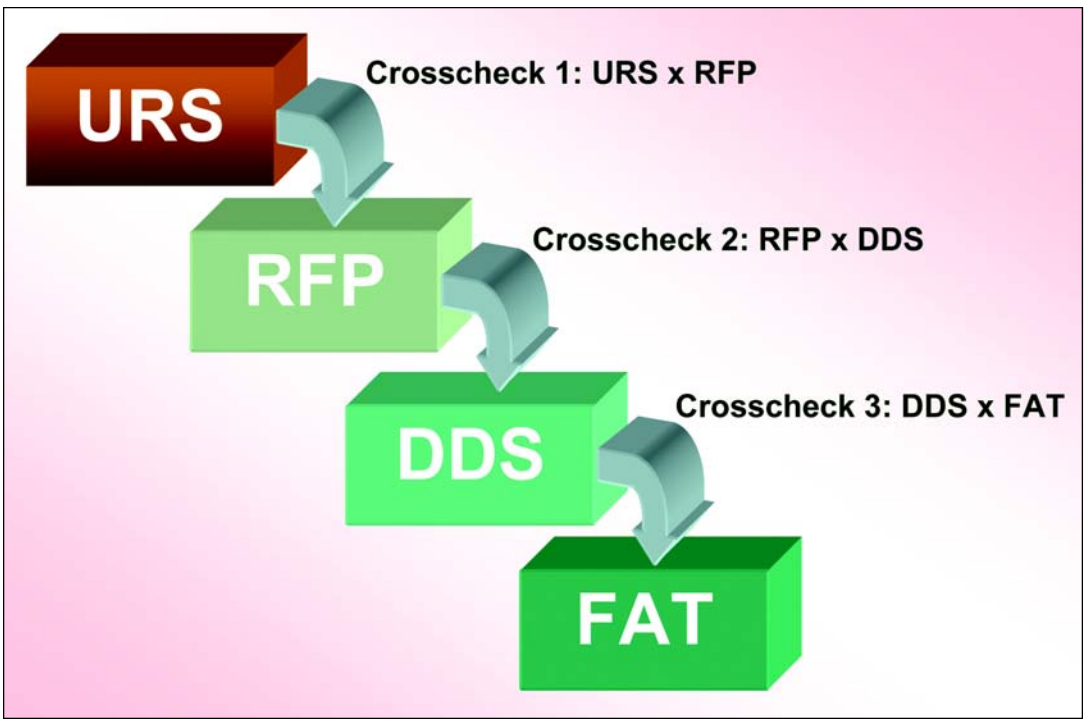

Figure 1. The three steps of design qualification.

Justification Factor	Sub-group	Description	Numerical Value Associated
SystemTechnological Complexity	**Highly** Complex	Any piece of machinery or system that is operated by one or more of the following sub-systems: SCADA, HMI, Controllers	**3**
	Semi Complex	The system or equipment has a controller but does not have a SCADA or an independent HMI.	**2**
	Low Complex	The system is manually controlled by mechanical of simple electrical panel buttons	**1**
Business Value	**Highly** expensive projects	Project budget over $100K.	**3**
	Medium Sized projects	Project budget between $10K and $100K.	**2**
	Low expense sized project	Project budget below $10K.	**1**
Product Quality Impact	**Direct** impact	Equipment or system that has a direct impact on the safety, efficacy or integrity of products.	**3**
	Indirect impact	Any system or equipment involved or supporting the production process, but does not determine its character.	**2**
	No impact	No effect is found from the system to the product quality.	**1**

Table A. Numerical values for the justification factors.

facility, its systems, and equipment, will demand not only understanding the concept and goals of these theoretical models at an early stage, but also creating the practical documented evidence of the facts, adaptations, and reasons during design changes that will help to achieve full compliance.

In this way, this article proposes a practical three-layer plan with the framework methodology at its upper level describing how to perform Design Qualification, step by step.

Background Survey and Motivation

Design qualification has been addressed in four approaches:

1. Enhanced Design Review (ISPE)

The ISPE Commissioning and Qualification Baseline® Guide[3] describes in detail a review activity for design aiming to accomplish conformity with operational requirements and regulatory expectations. Although not quoted as an FDA requirement, it brings to light the benefits of an enhanced structure review for any project. The results will mainly assure that the design is carried out in a controlled manner, facilitating, as per the text, a good start to any inspection by authorities. However, it must be noted, that the list of qualifications proposed in this publication remains at a business-driven level rather than a regulatory-based decision. How to do such work, as well as what exactly is a business-related issue in the face of inspections remains undefined.

2. Adequate Design (CFR)

This approach, stated by the 21 CFR Part 211,[4] refers to design within a statement of appropriateness. Its generality is so wide one can easily be confused by the extent of regulation requirements, and as a result, find difficulties in determining the scope of a design qualification. The specifications stand for requirements regarding construction, cleaning, maintenance, calibration, identification, procedures, and other issues rather than for the design itself. Consequently, those responsible for dealing with the qualifications are driven to gather all statements and translate them into "appropriate" design requirements under their best available judgment. In yet another guideline also published by the FDA on process validation,[5] further confusion by suggesting an examination of design at the Installation Qualification stage is revealed. This means reviewing the design when the system has already been installed – a meaningless exercise unmatched in the project life cycle. After all, what can be done to the design activity, other than post-mortem site corrections, if at the installation qualification phase the design requirements do not comply?

In short, in this approach the design qualification concept is somewhat hidden, whereas the major hint in the text is the term "intended use." Such a quote is the core motive for qualifying the design.

3. GMP Compliance Demonstration (EU)

This approach, adopted by the European Commission on Qualification and Validation,[6] clearly suggests a qualification exercise for the design phase, as the first validation activity. It also aims to demonstrate documented compliance with GMP.

In retrospect, this emphasizes the need to assess engineering, quality and process issues during the initial design. However, in practical terms, how far should one go for a successful GMP review during design? For instance, how much is plant space utilization– an issue extensively stressed in design for its budget related matters – a GMP criterion at the planning phase? What about production plant capacities, environmental safety, or automation levels? How to demonstrate their GMP compliance at the design phase? This is not clear from the text, which suggests that if authorities apply additional insight to this Guide it could help the European Pharmaceutical Industry achieve better qualification success at the design phase. Quite the opposite, the glossary of this document surprisingly reveals a more detailed definition

for design qualification, very much like the approach adopted by the International Committee on Harmonization (ICH) which is described below.

4. Verification Suitability (ICH)

This approach, stated in ICH Q7A,[7] introduces the concept of "intended purpose suitability" for a facility, system, or equipment. It actually defines a status for the design itself rather than a list of enhancing reviews, clued requirements, or unclear GMP inferences, as assumed by the other approaches. The ICH approach undoubtedly provides for the validation professional the base to develop the logical sequence for qualification activities at the design phase. Such an approach, although much more understandable, still leaves the "how-to-do-it" issue largely open.

From the above, all the approaches share a common situation. They leave ample space for interpretations, which in a complex project could induce diversity, more than standardization. For this reason, when starting design qualification in a new plant, it is recommended at the outset to establish a supportive DQ structured plan for this activity and only then concentrate on the actual detailed activity.

Developing a DQ Structured Plan

Effective design qualification for a new facility is achieved by developing in the organization a structure to deal with the following basic questions early in the project.

To begin with, what systems or equipment are designed for the envisioned production processes? What reasons justify qualifying their design? This means not only deciding the technology, the material flow concept, associated controls or supporting services, but also establishing clear-cut criteria that sustain decisions of what will or will not undergo design qualification. Risk assessment of critical organization issues used as a strategic tool will help selecting the technologies that will undergo DQ.

Next, at what time during project evolution should Design Qualification be activated for the selected technologies? Which events or phases can trigger this activity? This matter requires establishing when it is most appropriate to align design deliverables with their predetermined specifications. Choosing design related milestones in the natural course of the project will lead to the correct timing for DQ.

Finally, after the "What, Why, and When" are defined, the DQ structured plan will create the "How" is the qualification going to be performed? This issue relates to the work itself. It is setting up the hands-on methodology, responsibilities, reports, documentation requirements, formats, and standard operating procedures for all the do's and don'ts.

A DQ structure consisting of three layers was developed based on the concepts above to provide the answers for the exposed questions.

The Basic Layer – DQ Justification

Initially, suppose you are starting the design of a new facility. Should the following projects undergo design qualifications?

- a jacketed, double-cone processor with size reduction and vacuum drying capabilities, external HMI pre-set recipes, historical trends, security management, alarms, and upstream CIP interfaces
- an HVAC system which is planned to serve a 12-room granulation department with a common corridor and two air-lock sections in between
- an off-the-shelf, direct contact peristaltic transfer pump

Next, admitting that market shifting is a desktop variable, what about the following?

- For a budget approved 18 months ago, is the facility being built today the correct one for the business?
- Within the atmosphere of constant SUPAC and R&D innovation demands on the one hand and daily technological advances on the other, are you acquiring the right equipment for your processes?

It is clear from the above that any "Yes or No" answer is not as simple as it seems. Additionally, the entire project inventory will need a supporting rationale for justifying which of the equipment or systems will or will not undergo DQ.

Consequently, the justification process starts by using a risk assessment technique. First, identify the three major aspects in the company that will establish the decision making approach to perform Design Qualifications. They can be:

a. technological complexity: indicating the level of automation complexity of a project
b. business value: nominal budgets allocated or equipment cost, when known
c. quality impact: The degree of impact in the product quality, as described in the ISPE Guide[3]

Then, subdivide each factor into category levels with numerical values each, e.g., 1, 2, or 3 as shown in Table A. After examination of which levels best fit for each selected technology, their multiplication becomes your justified decision index. Finally, establish a criterion. For example, a system will undergo Design Qualification if the Complexity Business Impact (CBI) index equals 27, as the justification part in Table B illustrates for different types of equipment and utilities. In time, this justification tool will become sufficiently flexible in order to allow frequent updates during the design phase. They emerge from different sectors, such as process or technological development, finance and capacity trends, or different quality approaches altogether in a business. The result of such an assessment becomes the company's methodically justifiable DQ program, which also should be an integral part of the Validation Master Plan.

The Middle Layer – DQ Milestones

Projects following budget approval start by the design phase. For qualifying purposes, this phase is broken down into logical milestones with potential workable deliverables. The

JUSTIFICATION						DESIGN QUALIFICATION						
						Step 1 URS x RFP Deviations		*Step 2* RFP x DDS Deviations		*Step 3* DDS x FAT Deviations		Estimated Added Value
No.	Equipment, System or Utility	Technological Complexity	Business Value	Quality Impact	CBI Rate	Technical	Process	Technical	Process	Technical	Process	
1	Fluid bed Drier 1200L	3	3	3	**27**	10	6	6	3	12	5	**8%**
2	Fluid bed Drier 800L (1)	3	3	3	**27**	16	12	4	5	10	4	**9%**
3	Fluid bed Drier 800L (2)	3	3	3	**27**	16	12	4	5	10	4	**9%**
4	High Shear Mixer 900L	3	3	3	**27**	10	6	1	2	5	4	**12%**
5	Coater Machine 65"	3	3	3	**27**	14	8	1	4	8	2	**5%**
6	Diffusion granulator 50 c.f.	3	3	3	**27**	13	1	4	1	3	2	**5%**
7	Diffusion processor 20 c.f.	3	3	3	**27**	15	5	8	2	4	1	**2%**
8	Diffusion granulator 75 c.f.	3	3	3	**27**	10	1	9	6	5	0	**1%**
9	CIP Skids 500L	3	3	3	**27**	16	5	2	1	7	1	**10%**
10	R&D Fluid bed granulator 120L	3	3	3	**27**	4	7	8	0	6	1	**4%**
11	Compressing Machine 36 st	3	3	3	**27**	43	23	Not avail.	Not avail.	7	5	Undetermined
12	Purified Water System	3	3	3	**27**	20	10	7	2	3	1	**5%**
13	Capsule polisher	3	2	3	**18**	Design Qualifications submitted to policy constraints						
14	Conical Mill	2	2	3	**12**							
15	Metal Detector	1	1	3	**3**							

Table B. Justification index and qualification results.

first one, from the validation standpoint, is the User Requirement Specifications (URS). This is a document considered to be the foundation of the whole Design Qualification process. It contains for each equipment or system the requisites of the production process and it expresses the fundamental needs of all involved users in one text. A responsible committee formally approves the contents by involving representatives of different areas such as Engineering, QA, Process, Operations, and Validation.

For utilities such as HVAC or water systems, such a document is sometimes called Base of Design (BOD), which serves the same purpose. The URS contents are examined in a subsequent section of this article, as well as three other deliverables described hereafter.

Next, as the project progresses, procurement activities combine URS controlled copies with commercial requirements. A formal requisition for an offer is generally sent to potential vendors which return quotations for bidding purposes of the project purchasing phase. These quotations are presumably based on the original URS, and also have technical details attached. If a supplier is selected, a formal financially approved Purchase Order (PO) will be issued, containing the agreed commercial terms accompanied by the same technical specifications in the attachments received from the supplier. Such documentation represents a clear and tangible milestone for the project, and it is then called the Request for Purchase (RFP). This is when the next design qualification step finds its biggest potential to take place, becoming as a result, the second natural milestone.

The third target for the qualification work is the detailed design. For the project – here is when the manufacturer or supplier delivers detailed documentation that waits for the user's official approval so that the manufacturing of the equipment at the workshops can start running. These include engineering blueprints, mechanical drawings, detailed layouts, instrumentation diagrams, and software development documentation having the Functional Requirement Specifications (FRS) as the leading records. In general, these documents consist of a design package called Detailed Design Specifications (DDS).

The last milestone on the project design phase is the Factory Acceptance Test (FAT). In FAT the user expects to see (and test) the major items of the URS fulfilled before the actual system or equipment is shipped for installation. In other words, at this point, nothing remains to be designed so that the design phase of the project is considered to be complete.

All these four consecutive events, defined as project milestones, are workable turning points that trigger the Design Qualification exercise.

The Upper Layer – DQ Work

The difference between DQ and the classical IQ/OQ/PQ or Process Validation is the fact that when qualifying a design there are no clearly defined measurable acceptance criteria. There is a lack of pre-determined parameters to be compared to simply because the facility, equipment, and its processes do not yet exist. Therefore, qualification of the design phase is performed in three critical steps by crosschecking the delivered documentation along the project design advancement, as depicted in Figure 1, using the URS as the leading reference. The qualification work actually links every two pre-established milestones.

URS x RFP – Crosscheck 1

The first crosscheck qualifies the RFP by comparing it with the URS. Chances are that quotations will arrive in the format developed by the potential vendors. This means, the

quotations or their technical annexes do not follow the URS sequence arrangement at the paragraph level, as approved by the responsible committee. So the first item to qualify is the traceability of the URS itself. Placing the RFP side by side with the URS, qualification starts by carefully checking whether all URS paragraphs appear in the vendor specifications. At the same time, each item also is scrutinized for its contents to match the URS characterizations. If the items are found to be identical in both documents, the compliance is recorded. Here, paragraph citations, as well as the contents of the quote, are inspected with the same level of importance for the qualification work. This procedure for the URS x RFP crosscheck is illustrated in the flowchart of Figure 2.

Every difference revealed between the URS and the RFP generates a Design Qualification Deviation Report - *Figure 3*. This report indicates to which of the three categories the discrepancy belongs, namely an omitted-by-the-supplier item, an existent-but-modified-by-the-supplier item, or a new added item. In the example shown, an RFP modification was identified on the contact surface finish grade for the tank of the purified water project, generating as a result the DQDR #4.

Traceability is then assured by a record in a Verification Table, which follows all URS sections, as depicted in Figure 4. This table also will track the Design Qualification process from the start to its end, throughout the remaining two cross checking steps explained below. The table example is a real-life Design Qualification project for a 65" [165 cm] tablet film coater machine, showing 15 out of 96 traceable URS paragraphs developed for this system (characterizing the spray system, the inlet AHU, the CIP and control features, the safety, the direct and indirect contact parts).

Each individual deviation report, issued by the validation engineer in charge of the project, includes a description of the finding, which is presented in a DQ meeting of the responsible committee. This forum will decide whether or not the inconsistency revealed is acceptable for the design carry-over. Furthermore, the committee shall agree on two additional issues: The rationale justifying the deviation cause, and the corrective action to be taken. Such a procedure is performed for all deviation reports issued during the cross check qualifications. All deviations and associated required actions are recorded in a summary report for that step including the findings, paragraph numbers, deviation category and action to be taken by both user and vendor. Subsequently, this summary is addressed with the vendor for confirmation, necessary changes, and corrections at the design and project follow-up.

The vendor responses are expected to include corrective details and a timeframe to be finally post approved by the committee. The most appropriate time to send the DQDR summary report to the supplier is approximately a week before the RFP is legally issued by the PO placement. There are two reasons for this: first, any corrective action made to the design after PO placement is strongly unadvisable for all parties concerned. Second, the supplier is usually prone to agree to corrective changes without extra charge in the few days preceding receipt of the order from the customer. In time, when a budget sum is associated to each deviation found, it is optionally included in the DQDR becoming the design qualification added value of this item for the project.

The above methodology leads to a worth mentioning mid-way conclusion: there is no need for retroactive changes in the original URS. The URS is a document that reflects the best knowledge of all the issues agreed among the committee members involved by the time it is approved. As such, it should not be changed back when a new issue is raised during the actual design process. Redefining the URS on a documented controlled environment would lead to cumbersome change control procedures, unnecessary at the early phase of the project. Nevertheless, all inevitable changes during design, their justifications, and corrective actions required are registered in the DQ deviation reports. The full traceability for each case is ensured by recording it in the DQ Verification Table (Figure 4), as part of the DQ protocol described below.

RFP x DDS – Crosscheck 2

In a similar way to the first check, this step verifies if all the DDS contents can be traceable to the RFP paragraphs, which in turn were tracked down to the prior URS. In this way, this new phase of design qualification focuses simultaneously on drawings and on the FRS. Table C illustrates an omission detected on the FRS for the atomizing pressure control of the

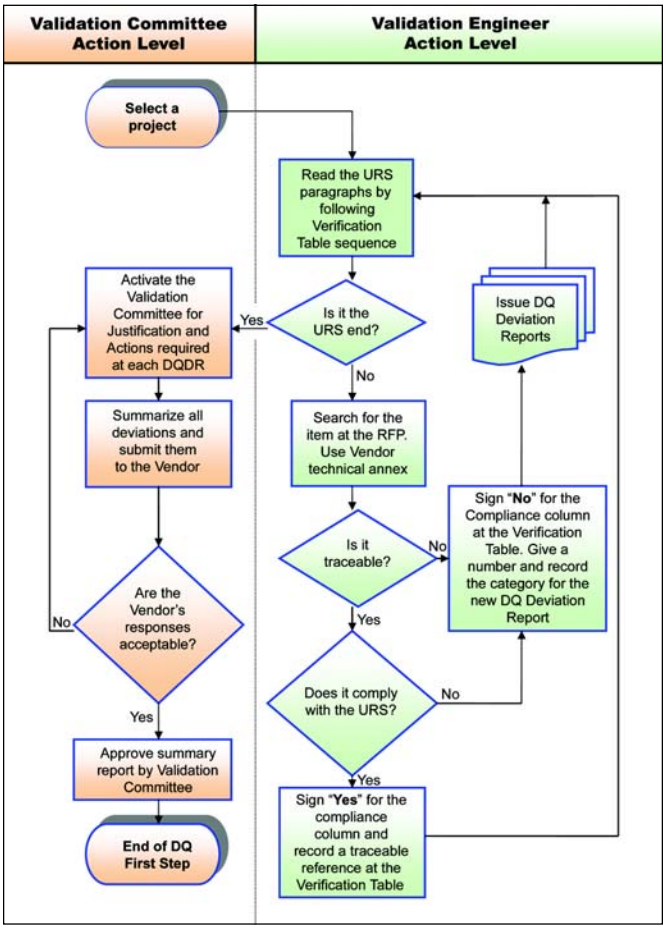

Figure 2. Flow chart for the design qualification URS x RFP crosscheck step.

DQ Protocol: D-P-P3S-01 | System/Equipment Identification: 35-VDT-001

DQ DEVIATION REPORT N° 04

The Paragraph number: 3.3.2 and 8.2.2 From the (URS)/RFP/DDS.
(Contents Description: 25 µm Ra surface finish) is compared with:

The Paragraph number: 4.4 and 4.6.2 From the (RFP)/DDS/FAT.
(Contents Description: purified water tank).

	OMISSION	MODIFICATION	ADDITION
DEVIATION CATEGORY	☐ The paragraph appears in the _____ but has been **omitted** from the _____.	☒ The paragraph appears in the URS but has been **changed** in the RFP.	☐ The paragraph **does not** appear in the _____ but has been **included** in the _____.
ASSOCIATED PROJECT VALUE (optional)		36,140 $	

Description of findings: proposed surface finish (31.5 µm) is below URS requirement (25 µm)

Rational or justification: increased chance for microbiological accumulation.

Action: vendor must correct proposal to meet URS requirement.

Name	Function	Department	Signature	Date
Elishai Shkury	validation engineer	systems validation		08.12.2003

Notes: —

Figure 3. Design qualification deviation report.

spray system (See "complies" column for the FRS documentation, at the URS paragraph line 3.3.4 - spray system - where an "N" is circled for "not complies"). This finding has generated a DQDR#23, where all three main issues are recorded, namely the description of the finding (*missing atomizing air pressure attribute as an acquired feature in the RFP approved documentation*), the justification for no design compliance (*it is a process related variable, part of the production steps and records*), and the corrective action necessary to be implemented at the design (*to include the feature in the SCADA – Supervisory Control and Data Acquisition - system*). This qualification procedure is similar to the DQDR #4 example at the URS x RFP prior qualification stage for the purified water tank project as described in the previous section.

At the end of this second crosschecking step, a new set of DQDRs are filled with rationales and action items. The summary of the new DQDRs is submitted to the vendor after approval of the reactivated committee so that the detailed design can be adjusted accordingly without necessarily changing the URS retroactively. However, it is recommended to identify the new set of deviation reports by a sequential number which follows the first crosschecking step (URS x RFP). Where needed, notes are introduced to the verification table referencing further annexes of extra detailed work performed.

DDS x FAT – Crosscheck 3

The last stage of qualifications for the design deals with the FAT results. The same tracing principle is used. The FAT DQ deviation reports are summarized as well, but the corrective actions agreed at this time will be decided to be implemented either at the commissioning phase during the Site Acceptance Test (SAT) or directly into the IQ/OQ/PQs.

DQ Protocol and Report

The DQ report is a document which will provide evidence that the system or equipment is designed for its intended use. It must be accurate and have supportive documentation for all the verification steps conducted during the qualification effort. It also should reflect the natural progress of design for the project in question. Reports with the following seven sections summarize this concept and respond in a high degree of compliance to any regulatory demand:

1. The approval section. It contains the names, functions and signatures of the representatives for the project team, usually Engineering, Operations (the User), Process, QA, and Validation.

2. The description section. A brief explanation of the equipment or system, its intended purpose, planned site location, phase in the production chain, process capacities, basic functional and automatic capabilities, cleaning features, and peripheral items associated, where applicable.

3. The URS section. This section contains the approved User Requirement Specifications, preferably the original set submitted to vendors for the initialization of the procurement phase. If electronic documents are the only means used, a read-only copy should be kept in the report file with pertinent details such as dates, revisions, approvals, and reply confirmations.

4. The attachments section. This section includes the list of all attached supporting documents, for example, engineering drawings, layouts, production process flowcharts, a summary of the bid analysis, design review meeting minutes, and FAT reports. It is a known fact, not all vendors do have the required records or certificates available on time. In such cases, a notification for project management must be issued detailing the missing data. This note is part of the DQ protocol, and when received, qualification work will continue for that part.

5. The project follow-up section. This is a general synoptic table with major completion dates for the URS approval, PO placement, DDS approvals, FAT, and shipment.

6. The qualification documentation section. This includes the Design Verification Table, all the associated DQDRs, and summary reports. This makes the design phase follow-up completely traceable for the project - *Figure 4*. It is

actually the documented evidence that the design for the equipment or system was carried out to suit its intended use as defined at the URS.

7. The GMP assessment section. This is a review section that includes a questionnaire considering items such as identifications of drawings and instrumentation, contact materials suitability, calibrations, safety, and an adequacy concluding statement.

Qualification Expertise

URS Contents

The approved URS is the basis for the entire design qualification process. When distributed among potential vendors, it becomes the acceptance criteria used by the future owner not only for qualifying the quotations received for that specific equipment, but also along the qualification steps in the design phase that will be continued for the entire validation life-cycle ahead. Yet, at early stages before approving it, the validation representative role is to support the URS consolidation phase, keeping in mind the subsequent qualification activities, as depicted in Figure 1. These activities will be essentially performed on the process functionality, engineering technical issues, and regulatory aspects characterized by the URS approving committee.

Afterwards an effective design qualification is better attained across the organization when the URS is formatted in a standard way for all different technologies or systems comprising the project. An example of the URS format and its contents is as follows:

- **Cover Page:** Company name and logo, project title, system identification by name and number, URS revision number, issuing date, and signatures dated from all parts of the approving team.
- **Revision History:** A page with a place to insert revision numbers, details, revision responsible, and recording of controlled distributed copies.
- **Table of Contents:** A page reference with all numerated sections and appendices.
- **General:** Aspects of the project such as the use, locations, access, safety statements, and an introductory section briefly describing the production process.
- **Scope of Supply:** This defines to the vendor demarcation plans, delivery, manufacturing and testing responsibilities, expected participations in training, qualifications, and start-up assistance.
- **User Specifications:** The user requirements encompassing all possible technical and process related issues such as batch sizes, manufacturing rates, auxiliary equipment involved, material loading and unloading features,

Item	URS	RFP	Complies ?	FRS	Complies ?	FAT	Complies ?	Init./Date	Note
General	1	N/A	Y N	N/A	Y N	N/A	Y N		
Scope	2	N/A	Y N	N/A	Y N	N/A	Y N		
3.2 Equipment scope									
Film coat	3.1	N/A	Y N	N/A	Y N	N/A	Y N		
Film coater unit	3.2.1	1.A Pg 4	Y N	45505 PHA 10/3/03 PG 4	Y N	Pg 9-10	Y N		
Solution preparation sys.	3.2.2	5.A Pg 22	Y N	45505 PHA PAGE 7	Y N	Pg 16	Y N		
Dust collection system	3.2.3	1.E Pg 7, 4.C	Y N	45505 PHA 10/3/03 PG 5	Y N	Pg 18	Y N		
CIP system	3.2.4	7A. Pg 18	Y N	45505 PHA 10/3/03 PG 13	Y N	Pg 17	Y N		
Inlet air preparation sys.	3.2.5	1.D Pg 6	Y N	45505 PHA 10/3/03 PG 5	Y N	Pg 13	Y N		
Tablet feeding system	3.2.6	N/A	Y N	N/A	Y N	N/A	Y N		
Automatic unloading	3.2.7	1A Pg 4	Y N	N/A	Y N	Pg 15	Y N		
3.3 Aqueous film coating system									
Agitated mobile vessel	3.3.1	DQDR01	Y N	DQDR01	Y N	DQDR01	Y N		
Solution pump & filtering	3.3.2	1B Pg 5	Y N	45505 PHA 10/3/03 PG7	Y N	Pg 16	Y N		
Solution flow meter	3.3.3	7F Pg 21	Y N	45505 SCN 10/3/03 PG 6	Y N	See PRINTS attach. to FAT	Y N		
Spray system	3.3.4	2B Pg 12, 1C	Y N	DQDR23	Y N	Pg 16	Y N		
Control, tubing	3.3.5	2C Pg 12	Y N	N/A	Y N	Pg 16	Y N		

Figure 4. The verification table.

process and final product quality parameters characterization, a list of monitoring parameters required with their specific measuring units, as well as start and end point restrictions for the process. In addition, all sorts of process related connections like vacuum, atomization, gas blanketing, treated air and steam, all with their associated cleanliness classifications.

- **Cleanability:** Definitions of required cleaning methods and options such as Cleaning in Place (CIP) or Washing in Place (WIP). Separated or integrated skids, as well as drainable features and additional side storage tanks are part of the requirements.

- **Automation:** Internal company standards, instrumentation required for the control parameters. Special features description such as alarm management, historical and batch data recording with HMI languages, and access level definition for automatic processes.

- **Materials of Construction:** Specifications for surface finishing grades of direct contact parts, gaskets, and lubricants where necessary.

- **List of Drawings:** This section contains a list of all necessary drawings for the project such as a floor plan (initial layout), process flow diagrams, and data sheets specifying services and surrounding conditions for support systems at the room level, where appropriate.

- **Glossary:** A straightforward list of all used acronyms in the entire text.

- **Appendices:** Technical and commercial appendices as part of the URS specify site conditions of work, plant utilities, maintenance and piping requirements, electrical and safety standards, packaging, marking, shipping, invoicing instructions, and all non-disclosure agreement conditions.

Moreover, it is highly recommended to insert a dedicated appendix for Validation Requirements. Vendors should be encouraged to fully address the Validation Requirements, as to commercial terms alike. This special appendix should contain:

- a Project Quality plan from the vendor
- a compliance declaration to 21 CFR Part 210, 211, and 11 for software controlled systems
- traceability for material certificates for all direct contact parts and surface finish tests, where applicable
- welder credentials, welding certificates, and procedures for high purity tubing systems under boroscopy inspection regime
- layouts, elevation, and instrumentation drawings
- demarcation diagrams
- IQ/OQ/PQ and FAT protocols
- calibration certificates for critical instrumentation
- operating and maintenance manuals with spare parts list

Additional guidelines for a successful URS:

1. Process Related Issues
   The effective text will clearly distinguish between the actual required specifications from the product or process limitations, which are most likely known by the user. When delineation is not comprehensible, vendors may overlook the specifications due to their own responsibility restrictions upon the product, as further illustrated in real-life cases.

2. Formatting
   In order to make it qualifiedly workable, the URS contents must be systematically marked making them traceable by the paragraph level. This means not bulleting, but numbering all sections, items, and sub-items in a simple, but logical way. It is worth mentioning that well established vendors in the market have their documentation practices not often changed. Consequently, differences between an owner's well organized URS and the vendor quote format will be found. As was pointed out in section URS x RFP, the structured URS approach will definitely help the qualification exercise making it an efficient traceability work, as required.

What to look for in the RFP?

There are additional important issues, neither technical nor process related, to be addressed before placing the PO. They are a mixture of purchasing and logistics activities, i.e., after sales service, payment conditions, transportation and crating, non-disclosure agreements, and so forth. As mentioned before, all these items are out of the design qualification scope of the present model. In practice, after bid analysis, the technical proposal of the selected vendor is usually attached to the commercial PO, thereby transforming it into an official RFP. With that in mind, attention should be placed before, but close to the PO placement on the following:

- working volumes, capacities, minimum, and maximum batch sizes
- safety issues, dust explosion classes, equipment dimensions, and system interfaces
- RPMs, speeds, loading, unloading, flow, and nominal production rates
- filtering efficiency, heating, cooling, and pressure specifications
- materials of construction for direct contact parts
- alarms, interlocks, manual, and automatic control features
- data recording, HMI languages, and parameter exportation
- all peripheral equipment specifications

What to look for in the DDS?

By following the verification table, but before approving the proposed detailed design, the qualification exercise should verify the following:

- The detailed manufacturing drawings in all mechanical features and legends. Where possible, refer them to the specifications of previous documentation.
- The Process and Instrumentation Diagrams (P&ID) in their details namely, numbers, codes, symbols, names, units, and process.
- An instrument list by tracking it on working ranges, units, calibration traceability, accuracy, and physical accessibility (production or technical areas) of each item, as it would seem defined in the original URS and confirmed at the RFP documentation.
- A detailed description of all the Sequence Of Operations (SOO), sometimes called Functional Requirement Specifications (FRS) that reflects the automation and control conditions of the URS in all logical aspects. This document should be provided in a traceable matrix or available index as the base for software development and qualification.
- All possible out-of-specification situations with associated alarm messages quoted at the written word level.
- HMI screen definitions according to the company standards where available for words, colors, fonts, and language.
- Hardware, software, and firmware detailed specifications (each of these should be a separate document).
- Software development procedures and a CFR Part 11 compliance gap analysis with software deliverables as per the validation appendix of the URS.

What to look for in the FAT?

This is the last design qualification step. It takes place after the actual FAT is performed so that it has the advantage to be based on the actual testing results. A detailed FAT checks documentation, equipment operating ranges, surface finishing grades, software controlled outputs, and process outcomes in cases where a placebo/product test is performed. Previous work published[8] is recommended for those readers who are interested in getting prepared for a detailed FAT. Since an acceptance criterion is tangible and measurable at this point of the project for its features, it becomes straightforward to make the GO/NO-GO decision during every test. However, as a preparation sub step, the design qualification should focus on the extent of the tests by previously checking the FAT vendor protocol versus the initial URS, as well as all the deviations that occurred during the earlier RFP and DDS design phases. If the vendor has no FAT protocol available, it should be developed by the user. At last, the FAT report is qualified by the crosschecking technique. Those tests considered to have failed or not performed due to tight budget/scheduling constraints will be recorded in the DQDR and transferred to the IQ/OQ/PQ protocols. Such procedure concludes the design qualification lifecycle.

A New Pharmaceutical Plant Case Study: DQ Real-Life Examples and Lessons

A DQ project using the present model was implemented over a span of one and half years on 13 major pieces of processing equipment, three critical systems, and two building facilities for a new 250,000 sq. ft. [23,000 m^2] OSD, liquids, and ointments plant in the Israeli pharmaceutical industry. The qualification staff comprised of two validation engineers (one for equipment and one for critical systems and facilities), and a team leader. The responsible committee had representatives from QA, Maintenance, Engineering, Production, and Technology. Table B shows in the Design Qualification part the number of deviations for 11 pieces of processing equipment and one critical system. Some cases had minor deviations gathered into only one DQ report. A total of 478 reports were recorded on the finalized projects listed in the table by the qualification start date.

After a case-by-case examination, all the reports were intentionally dichotomized into two categories: technical deviations and process related deviations. Records for the technical deviations category related to mechanical and manufacturing discrepancies such as incorrect drawings, outstanding dimensions or fittings at detailed design, unexpected different construction materials, change in surface finish grades, omitted safety standards, modified filtration levels, missing parts or tooling, and incomplete engineering documentation, and even substitution of pre-approved models for parts used during assembly at pre-delivery inspections. The process related category, in turn, recorded deviation reports for items such as omission on control features, modified automation aspects, unfinished software, misplaced instrumentation, incorrect performance capabilities, inaccurate flow specifications, partial sequence of operations, lack of interlocks, missing alarms, HMI inconsistent screens, altered failure safe definitions, inflexible feeding rates, nonadjustable filling volumes or rotating speeds, pressures, loading/unloading rates, inappropriate working ranges and scales.

An extensive evaluation of these real-life examples resulted in the following remarks which are well worth mentioning:

Inappropriateness and Similar Deviations among Different Suppliers

Vendors alike did not confirm specific system output performances such as spray rates, air velocities, differential pressures, speeds, yields, and have overlooked explicit working ranges for product temperature. Moreover, cycle times, endpoint of process control, or interlock fail safe protections have been omitted from the technical part of most proposals, even with full product characteristics information available. This range and number of incompatibilities do not necessarily imply low quality level on the work performed by the vendor side. It is the combination of two facts: the first is that screening out the project design under magnifying lenses at its earliest stage may generate premature DQ reports. The second is the exaggeration on requirements set by users that

naively expect to find solutions for their current production troubles on the new technology. This situation calls for sharpening the URS contents, as previously mentioned. The participation of technological personnel in the DQ responsible committee ensures process expertise inputs and avoids setting requirements out of the vendor's capabilities and scope.

Converging Trend

The number of deviations found decreases as the project advances for each qualification project. This expected, but quantitatively concluded, converging trend occurs due to the fact that fewer design modifications are raised as the project nears the installation phase. It is also likely that internal or outsourced design engineers will keep to the user definitions as they participate in the screening qualification committee. The result is fewer deviations along the project pipeline.

Steady Ratio between the Number of Technical and Process Related Design Deviations

With two exceptions only, all three qualification steps had the total number of deviation reports of the technical category superseded by a twofold trend in the number of deviation reports for the process related category. This ratio suggests emphasizing the attention on the technical manufacturing issues more then to its production and process features at least during the early stages of the project.

Model Consistency and Adaptations

Table B contains conclusive facts for projects with finalized design qualification. Other projects like Compressed Process Air, Material Handling, Process and Stability Rooms underwent the same roadmap model of Design Qualification. Their similar, midway results obtained by the time this article was written confirmed the usefulness of the model.

However, the model presented, due to its flexible nature and simplicity, can be used for complex supporting utilities and API production systems as well as with very small adaptations. For example, mechanical issues of HVAC systems are tested separately from their off-line software development, while the duct subsystems are not tested until air balancing starts close to OQ. Since all these issues are being handled by different suppliers at different dates, it ends up with a multidimensional DQ inside one single project. This illustrates the need for further break down of the three major crosschecks into sub steps with different milestones for each.

Added Value

DQ is the first step in the qualification process. When properly performed, it has the biggest cost saving potential for the project. Table B also shows the percentage estimated on direct and indirect costs associated with every DQ deviation for each project budget, reflecting the cost benefit achieved by this activity. A 12% added value shows the impact for savings, giving a clue to management decisions when to start involving validation personnel in the project. The figures have proven – the sooner the better.

Organization

To help accomplish the DQ program at the completion of a new facility design, it is highly recommended to employ a skilled validation engineer to lead the DQ responsible committee. However, he must work independently of project managers, who may jeopardize the design qualification work in favor of tight schedule interests.

Future Qualification Phases

In the major sense, the technical and processing issues raised during design qualification correspond to installation and operational issues, respectively. The deviations found for both aspects of the system provide at an early stage potential contribution for developing protocols aiming the 'en-route' validation phases: Installation and Operation Qualifications. In a quality oriented environment the information transfer from DQ to IQ/OQ/PQs leaves motivation and space for extension of the presented methodology.

Concluding Remarks

The objective of this article was to provide a model with tools capable of supporting the design qualification process from strategy to report. Although changes are likely to be inevitable during design, the "right first time" aspiration concept in the whole pharmaceutical industry will benefit from the use of this model in the following:

1. the basics for establishing a flexible and justified policy for design qualifications
2. the practical way of dealing with design deviations by a simple and methodical technique
3. the approach that keeps the essence of the facts and avoids unwanted retroactive URS corrections or cumbersome change control procedures early in the project, but ensures full traceability at the design phase
4. the controlled documentation of rationales for required regulatory justifications of design changes
5. the documented evidence that the defined "intended use" of a system or equipment is maintained from the start and is followed all the way through the natural project design milestones

In the long run, the methodical approach for DQ as presented will provide evidence of early overall compliance and maximize the cost benefits of the efforts put into validation from the beginning of the project.

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Project Management of Automated Systems Validation

by Jim Verhulst

This article focuses on validating process automation systems for a typical batch biopharmaceutical project and presents new ways to think about organizing the effort. In addition, it defines a typical framework of related documents needed for success, and describes new practices and tools needed to manage the inherent complexity of these projects.

Introduction

Several years ago, the project director for a large construction firm told me that automation work really scared him. He knew a great deal about building the other aspects of the project from previous experience, but how to control the automation team was a mystery. Worse yet, he continued, the automation system would have to be validated[1] in some way. This unfortunately, is the case for many project managers I have met. Because of all the technical jargon, they feel very uncomfortable with an important part of the construction process, not realizing that it is in many ways similar to putting together the concrete, steel, and process piping with which they are familiar. Automation systems also are specified, designed, and tested prior to their use in the facility. Data flows and storage facilities are similar to fluid flows and holding tanks in that there is a need to provide capacity and to prevent contamination in both worlds. The big difference to project managers is visibility. They can readily see progress and test quality when dealing with tangible components. Software is too often invisible and its status and quality assessment requires the opinions of yet more "software types." The ready availability of straightforward tools and techniques that make software visible and testable would go a long way toward bringing software into the project mainstream.

I also have met Quality Assurance and Validation Managers who, because they did not really understand how automation systems get designed and built, felt uncomfortable with developing an automated system validation strategy.

Because of the specialized and technical nature of the work, automation projects, which are usually sub-components of much larger construction projects, are often assigned to computer programmer types. These people may be new to project management and have only limited experience with processing equipment. The QA and validation personnel assigned to

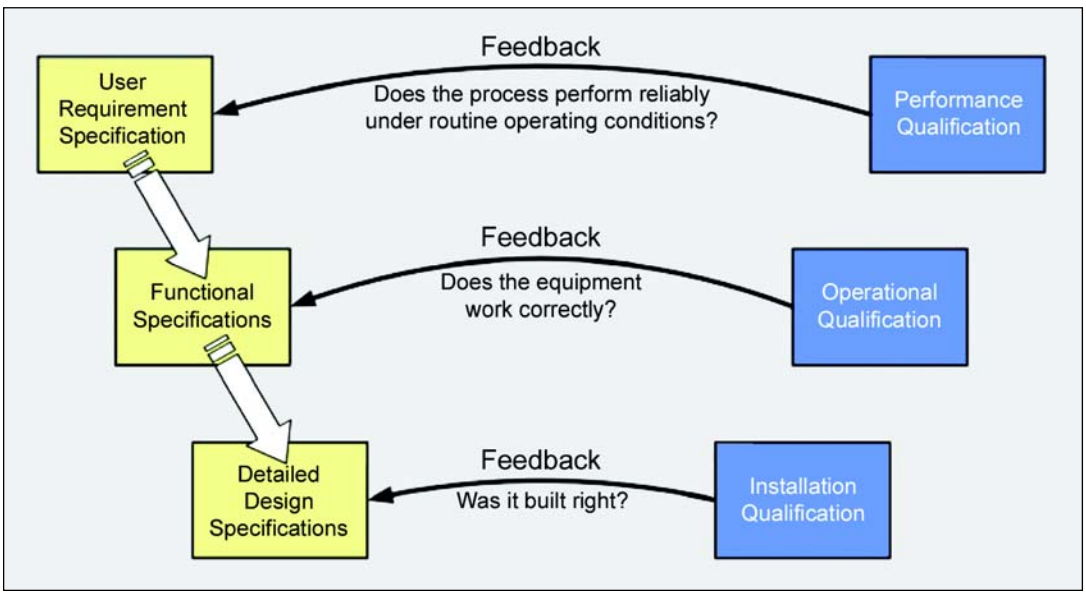


Figure 1. Feedback and the GAMP waterfall.

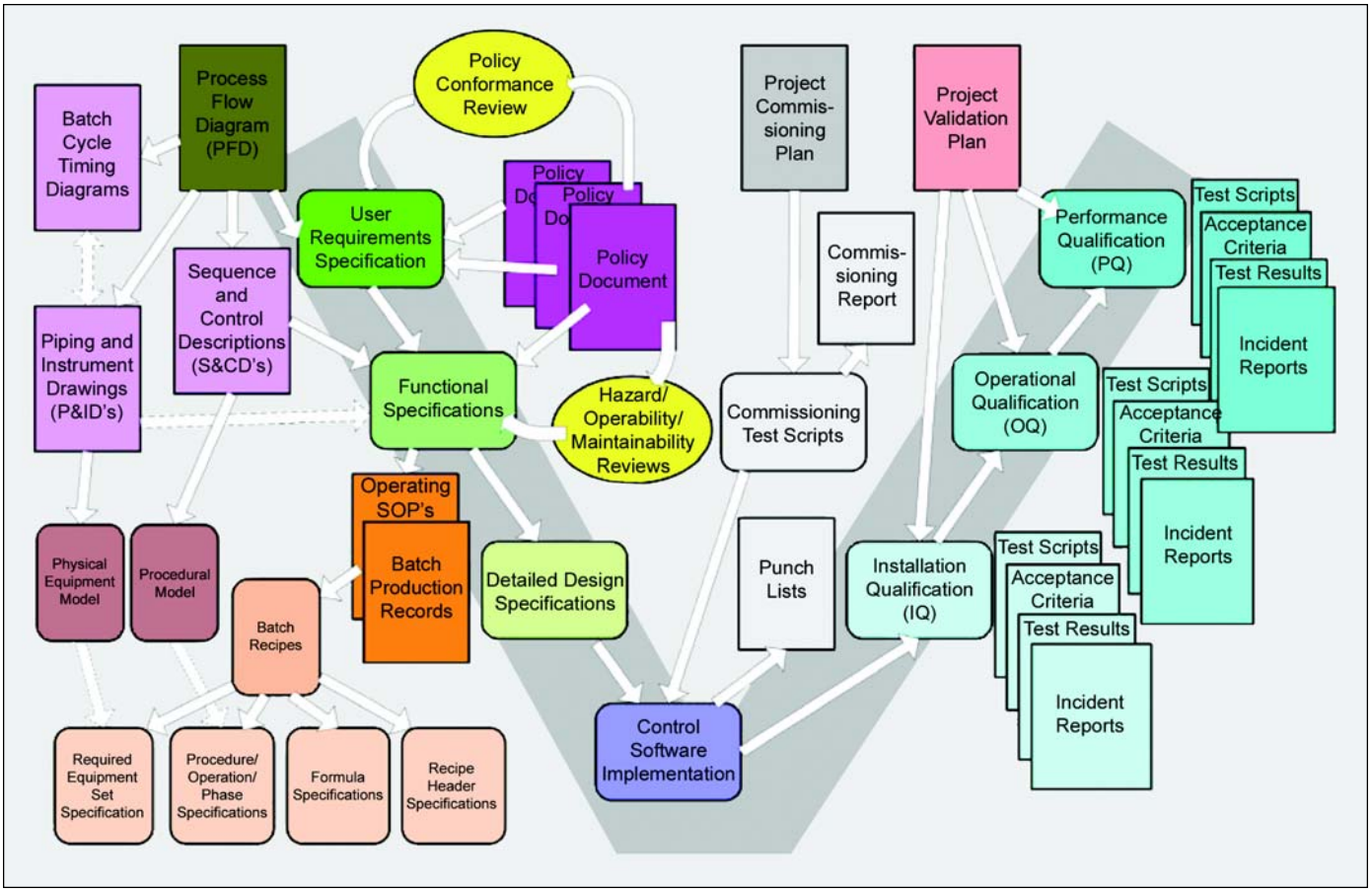


Figure 2. Additional necessary project documents.

the project also may lack experience, especially with large, integrated automation installations.

Automation Projects

Like other kinds of construction projects, an automation project has to meet defined schedule, cost, and quality standards. Because automation equipment and systems become integral parts of the physical manufacturing equipment they control, they can significantly impact the profitability, throughput, operability, maintainability, and safe operation of the finished production facility.

Projects we have studied vary greatly in achieving those objectives. The usual complaint is that the system is late, closely followed by validation of the system is both late and over budget. Both of these problems can be traced to incomplete and hurried project planning. It is fairly common to hear things like, "Let's get started, we'll figure out the validation part later." These are crucial mistakes and will become clear below.

Generally accepted project management practice organizes project activities into phases such as design/review, procurement/delivery, and commissioning. Each project phase has its tasks and resource requirements. Project management for the automation area should be consistent with the rest of the project. Each project phase has its deliverables. With software, these deliverables are usually documents. The preparation of a document for every specification and every test of that specification is actually a project task requiring appropriate resources.

The project also must interface with the existing organization. In general, the corporation for which the project is being built (the Owner) has in addition to the Engineering, Maintenance, and Production functions, Quality Assurance, Regulatory Affairs and Validation Departments. These three have somewhat different responsibilities. Although this may be done differently from one Owner to another, in general:

Quality Assurance (QA) is responsible for:

- ISO 9000 style auditing and review that asks the questions: "Do the entities being audited have appropriate and comprehensive procedures and are they following them?"
- batch records review prior to product release
- Quality Control (QC) - primarily laboratory analytical bio/chemistry tests and controls
- document management and control

Regulatory affairs is the primary interface to the FDA, especially with regard to notification of process or equipment changes and their impact on sterility, purity, potency, stability, and efficacy.

Validation is often a part of Production or Engineering although it may report to QA. Cases could be made to have Validation report to Regulatory Affairs (more familiar with FDA) or even the Owner's Legal Department because the

Validation Group is, in fact, developing the basis of a legal defense, should it ever be required. Validation responsibilities include:

- developing documented evidence that will stand up in a court of law by writing and executing IQs, OQs, and PQs
- enforcing Change Controls to maintain the validated state

The capital project has its own Quality Management function that is responsible for:

- design and documentation reviews
- monitoring construction activities
- project change control/developmental change control (usually considered pre-validation change control and good engineering practice)
- Factory Acceptance Test (FAT) and Site Acceptance Test (SAT) commissioning tests

Obviously, a capital project will proceed more smoothly if each group understands the charter and scope of the others. Commissioning (done by the project team) should lead logically to Validation (the responsibility of the Owner). The QA batch records review group should work closely with the project programmers who are developing the batch reports. QA should be allowed to critique the software development activities to assure that proper procedures are being followed.

Writing automation software for a biopharmaceutical facility is, in the simplest case, the task of configuring a Configurable, Off-The-Shelf (COTS) software application to produce a system with the desired characteristics. Simple configuration is rarely the case. Most systems are combinations of COTS configurations and custom software scripts and code. But for the most part, the project's engineers and programmers get to stand on the shoulders of giants, so to speak, which are the vendor companies who have invested considerable time and effort to produce the COTS software.

This article does not address the development or testing of the COTS software itself. However, the tools used by firms building COTS software are worth considering. Most large-scale software development efforts use complex and very competent tools that have been around for decades. The problem for a capital project manager is that these tools are often too expensive and take too long to learn to use effectively. There are very few mid-sized tools available. Cost and schedule constraints often leave the project manager with homegrown applications that may be incomplete and lack vendor support.

It's time to re-think current practices and to find better ways of doing things. Better tools are clearly needed, especially for larger capital projects. Project managers must be able to quickly measure construction progress against schedule. They also want to be able to determine the suitability of the software designs and code modules that have been produced to date so that if rework is required, it can be put into the project schedule and budgeted.

Several firms are starting to supply new and right-sized software tools that help make automation software development more accessible. The tools do this by providing the complete list of tasks, specifications, schedule milestones, and the progress of software testing. This visibility is the first step in controlling the project. Project managers and automation engineers both know that you can't control what you can't measure. As you also will discover, managing the complex relationships between documents and sections of documents is the key especially when the inevitable changes occur. Careful selection of tools is required. The real gains are not to be found in reducing the clerical effort with new tools, but rather in having a real-time overview of project progress.

One of the advantages to the use of automated tools is that they can become a "leave-behind" that enable operations and maintenance personnel to continue to track and control an automation project throughout its entire lifecycle.

Having said all that, better tools are only a part of the solution. The path forward also requires a clear understanding of the tasks at hand and the practices needed to organize and execute them. Many project managers only learn the full extent of the problem sometime during the project. By then it is too late.

GAMP® 4 to the Rescue

ISPE's GAMP 4, a Guide to Good Automated Manufacturing Practice,[2] is a big step forward in formalizing a framework for the design and qualification processes. It promotes a consistent, practical approach to developing, installing, and operating compliant systems, which meet regulatory requirements. Here is a little background on the approach.

The Design-Test Result Feedback Concept

Feedback is a core concept in both GAMP 4 and in automation design although it may be known by different names. Feedback is well known to all automation engineers because the term is the original basis of automated control systems. For control systems, the idea is to measure a process variable, compare it to a desired value, and calculate the difference between the two. This difference is known as the error. The control system then changes the value of a separate system variable, (one that affects the process variable), to reduce the error to zero. The concept in lay terms goes like this:

- If the shower feels too hot, reduce the flow of hot water until the desired temperature is reached.

The use of feedback in GAMP 4 is indicated in Figure 1. Here, the term is related to the pass/fail status of the validation test execution and the related deviation and remediation reports. It is important to note that validation and automation engineers are both employing the same feedback concept, even though it is being expressed using different words.

Extending GAMP 4 Thinking

As good as GAMP 4 is, there is still more work to be done. To begin with, GAMP 4 has a narrow perspective, that is, it tends to define all process automation systems as isolated services,

much the way a database server operates.

Next, and this is hardly a criticism, GAMP 4 is limited in scope. The GAMP Forum wisely chose to address only regulatory issues (a good decision or they'd probably still be writing GAMP 4). Most projects involve many more document types beyond those pertaining solely to regulatory concerns. Figure 2 illustrates this point. (Consider this diagram, which explains a medium sized batch control project to be a superset of the things a smaller project should at least consider to see if any of the documents apply. However, Figure 2 also could be a sub-set of a large project with many integrated systems.)

Note the limited coverage (indicated with the light gray background in Figure 2) that GAMP 4 provides for a typical batch automation project. Although additional specifications and recommendations have been published since, the original GAMP 4 V-Model had significant limitations for a real world batch control project. Among these:

- The methodology works well for a single system, but it does not address system-system integration. There is no mention of specifications that are meant to cover a number of related systems.
  - All systems should be built from the same parts and pieces if possible. For example, using the same version of only one database manager, even though the databases and database applications may be different.
  - where systems are meant to work together as complimentary parts of the same puzzle
  - where systems must co-exist on the same network or computer hardware

- No mention of rapid prototyping practices,[3] iterative design and development, or other life cycle models.

- Little mention of safety, maintainability, operability, or design reviews.

- Little mention of commissioning tests.[4]

- No interface with S88 batch systems components. (ANSI / ISA S88.01 is an international standard describing batch process control terminology).

- No mention of corporate and project policies that impact writing the URS and the test plans.

- Limited advice on change control procedures. All projects must accommodate several levels of revision and changes as the project is defined.

The good news is that the recently published GAMP Good Practice Guide: Validation of Process Control Systems, addresses some of these issues:

- Factory and Site Acceptance Tests (FAT and SAT)

- safety reviews

- design reviews

- system interface design issues

The ISPE Baseline® Guide on Commissioning and Qualification[5] also helps to fill some of these gaps. It "focuses on the engineering approaches and practices involved in providing facilities in a timely manner that meet their intended purposes." The Guide describes the organization and content of the Commissioning Plan document and provides guidance on the management and execution of commissioning activities such as inspection, start-up, adjustments, performance testing, training, turnover, and close-out.

It should be mentioned here that software testing is a commissioning activity that should occur even in a non-GMP implementation. The GAMP V-Waterfall works well here too because it develops the relationships between specifications and test content and provides the basic acceptance criteria for the commissioning tests. Recognizing this, many firms now employ rigorous commissioning prior to validation. Problems found during commissioning are handled under developmental change control and do not generate the complex paperwork of a qualification incident or validation deviation.

Project Management Challenges

Automation project managers are often confronted with challenges that are the result of fast-track execution. Recognizing these issues early on and developing strategies to deal with

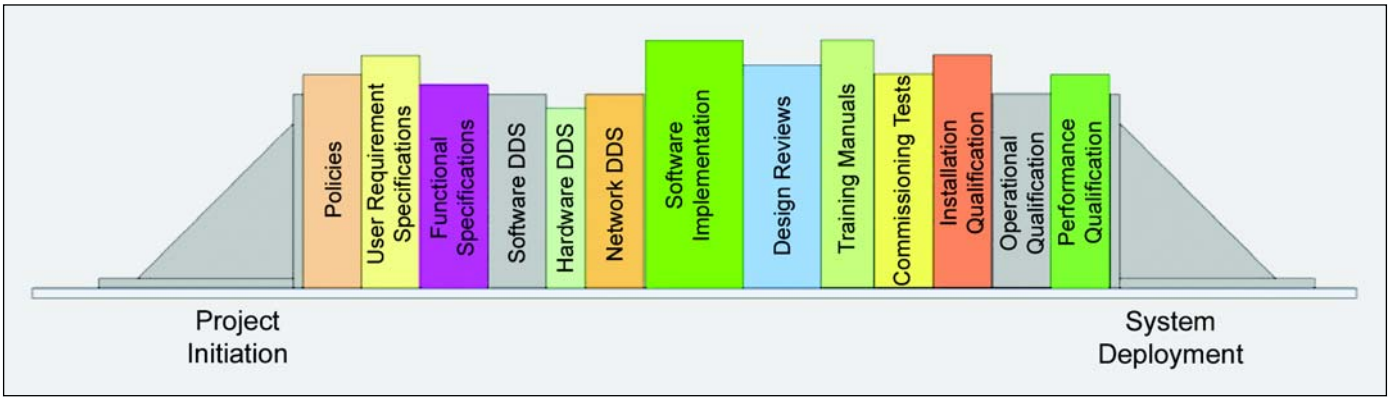


Figure 3. Project bookshelf.

them are key to success. As explained in the paragraphs that follow, these include:

Incomplete Design Specifications

Automation project managers often need to work with incomplete and preliminary information. Some of this is caused by the process design itself. Process development specialists working toward yield and purity goals in the lab often have the latitude to change conditions, even late in the game to meet these targets.

Design Policies Not Clearly Established

Manufacturing facilities are complex, integrated entities in which the interests of all the various stakeholders must be balanced for efficient operation. The role and importance of high level policies in achieving this balance are explained in detail later in this article.

Change Control Strategy

Specification changes ripple down through the construction project as either specifications that are late or specifications that change once they have been defined. These changes often affect other facets of the project design and impact cost and schedule. Obviously, a well established and efficient change control process is mandatory for a well run project.

Testable Requirements and Specifications

Writing test plans should be, in large measure, the task of efficiently organizing the test execution so that the tests demonstrate the desired functionality of the equipment. In fact, most of the time is spent figuring out what the specifications actually mean so that comprehensive and quantitative tests can be written. We sometimes find tests that have no basis in the specifications, and often that is the result of incomplete or vague specifications. The GAMP 4 Requirements Traceability Matrix (RTM) addresses this issue. The problem is keeping the RTM up to date in the face of design changes. Knowing this up-front, the project manager can assign sufficient staffing and buy the right software tools to keep the RTM current and useable.

Automation and the Project Critical Path

Another reason project managers worry about automation is that experience has taught them that automation commissioning is almost always on the project critical path. And this makes sense. Simulation can help, but automation and control strategies cannot really be finished until all the wiring is done, all the transmitters calibrated, and all the control parameters are adjusted for the irregularities of the real world. The goal of the automation project manager is to make that part of the critical path as short and predictable as possible. No offense meant, but most computer programmer types are not very good at commissioning since they usually lack the process and equipment experience. Again no offense intended, but QA and validation types often lack both the computer science and process backgrounds. Commissioning and qualification of automation systems will fall to a rather specialized, multi-discipline group if the project schedule is to be maintained. These resources may be difficult to find.

Project Bookends Concept

This is a very simple, yet often overlooked principal. Every well run project has clearly defined objectives. Satisfying these objectives is the finish line for the project. Knowing when the objectives have been accomplished is a key measurement for any project. Obviously, the specifications and the acceptance tests should come in pairs, which can be thought of as bookends. The project's defining documents are the left bookends on the project timeline. The commissioning tests, validation tests, and project evaluation documents are the right bookends.

Automation tasks rather naturally form the specification - test pairs described. For example, if a design specification says that the display screen background color shall be navy blue, the test asks whether the screen background color is navy blue. If a control sequence dictates that valve XV-1003 should open at a particular point, the test verifies that the valve actually opens. (This is not to imply that writing the specifics of just how to perform the test is simple; it often takes skilled and knowledgeable people to design these tests. But this process starts with knowing which tests must be performed).

Bookends also bring accuracy and closure to project estimates. Project managers can now see all the tasks between the start and finish lines and can deal with them appropriately. Automation tasks and tests are now de-mystified and brought into clear view where they can be staffed, scheduled, cost estimated, and managed.

The Project Bookshelf

Compiling all the specifications and tests into usable documents results in a project bookshelf that looks something like Figure 3. Getting consensus on not only the specifications, but also for the tests and the acceptance criteria by which the tests pass or fail, is of critical importance.

- Completing the IQ is important to sub-contractors who want to be paid at mechanical completion.
- Completing the OQ is normally the most financially significant milestone for the construction project managers. It is at this point that ownership of the facility usually passes to the operations and maintenance groups.
- The PQ and the corresponding process validation are the most significant for the Owner team that will obtain a license to operate the facility to be able to sell product.

These tests and their acceptance criteria have to be decided up-front. Needless to say, a project manager will be in a poor negotiating position with the sub-contractors if the acceptance tests are added or changed later on in the project.

The URS is not the Top Design Level Document

Because the User Requirements Specification for an automa-

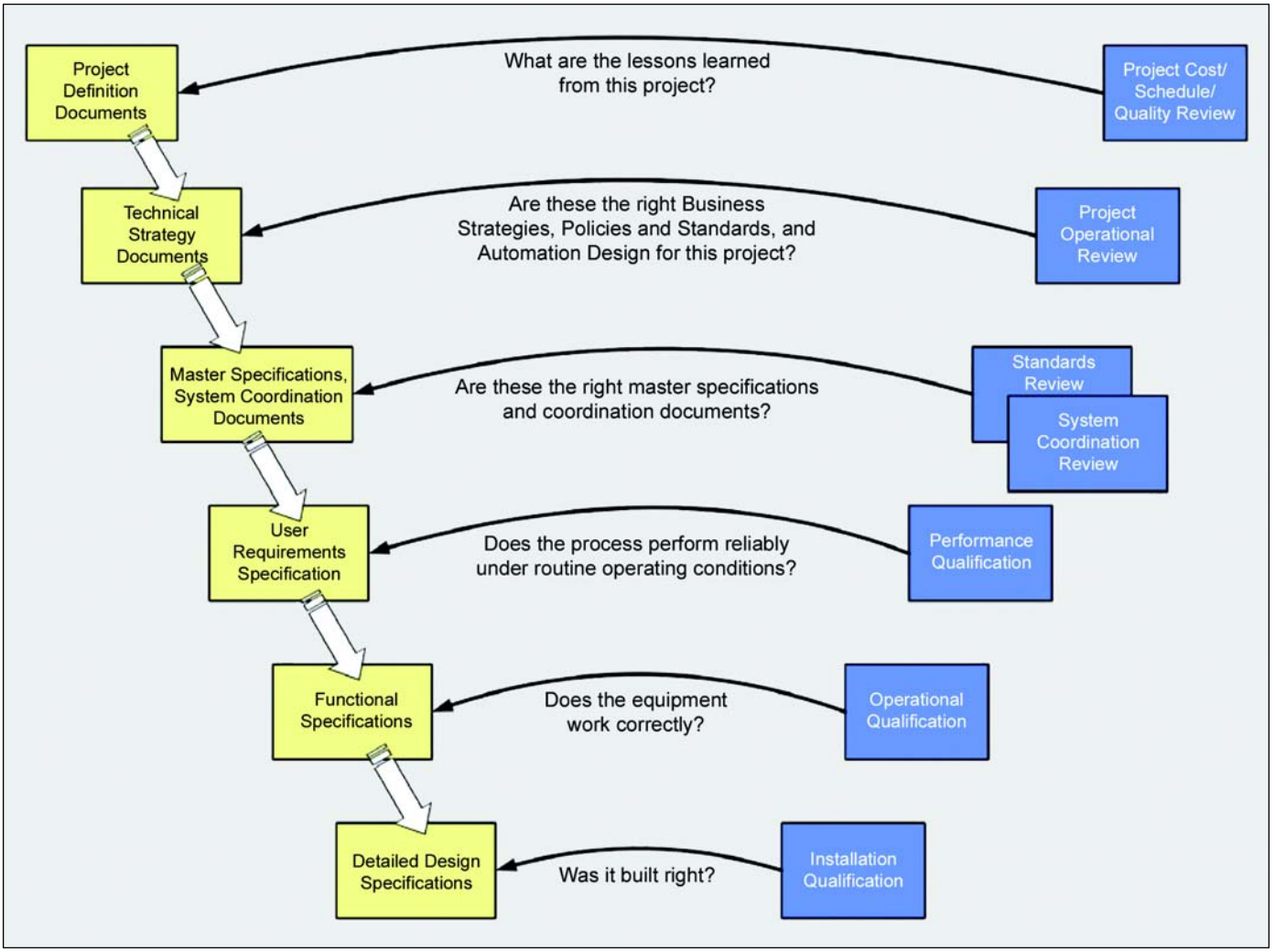


Figure 4. Six layer waterfall diagram.

tion system is such an important document, design engineers and project managers often hurry to start writing it. However, all User Requirements Specifications need to have a traceable basis and solid justification or they will be subject to change once the project is underway.

A URS is actually driven by the documents in three levels above it. I will call them the Project Definition Documents, the Technical Strategy Documents, and the Master Specifications, System Architecture Design, and the Coordination Documents. However, there is no consensus on this nomenclature. The new levels are shown in Figure 4.

The feedback concept is used in these upper levels as well. In the biopharmaceutical world, feedback at the upper levels may be called review, critique, lessons learned, project evaluation, or benchmarking.

These three new upper levels need to be defined and codified before the writing of the URS can begin. A draft URS may identify where additional upper level decisions, documents, and policies need to be defined.

For the project manager, these layers can be thought of as a project workflow that progresses from top to bottom as shown in Figure 5. Please note that the FS and DDS levels shown in Figure 4 have not been shown in Figure 5, only for clarity.

As can be seen in Figure 5, there are many more documents to be considered beyond those described by GAMP 4. (Note how the URS for the Process Control System, located in the lower center of the diagram, is overshadowed by all the other required tasks, policies, and documents). Here is a list of typical documents:

Project Definition Documents

- business operational requirements
- enterprise-wide design policies
- project authorization, organization, and schedule

Technical Strategy Documents

- Business operational strategies, e.g., the project will include a production scheduling functionality.

- Project specific design and operating policies. These policies are derived from the appropriate enterprise-wide policies and adapted to this specific project. There could be as many as 50 different policy documents that may be needed for a large project. Some of these may already exist and may be re-used from other projects. Others may have

to be created from scratch. There are at least 12 different types, or classes, of policies. For example, control system design, record-keeping, and simulation policy classes may all be needed. Policies are working documents for all the stakeholders where agreed-upon decisions that need to be applied uniformly across the project can be stipulated. These policies form the basis and justification for decisions made in the layers below.

- Sized process and utilities definitions (sometimes called the basis of design). These usually start as sized Process Flow Diagrams (PFDs) and Utilities Flow Diagrams (UFDs). The Process and Utilities Piping and Instrument Diagrams (P&IDs and Utilities P&IDs) are derived from the PFDs and UFDs. The design engineers recognize that process and utilities designs have much in common, have numerous mechanical interfaces, and should employ the same construction techniques if possible.

- The plant master electrical design describes, among other things, the distribution and location of motor control centers and whether bus communication technologies will be used. It also describes the standby power system (often called emergency generators), and the Uninterruptible Power System (UPS), and the plant electrical and instrument grounding systems.

- Automation and control strategies are normally broken into three parts according to ISA/ANSI S88.01 conventions: S88 recipes, the S88 physical model design concepts for both process and utilities (closely related to the P&IDs), and the S88 procedural model. This last model describes the control algorithms and processing sequences to be used by the automation system.

Master Specifications and System Coordination

- The Master Specifications and System Coordination (MS/SC) documents level is a meta-layer that defines the relationships between multiple automation systems and specifies practices and components that should be used by all systems if possible. Documents in this layer:
  - Establish common specifications for equipment and systems to simplify training and reduce the variety and number of spare parts.
  - Specify compatible components of a larger design, e.g., a Supervisory Data Acquisition and Control (SCADA) system and a data historian.
  - List components from different systems that must be able to coexist, e.g., the same version of a database manager installed on shared hardware.

- Master Specifications exist in two forms, each with their own revision histories:
  - Master Specification templates that are used to derive Master Specification instances. Templates are revised based on project experience so that the templates are ready to use for the next project. This is analogous to the control of most of the other specifications - one wants to learn from experience.
  - Master Specification instances initially contain short-lists of products and services from approved vendors. These will become part of the Request for Quotation (RFQ) to these vendors. These general specifications will be refined to detailed specifications, suitable for procurement from the selected vendor, later in the project once the technical and commercial reviews of the bids have been completed.

- Examples of Documents in the MS/SC meta-layer:
  - system architecture diagrams (often modeled as UML diagrams to show system-system interactions)
  - list of preferred or allowed database management software
  - preferred or allowed document management systems
  - network architecture diagram
  - preferred or allowed computer hardware suppliers
  - preferred motor control center equipment

New Tools, New Thinking

Several companies are building and selling new document management tools to help manage automation project complexity. However, some re-thinking of current practices and project execution strategies also may be needed.

Clarify the Meaning of "Quality"

An old joke among project managers, when referring to the cost/schedule/quality triad is "Pick two of three." You can have price and quality at the expense of schedule, and so on. New thinking on project quality leads one to a simple rule for quality - that all quality measurements must be quantifiable. This in turn leads to the conclusion that quality becomes "It meets the spec, end of discussion." There are many advantages to this way of thinking:

- tight specifications can be bid accurately by knowledgeable sub-contractors
- accurate bids yield realistic schedules
- commissioning and validation personnel cannot introduce new or vague interpretations

The price, of course, is that this puts a significant burden on specification and test writers early in the project. This definition is also at odds with most rapid prototyping concepts. But knowing this in advance, resources can be found and allowances can be made. More discussion of this point is included below.

A New Paradigm for Project Design

The planning for any new automation project should consider multi-system design to be the norm. This implies a clear definition of how the systems are related and how data passes from system to system. Multi-system design should define topics like system interfaces, data custody and quality, reliable operation and communications (especially when one or

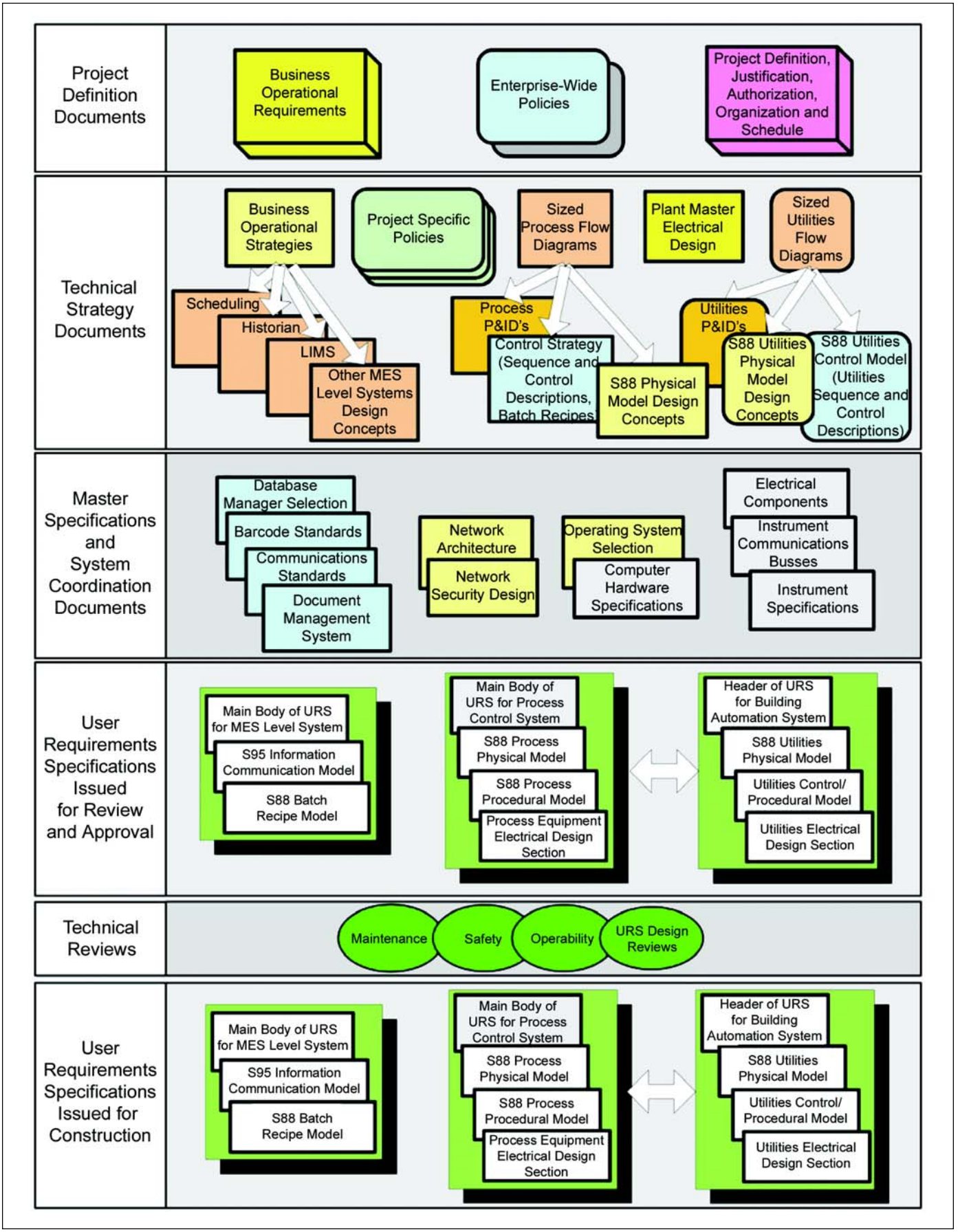


Figure 5. Examples of upper layer documents.

more components may be temporarily unavailable), and US FDA 21/CFR Part 11 compliance.

New project planning also should extend the GAMP 4 Requirements Traceability Matrix (RTM) to the upper level documents. This will assure that each specification has proper definition and justification.

Emphasize writing testable specifications. Avoid using vague terms that are difficult or impossible to test. For example, "Report generation will not affect the operation of the rest of the system." Substitute the following, for example, "The server shall be sized so that the Central Processing Unit (CPU) Usage, as shown on the system performance screen, does not exceed 70% load while generating the XYZ report".

Staff up early to be able to do all the top down planning required during the design phase. It often takes time to assemble a project team. Many project managers, aware of long delivery times for some equipment items, favor putting resources on design activities and wind up in the position of saying "Let's get the design and procurement phases started, we'll figure out the commissioning and validation later." The left bookend is in place, but right bookend is undefined. This unfortunately can lead to open-ended costs, uncertain schedules, and vague staffing requirements for commissioning and validation; not what anybody wants.

Get consensus from stake-holders early on in the design phase. Focus on the primary documents first. For example, the use of policy templates to formulate project policies raises questions early in the design stage that may otherwise arise late in a project. While the project is running, these policies serve as impartial referees when disputes occur between stake-holders. Master Specifications and Coordination documents make clear how the various parts of the project puzzle all fit together and avoid incompatibilities once the multiple systems are integrated together.

Include all commissioning and validation activities in the list of project tasks to produce a complete, reliable, and manageable project schedule. If every specification has a corresponding test, project commissioning and validation costs and schedules can be accurately estimated. Having a complete project schedule is very important to upper management and to project managers who have to staff the project.

Recognize that in an automation software project, the preparation of a document for every specification and every test of that specification is actually a project task. Each document is a quantifiable entity.

Most document preparation tasks can be estimated accurately from past experience, but in some cases, a rapid prototyping approach is justified. Special handling is required for these.

- Significant allowances must be used for poorly defined, or first-of-a-kind efforts, and it is important to know which documents these are
- Identifying difficult tasks and their place in the critical path, often leads project designers to substitute standardized, proven technologies for critical tasks
- If there are instances where rapid prototyping is appropriate, these need to be identified early, and placed near the beginning of the schedule so that there is time to write the detailed specifications and tests.

Knowing which documents are what degree of difficulty helps project managers to prioritize tasks and focus on justifying and obtaining experienced resources to reduce risks of these documents being late or inaccurate.

A New Validation Paradigm

A new paradigm for validation may be required to reduce the time and cost of validation. This will change the roles and timing of the validation effort somewhat.

- Quality/validation personnel must be involved from the beginning of the project.
- Project management must find ways to break down the "engineering discipline" walls between QA and engineering if these exist.
- The design engineers should write most of the tests because they understand the underlying principals and assumptions.
- Quality personnel will move to support and audit role where their input is primarily on the "testability" of the specifications and auditing the procedures used by the design engineers.
- Validation personnel should assist with the commissioning effort, as this is in many ways a "pre-function" for the validation activities.
- Validation personnel should be in charge of the execution of the qualification activities. Obviously, this has to be done in coordination with Engineering and Production personnel to ensure safe operation during the tests.

New Group Collaboration Tools

Most biopharmaceutical concerns have been using the industry-standard document preparation and management tools[6] for some time. Many firms also use newer group-oriented software tools and databases. These are useful and several have gained broad acceptance. However, the next generation of tools needs to go further to:

- fully Web-enable collaboration
- support the full system lifecycle[7]
- allow the requirements traceability matrices to be generated automatically as contributors from multiple locations work on the web of interrelated specifications and acceptance tests
- manage the six (or possibly more) layers of documents described in Figure 4
- be extensible and adaptable to be able to handle future revisions of GAMP (but that's a topic for another article)

Conclusions

At first glance, project management of automation systems development and validation, (and by association, GAMP 4), appears to be complex and arcane. The purpose of this article

has been to help explain the concepts involved. Automation validation projects can be considered variations of more commonly understood projects, such as piping and equipment installation, because the same basic principals apply. Some new thinking (or re-thinking) is required, but experienced design engineers and commissioning and validation personnel are already familiar with the processes involved.

New tools will be helpful in promoting needed visibility and these will become available as the industry moves to more standard practices. One of the advantages to the use of standardized procedures and automated tools is that they can become a "leave-behind" that enable operations and maintenance personnel to continue to track and control an automation project throughout its entire lifecycle.

The author does not claim to have the final word on this complex topic. On the contrary, my hope is to inspire further dialog and discussion that will move the field forward.

Many thanks to the reviewers who helped to direct and refine this article.

Glossary of Terms

CBER - US FDA Center for Biologics Evaluation and Research

CDRH - US FDA Center for Devices and Radiological Health

GAMP 4 - A Guide to Good Automated Manufacturing Practice produced by the GAMP Forum, ISPE Community of Practice

ISPE - International Society for Pharmaceutical Engineering

S88 Batch - ANSI/ISA S88.01 standard describing batch process control terminology

URS - User Requirements Specification

FS - Functional Specification

DDS - Detailed Design Specification

IQ - Installation Qualification

OQ - Operational Qualification

PQ - Performance Qualification

UML - Unified Modeling Language

Software Validation - In the FDA document "General Principles of Software Validation; Final Guidance for Industry and FDA Staff," dated January 11, 2002 and issued by CDRH and CBER, the FDA defines software validation as: 'confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.'

References

1. The term Validation is used here to mean Installation, Operational, and Performance Qualification.

2. *GAMP 4, Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.

3. Rapid prototyping can be used to develop a concept, test machine performance, data throughput, and to refine the specifications. However, to be successful, rapid prototyping should only be used to develop and refine specifications. Otherwise, rapid prototyping can be at odds with top-down design.

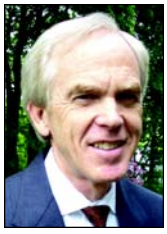
4. The term Commissioning is meant to be a broad parallel of the mechanical commissioning activities. These normally include the pre-operation activities (e.g. inspection, mechanical adjustment, loading of lubricants, motor rotation checks, piping leak tests, etc.), and the start up activities that involve the gradual application of load and the measurements made while running under load for a period of time.

5. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.

6. Microsoft® Word™ and Excel™ are commonly used. Documentum™ from EMC Corp. is perhaps the best-known document management system, but there are many more, some of which are more appropriate for smaller projects. Adobe® Acrobat™ with its Portable Document Format (PDF) also is widely used for document review and distribution.

7. Software and system lifecycle normally includes the following phases: Planning, Specification, Design, Implementation, Testing, Deployment and Acceptance, Documentation Turnover, Ongoing Operation, and Archiving when the system is retired.

About the Author



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Microwave Extraction of Antioxidant Components from Rice Bran

by W.H. Duvernay, J.M. Assad, C.M. Sabliov, M. Lima, and Z. Xu

This article discusses the assessment of extraction temperature and time for the microwave extraction of rice bran oil and vitamin E yield.

This article represented the South Central Chapter as a finalist in the International Student Poster Competition/ Undergraduate Level Division held at the 2004 ISPE Annual Meeting in San Antonio.

Background

The effects of extraction parameters, extraction temperature and extraction time were assessed for microwave extraction of rice bran oil. The objectives of the research were: to effectively extract rice bran oil from rice bran using microwave assisted extraction and to analyze the influence of temperature and extraction time on the rice bran oil and vitamin E yield. Results showed that the extraction time had a minimal effect on the vitamin E and rice bran oil yield at all temperatures. Temperature, on the other hand, had a significant effect on the oil and vitamin E yield. More vitamin E was extracted at 140°C (P less than 0.05.

Introduction

Rice is a primary source of food and nutrition for billions of people around the world and is an important global economic factor. Louisiana is one of the largest rice producing states in the nation. The total value of rice produced on Louisiana rice farms in 2002 was 159.6 million dollars. Of this amount, 122.8 million was the gross farm income, the money made directly from selling the processed rice. The remaining 36.8 million was gained from using the by-products of the rice milling process.[1] The husks and the bran account for the largest amount of these by-products. Today, most rice farmers sell their bran as animal feed. Farmers could increase their rate of return if they could sell the bran to the food industry and/or pharmaceutical companies which would be able to utilize the antioxidants for health purposes. If the vitamin E and other antioxidants can be extracted from rice bran, this would maximize profits and allow for a more complete utilization of the rice by-products.

Rice bran is of interest to the pharmaceutical industry because it contains 15-20% oil by weight with high concentrations of vitamin E components (tocopherols and tocotrienols). Crude rice bran oil is composed of 88 to 89% neutral lipids, 3 to 4% waxes, 2 to 4% free fatty acids, and approximately 4% unsaponifiables.[2] Vitamin E components exhibit antioxidant activity and are proven to have various medical benefits which include reducing cholesterol levels, decreasing early arteriosclerosis, and preventing heart disease.[3] The components of vitamin E include alpha-tocopherol (aT), alpha-tocotrienol (aT3), gamma-tocopherol (gT), gamma-tocotrienol (gT3), beta-tocopherol (bT), delta-tocopherol (dT), and delta-tocotrienol (dT3). The vitamer of greatest interest in nutrition is the most biopotent one, alpha-tocopherol.[4]

Two major extraction methods conventionally used to extract vitamin E components from rice bran are Soxhlet extraction and solvent extraction. Solvent extraction is the most com-

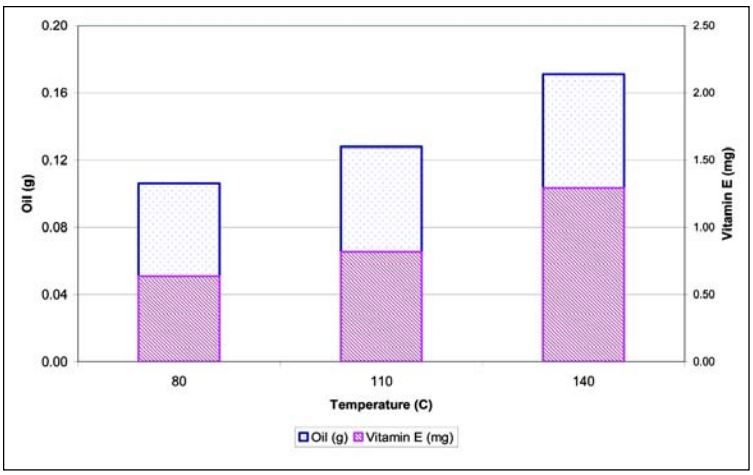

Figure 1. Oil and vitamin E components extracted per gram of rice bran at different temperatures (80, 110, 140°C) for 15 minutes at a 3:1 solvent:rice bran ratio.

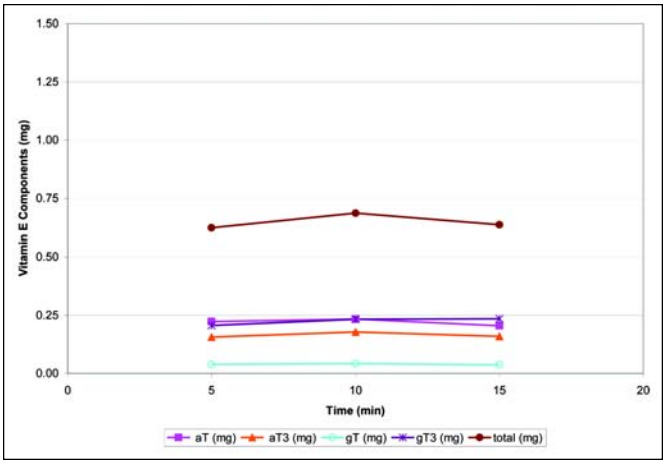

Figure 2. Vitamin E components extracted per gram of rice bran for different times (5, 10, 15 minutes) at 80°C with a 3:1 solvent:bran ratio.

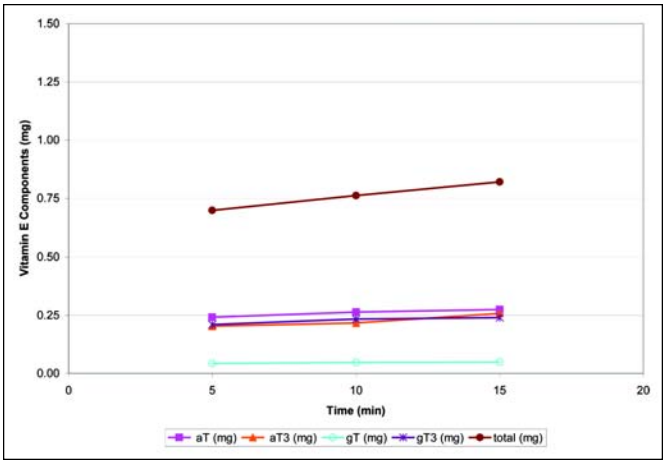

Figure 3. Vitamin E components extracted per gram of rice bran for different times (5, 10, 15 minutes) at 110°C with a 3:1 solvent:bran ratio.

monly used batch method that is applied to extraction of lipids from foods. It involves mixing of the substrate matrix with the solvent at the extraction temperature for a predetermined extraction time. Soxhlet extraction is performed by repeatedly washing the solid with an organic solvent, usually hexane or petroleum ether, in a glass apparatus during reflux. Disadvantages of the solvent and Soxhlet procedures include long extraction times, and large solvent volumes needed.

Microwave-assisted extraction is a novel process that uses microwave energy to heat the solvents and the sample to increase the mass transfer rate of the solutes from the sample matrix into the solvent. The combination of solvents and heat is expected to increase the extraction yield as compared to other methods.[5] Because of the heat produced, microwave-assisted solvent extraction takes 10-30 minutes, whereas the other methods can take hours or days to complete. The amount of solvent used in microwave extraction is also considerably less than the amount used in the other extraction processes.[6]

Microwave-assisted extraction is a relatively new extraction technique and has been successfully employed to extract tea polyphenols and tea caffeine from green tea leaves,[7] piperine from black pepper,[8] capsaivinoids from capsicum,[9] phenolic compounds from grape seeds,[10] puerarin from Radix puerariae,[11] and color pigments from paprika.[12]

The goal of this project is to use microwave extraction as means to effectively extract vitamin E components from rice bran. The objectives of this research were 1. to extract rice bran oil and constitutive vitamin E components from rice bran using microwave extraction and 2. to study the influence of processing parameters, temperature and time, on the vitamin E yield.

Materials and Methods

Rice bran was obtained by milling 11.4 kg samples of Cypress rice with a pilot scale rice mill located within the Biological and Agricultural Engineering Department at Louisiana State University. The pilot scale system of unit operations in order consists of a paddy husker with separator, a rice whitening machine, a wet polishing machine, and a color sorter. The first two unit operations of the mill were used to produce rice bran samples with a roll gap distance of 1.5 mm (husker) and a flow rate of 123 g/s (whitening machine). Samples were used immediately after milling.

Samples of 20 g freshly ground rice bran were prepared in 3:1 isopropanol to bran ratios. Isopropanol (a polar compound) was used as the solvent because polar solvents were proven to absorb microwave energy better than non-polar solvents. The samples were placed in one of three pressure controlled Teflon vessels included in the Microwave Extraction System along with a magnetic stirring rod. Once the extraction was complete, the samples were allowed to cool for 10 minutes. A vacuum pump was used to filter the solvent and oil mixture from the rice bran and the volume of each sample was recorded.

A 5 ml portion of each sample was stored in a sealed, opaque container and placed in a refrigerator to minimize exposure to oxygen, light, and heat. Finally, the isopropanol was evaporated from the sample and the remaining oil was analyzed for Vitamin E components by normal phase High Pressure Liquid Chromatography.[13]

Microwave System

The Microwave Extraction System chosen in the present research allows for control of pressure, temperature, and energy input. It contains up to six pressure controlled Teflon vessels which are placed on a rotating platform. A motor driven magnet is used to spin stirring rods inside each of the vessels and consequently mix the sample. Multimode irradiation evenly distributes heat throughout the samples as they rotate inside the cavity. The temperature inside the microwave system is measured using a fiber optic sensor with a gallium arsenide crystal tip and a protective tube inserted directly into one of the three vessels.

Statistical Analysis

The experiment was designed as a two-factor (time and

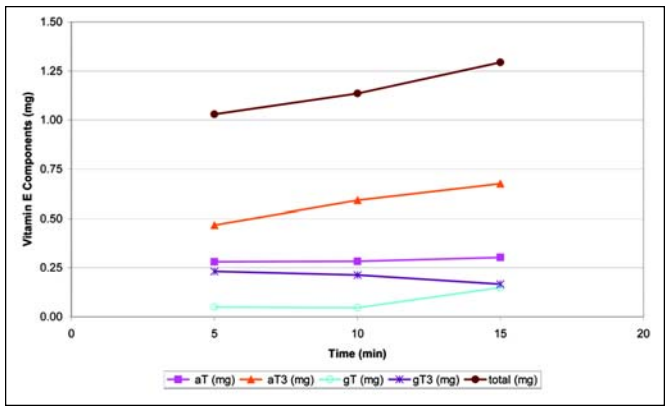

Figure 4. Vitamin E components extracted per gram of rice bran for different times (5, 10, 15 minutes) at 140°C with a 3:1 solvent:bran ratio.

temperature) factorial treatment structure with three levels for each factor and two replications for each treatment combination. The experimental data was analyzed by a two-way procedure. Multiple comparison tests were performed to determine the significant difference between treatments at $P < 0.05$.

Results and Discussion

The influence of processing parameters, extraction temperature and extraction time on the amount of oil and vitamin E components, alpha-tocopherol, alpha-tocotrienol, gamma-tocopherol, and gamma-tocotrienol extracted was assessed - *Figures 1, 2, 3, and 4.*

Influence of Temperature on Oil and Vitamin E Yield

Oil and total vitamin E components extracted per gram of rice bran at different temperatures (80, 110, 140°C) for 15 minutes at a 3:1 solvent: rice bran ratio were measured - *Figure 1.* As temperature increased, oil yield and vitamin E yield increased. As temperature increased from 80°C to 110°C, oil yield increased by 0.02g (from 0.11g to 0.13g), an 18% increase. A 31% improvement (from 0.13g to 0.17g) occurred when the temperature was increased to 140ºC. Vitamin E yield increased across this temperature range as well. From 80ºC to 110ºC, 0.2mg (33%) more vitamin E was extracted. A more significant change of 0.5 mg (63%) was observed when temperature was increased from 110°C to 140°C.

Influence of Extraction Time on Vitamin E Yield

The influence of extraction time on the amount of vitamin E components, extracted per gram of rice bran at 80°C was analyzed. The mass of all four vitamin E components, including the target component alpha-tocopherol, showed minimal changes as the extraction time increased from 5 to 15 minutes for all temperatures. This lack of increase shows that maximum yield can be achieved in only 5 minutes at this temperature.

Vitamin E components extracted per gram of rice bran for different times at 110°C is illustrated in Figure 3. Over the 10 minute time range the vitamin E yield improved from 0.70 mg to 0.82 mg at 110ºC, an increase of 17%. This differs from the samples extracted at 80°C because of the noticeable rise in vitamin E extracted at each time interval. However, there was no significant difference in the amount of vitamin E extracted between 10 and 15 minutes, indicating that a 10 minute exposure time is ideal at this temperature.

Figure 4 shows the amounts of vitamin E components extracted per gram of rice bran for different times at 140°C. The vitamin E yield increased from 1.03 mg to 1.29 mg by increasing extraction time from 5 to 15 minutes. This is a 25% increase compared to that observed at 110°C. The maximum yield of 1.29 mg was found to occur at 15 minutes. The mean yield at 140°C was determined to be 1.15 mg, the largest of the temperatures tested. At lower temperatures, extraction time had minimal affects on the vitamin E yield. However, as extraction times were increased at higher temperatures, greater vitamin E yields were produced. The higher amount of vitamin E extracted at higher temperatures may be explained by a disruption of the physical structure of the source material which would increase diffusion rates and result in a yield increase.

Statistical Analysis

Statistical analysis of the results (Table A) showed a significant increase ($P<0.05$) in the amount of oil extracted at 140°C as compared to the 110 and 80°C treatments (for 5 and 15 minutes extraction time). Vitamin E yield increases significantly by increasing the temperature from 110 to 140°C for all extraction times. The 80 and 110°C treatments were not significantly different from each other.

Solvent Extraction versus Microwave Extraction

The oil extraction yields obtained in this study were comparable to those found in the literature. Isopropanol extracted oil from rice bran was reported to be in the range of 16.3% and 17.2% (% of rice bran).[14] By microwave extraction, 10.40% oil was extracted at 80°C for 5 min and 17.12% was extracted at 140°C for 15 min. In terms of vitamin E yield, the minimum amount of tocopherols extracted by microwave extraction

Time (min)	Temp. (°C)	Crude Oil (g/g rice bran)	Vitamin E (mg/g rice bran)
5	80	0.104 ± 0.004^{a}	0.624 ± 0.002^{a}
	110	0.105 ± 0.024^{a}	0.697 ± 0.191^{a}
	140	0.150 ± 0.027^{b}	1.029 ± 0.108^{b}
10	80	0.108 ± 0.004^{a}	0.686 ± 0.012^{a}
	110	0.140 ± 0.020^{a}	0.762 ± 0.006^{a}
	140	0.149 ± 0.015^{a}	1.135 ± 0.100^{b}
15	80	0.106 ± 0.008^{a}	0.636 ± 0.021^{a}
	110	0.128 ± 0.004^{a}	0.820 ± 0.027^{a}
	140	0.171 ± 0.010^{b}	1.294 ± 0.159^{b}

The results are expressed as g crude oil/g rice bran and mg Vitamin E/g rice bran. Significantly different values ($P < 0.05$) of oil and vitamin E in the same column of each time are indicated by different letters [a,b].

Table A. Crude Oil and Vitamin E Extracted with Different Times and Temperatures using a 3:1 solvent:bran ratio.

was 261.8 ppm at 80°C for 5 minutes and the maximum was 453 ppm at 140°C and 15 minutes, as compared to the solvent extracted 343 ppm tocopherols reported by Hu, et al.[2] The amount of tocotrienol extracted by microwave extraction varied between 361 ppm (80°C and 5 minutes) and 841 ppm (140° for 15 min) by microwave extraction as compared to only 265 ppm extracted by solvent extraction.[2] These results show that microwave extraction results in comparable oil yields and higher tocopherol and tocotrienol yields with respect to conventional extraction methods.

Conclusion

Microwave extraction was used to successfully extract vitamin E from rice bran. Over a temperature range of 80ºC to 140ºC, an increase of 104% vitamin E yield occurred. At lower temperature, time had little to no effect on yield, but as the temperature increased, so did the effect of extraction time on the vitamin E yield. Optimum parameters for extraction of vitamin E from rice bran were 140ºC for 15 minutes at a 3:1 isopropanol to rice bran ratio. Microwave extraction was found superior to other methods for obtaining high yields of tocopherols and tocotrienols from rice bran.

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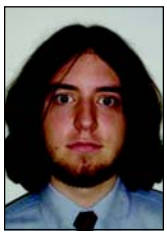
William Hauser Duvernay is currently enrolled as a junior at Louisiana State University in the Department of Biological and Agricultural Engineering. He is employed as a Chancellor' Aid student worker in the bioprocess engineering lab. His interests include pharmaceutical and environmental engineering. Duvernay belongs to both ISPE and AICHE and is currently starting a Student Chapter of ISPE at LSU. He is also the Ag Council Representative for the Biological Engineering Student Organization on campus.



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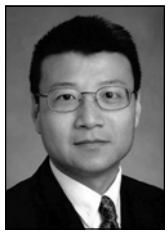
ing Student Organization and she is in the process of starting an ISPE Student Chapter at Louisiana State University. As a new faculty member, Dr. Sabliov plans to build a bioengineering program internationally well known for its innovation, fundamental approach, and industrial applications.

Marybeth Lima is an Associate Professor in the Biological and Agricultural Engineering Department at Louisiana State University; she began her faculty career at LSU in 1996. Her current responsibilities include teaching undergraduate courses in biological engineering and engineering design. Lima's research contributions have included the broad areas of food processing and engineering education. She has authored or co-authored 22 refereed publications concerning food and bioprocess engineering and engineering education. Lima has performed extensive work in engineering education and has pioneered the use of educational techniques such as service-learning and the integration of communication and teaming skills across the biological engineering curriculum. Lima is passionately committed to improving the community through engineering-community partnerships that bring the principles of engineering alive for children and tangibly use engineering to enhance democratic society.



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This article describes the ChPP credential and the next milestone in its development.

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ISPE Professional Certification Program: Raising the Image of the Pharmaceutical Profession

by Jerry Roth, P.E., ISPE Director of Professional Certification

Introduction

The pharmaceutical industry is facing significant issues in its quest to enhance product safety and quality and improve the health of the world population. Some of these issues include regulatory harmonization and compliance, business globalization, and facilitating innovation and efficiency in the research, product development, and manufacturing areas. Consequently, technical pharmaceutical professionals are being challenged to seek new technologies and apply them in a risk-based approach to achieve quality by design. Academia is tuning in to the pharmaceutical industry's specific needs and adapting curricula to better prepare students for making significant contributions to their employers' mission. Government regulators are encouraging a risk-based approach in applying new innovative technologies.

Pharmaceutical professionals involved in the design and operation of product development and manufacturing processes and facilities aspire to attaining greater strides in the industry value chain. For industry to successfully achieve real innovation, these professionals need to merge science with engineering, and apply risk-based approaches to raise the bar on product quality and safety. The professionals that possess a good science-based academic background in addition to diverse industry experience and knowledge can make a significant contribution, if not lead the way, to industry innovation.

ISPE supports the industry innovation trend and recognizes that the pharmaceutical professional can make a difference in the speed and quality of innovation. ISPE is acting as a catalyst for innovation in a number of ways. First, the Society is collaborating with academia to develop curricula focused on industry needs. By providing a platform for teamwork between industry and government, ISPE is promoting better understanding of regulatory requirements and helping companies achieve a higher degree of compliance. In addition, ISPE is implementing a professional certification program to raise the image of pharmaceutical professionals, increase their competency, and provide greater value for their employers.

Objective

Professional certification is the process of conferring a time-limited credential to a professional once it is verified that she or he meets the established criteria. One type of credentialing involves certifying individuals who have been found to meet specified competence and qualification criteria. With its new certification program, ISPE's fundamental objective is to improve competence, quality, and effectiveness for its Members and other pharmaceutical industry stakeholders.

ISPE's Professional Certification Commission (PCC) was established to create a certification program and develop credentials that benefit credential holders and the companies their work for. The first professional certification credential to be offered is the Chartered Pharmaceutical Professional (ChPP).

A Chartered Pharmaceutical Professional:

- Has command of the objectives and methods of the following areas of knowledge: drug development process, quality systems, production systems, facilities and equipment, regulatory issues, materials management

The ChPP credential is the first professional certification to be offered to the global pharmaceutical industry covering research to manufacturing. Not only can the new certification bring recognition and opportunity to the credential holders, but it will provide great value to the industry.

and economics, and information data management and control

- Delivers innovation by synthesizing and integrating diverse input into productive and cost-effective, cross-functional approaches and risk-based solutions.

The next step in developing the ChPP credential is referred to as a job analysis: the process of identifying the knowledge, skills, and abilities of professionals in the pharmaceutical industry in order to determine standards of performance, experience, and knowledge required for the ChPP credential. The PCC will solicit proposals from qualified firms and award a professional services contract for the job analysis by mid-August 2005. Then, the PCC will work closely with these consultants to select the most appropriate methodology for conducting the job analysis. Generally, the job analysis is conducted in two phases: Phase 1, Role Delineation and Phase 2, Assessment Specification.

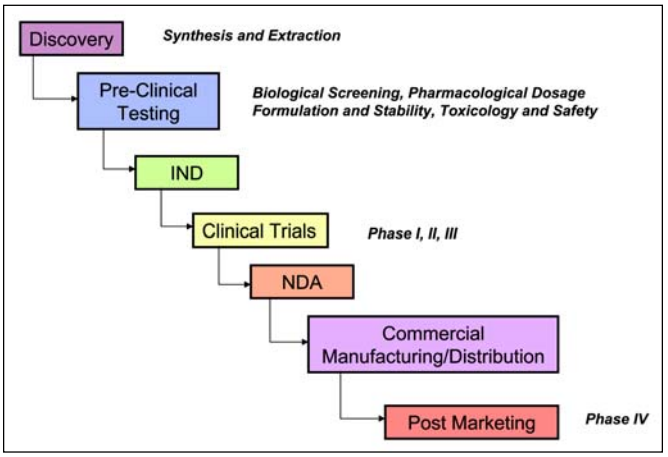

Figure 1. Drug development process.

Phase 1 - Role Delineation

Phase 1, Role Delineation involves defining the key knowledge areas, skills, and experience that will provide standards for the ChPP credential-holder to meet. The PCC and the job analysis consultants will develop an interview questionnaire to be used in telephone interviews with a sampling of employers in which targeted pharmaceutical professionals work. This sampling will be quite diverse, covering all aspects of the drug development process (see Figure 1) including companies that manufacture drug products for the industry, as well as those that supply services and equipment in support of the drug development process.

An additional survey instrument will be prepared to gather input from professional practitioners (ISPE Members and non-members). These data will determine the knowledge, skills and abilities required for competent performance in their jobs. The information collected from telephone interviews and the Internet-based survey will be analyzed by psychometrichons, thereby creating a link between the knowledge/skill sets and the job tasks. This process validates the credential requirements and serves to establish the type of assessment required.

Phase 2 - Assessment Specifications

Phase 2, Assessment Specifications identifies the methods and criteria that provide the determining factors for conferring the credential. There are many types of assessment criteria (education, work experience, continuing education, oral interviews, written examination, etc.) which can be combined to define the qualifications of eligibility for assessment. Both the eligibility criteria and assessment requirements will be the work product of the assessment specifications phase. This document and supporting data is then used in creating the appropriate assessment for the credential.

The professional certification commissioners encourage all industry professional practitioners to participate in the surveys to achieve a good sampling throughout the industry and provide a statically sound data base.

For more information, contact Jerry Roth, ISPE Director of Professional Certification at e-mail: jroth@ispe.org.

Country Profile

A look at the Pharmaceutical Industry in

THE UNITED STATES

Produced in collaboration with ISPE United States

ISPE

Engineering Pharmaceutical Innovation

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US Pharmaceutical Industry: Trends, Paradigms, and Challenges

by Janice Abel, Director, Pharmaceutical Business, Invensys

Market Trends and Challenging Times

According to the Pharmaceutical Research and Manufacturers of America (PhRMA) organization, pharmaceutical products are the cheapest weapon we have in our efforts to reduce overall medical expenses. The value of new therapeutics is immeasurable in terms of saving and improving lives, and as a result, is often underestimated. Pharmaceutical therapeutics strengthen our economy by improving productivity and reducing worker absenteeism. On the other hand, US prescription drugs are the most expensive in the world, and the US spends more money on drugs than the UK, France, Germany, Italy, Spain, and Japan combined. Europe spends 60% less per person than the US due to tough price controls on drugs. US drug prices have risen at about 10% per year which is more than three to five times inflation, causing public concerns in the US.[1] In addition, scandals are erupting on an almost daily basis in the pharmaceutical industry – there are concerns about the efficacy and dangers of several best-selling drugs which have led to product withdrawals and worse. US Government officials are asking for tougher oversight of the drug industry.

This article will provide a factual US market overview that reviews and summarizes the market trends and challenges that are being faced by the industry in the US today. This information on the US pharmaceutical manufacturing market is being provided as an

Pharmaceutical Engineering would like to extend a special thank you to the Chapter Champions who developed the information for this US Country Profile.

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...and a special thanks to Janice Abel for developing the introduction to the US Country Profile.

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US Pharmaceutical Industry: Trends, Paradigms, and Challenges

introduction to the United States Country Profile, which has been developed jointly by ISPE's US Chapters. For the purpose of this profile, the United States was broken down into four geographical regions, and the Chapters located in those regions collaborated on the development of the "regional" profiles. The breakdown is as follows:

Midwest Region

Great Lakes Chapter
(Ohio, Indiana, Illinois, Michigan, Wisconsin, Kentucky)
Web site: www.ispe.org/greatlakes

Midwest Chapter
(Kansas, Missouri, Iowa, Nebraska, Minnesota)
Web site: www.ispe.org/midwest

South Central Chapter
(Texas, Oklahoma, Louisiana)
Web site: www.ispe.org/southcentral

Northeast Region

Boston Area Chapter
(eastern Massachusetts, Maine, New Hampshire)
Web site: www.ispe.org/boston

Delaware Valley Chapter
(eastern Pennsylvania, Delaware, southern New Jersey)
Web site: www.ispedvc.org

New England Chapter
(excluding Boston area)
Web site: www.ispe.org/newengland

New Jersey Chapter
(New Jersey, New York, northeastern Pennsylvania)
Web site: www.ispe.org/newjersey

Southeast Region

Carolina-South Atlantic Chapter
(North Carolina, South Carolina, Georgia, Florida, Alabama, Tennessee)
Web site: www.ispe.org/carolina-southatlantic

Chesapeake Bay Area Chapter
(Washington, D.C.; Maryland; northern Virginia)
Web site: www.ispe.org/chesapeakebayarea

West Region

Greater Los Angeles Area Chapter
(Los Angeles, Orange, Ventura, Riverside Counties)
Web site: www.ispe.org/greaterla

Pacific Northwest Chapter
(Washington, Oregon)
Web site: www.ispe.org/pacificnorthwest

Rocky Mountain Chapter
(Colorado, Utah)
Web site: www.ispe.org/rockymountain

San Diego Chapter
(North to Orange County)
Web site: www.ispe.org/sandiego

San Francisco/Bay Area Chapter
(northern California)
Web site: www.ispe.org/sanfrancisco

Pressures from regulatory agencies, the government, and public pressure to reduce the overall healthcare costs are impacting the US pharmaceutical market. Even with all these setbacks, the US pharmaceutical market is still an excellent performer when compared to other industries.

The US pharmaceutical industry grew at a rate that is estimated to be between 7% and 7.5%, compared to a global growth of approximately 8%. The US is the largest market with 45% to 46% of the total global market - *Table A*.

The pharmaceutical manufacturing industry is a dynamic industry, one of the best to work in – with very low turnover rates. Because of the global economic growth, demographics of an aging population, and the production and demand for newer and more specialized therapeutics, the industry will continue to flourish and remain strong in the US.

Market Segments

From a market perspective, the pharmaceutical manufacturing market can be broken down into separate sub-segments that include generics, biopharmaceuticals, contract manufacturers, and large pharmaceutical companies (medical devices will not be covered in this overview). In 2004, the sales growth of biotech and generics were greater than the total market growth - *Figure 1*. The largest sub-segment growth over the past year at 17% was in the biotech industry. The generics market segment grew by 10%. Generics grew at a slower pace than in previous years; however,

World Audited Market	2004 Sales (US$B)	% Global Sales	% Growth Year-over-Year (Constant $)
North America	248	47.8	7.8
Europe (EU)	144	27.8	5.7
Rest of Europe	9	1.8	12.4
Japan	58	11.1	1.5
Asia (excluding Japan), Africa, and Australia	40	7.7	13.0
Latin America	19	3.8	13.4
Total IMS Audited*	**$518**	**100%**	**7.1%**

Table A. 2004 pharmaceutical sales by region. (Source: IMS Health)

Continued on page 4.

US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Continued from page 3.

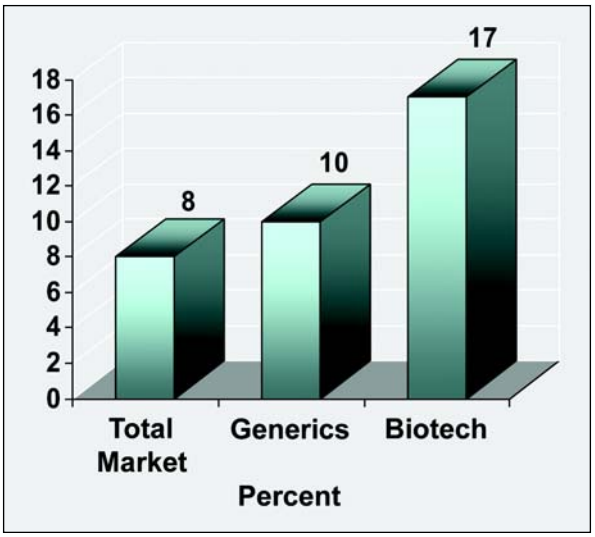

Figure 1. Dollar growth 2004 vs. 2003. (Source: IMS Health)

sales of generics accounted for 30% of the US sales in 2004 of prescription drugs.

Overall, the industry delivered solidly with 31 New Molecular Entities (NMEs) in 2004 which was up significantly from 2003. Eighty-two drugs have sales over $1 billion - defined as blockbusters. This was substantially more than the preceding year. Typically, newer blockbusters are produced from the new biotechnology drugs and target specialty markets such as oncology.

The number one company ranked by healthcare revenue in 2005 and 2004 was Pfizer. The number two company in 2004 by US sales revenue was GlaxoSmithKline, followed by Johnson & Johnson. Also of note is that in the list of top 50 global pharmaceutical companies, many biotechnology companies are now included – such as Amgen, Genentech, Serono, and Genzyme.

Out of the top 50 global pharmaceutical companies (by healthcare revenue), 19 have corporate headquarters located in the US, 18 have headquarters in Europe, 12 in Japan, and one in the Middle East.

Industry Challenges

The following discussion will consider some of the industry sub-segment challenges, trends, and paradigms for pharmaceuticals, biopharmaceuticals, generics, and contract manufacturers. Issues will focus mostly on research, clinical and manufacturing.

According to PhRMA, for each additional $1 spent on newer pharmaceuticals, $6.17 is saved in total healthcare spending. Even new medicines, which cost more, save an average of $111 when compared with other hospital and non-drug costs that are required.

Advances in prescription medicine have immense potential for improving lives. Research and development environments in the US are constantly challenged with potential new scientific discoveries in the life sciences into real products with therapeutic benefits for real people.

Expenditures for R&D in the US pharmaceutical companies are shown in Table C. In 2003, the company with the highest research and development expenditures was Pfizer with $7.13 billion - 37.8% more than in 2002. Pfizer's expenditure was almost twice that of any of its major competitors. Sanofi-Aventis ranked second with $4.8 billion, followed by J&J with $4.68 billion in 2003.

The fastest growing companies, as measured by their growth percentage in 2003 are shown in Table D.

Schwarz Pharma AG, a specialty pharmaceutical company, generated the greatest increase in healthcare and consolidated revenue in 2003 with a 55.3% growth, followed closely by biotechnology company Amgen.

Rank 2003	Rank 2002	Company	Revenue in 2003 ($/thousands)
1	1	Amgen Inc.	8,356,000
2	2	Genentech Inc.	3,300,327
3	3	Serono SA	2,018,617
4	5	Chiron Corp.	1,766,361
5	4	Genzyme Corp.	1,713,871
6	7	MedImmune Inc.	1,054,334
7	11	Gilead Sciences Inc.	867,864
8	8	CSL Ltd.	856,206
9	9	Cephalon Inc.	714,807
10	6/12	Biogen Idec Inc.	679,183
11	10	Celltech Group Plc.	577,328
12	13	Millennium Pharmaceuticals Inc.	433,687
13	14	Genencor International Inc.	383,162
14	21	Acambis Plc.	276,326
15	18	Celgene Corp.	271,475
16	26	Actelion Ltd.	228,589
17	19	Berna Biotech Ltd.	191,227
18	16	Nabi Biopharmaceuticals	176,570
19	22	InterMune Inc.	154,138
20	28	Enzon Pharmaceuticals Inc.	146,406
21	24	Ligand Pharmaceuticals Inc.	141,140
22	65	Neurocrine Biosciences Inc.	139,078
23	36	Cangene Corp.	130,309
24	29	Aeterna Laboratories Inc.	118,756
25	30	ImClone Systems Inc.	80,830

Table B. The 25 global biotechnology companies ranked by healthcare revenue.[2] (Source: Med Ad News, September 2004)

US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Rank 2003	Rank 2002	Company	Healthcare R&D 2003
1	1	Pfizer Inc.	7,131,000,000
2	16/5	Sanofi-Aventis	4,797,560,000
3	3	Johnson & Johnson	4,684,000,000
4	2	GlaxoSmithKline Plc.	4,560,773,100
5	6	Novartis	3,756,000,000
6	7	Roche	3,542,440,910
7	4	AstraZeneca Plc.	3,451,000,000
8	8	Merck & Co.	3,178,100,000
9	10	Eli Lilly and Co.	2,350,200,000
10	9	Bristol-Myers Squibb Co.	2,279,000,000
11	11	Wyeth	2,093,533,000
12	12	Abbott Laboratories	1,733,472,000
13	17	Amgen Inc.	1,655,400,000
14	13	Schering-Plough Corp.	1,469,000,000
15	14	Bayer	1,413,243,500
16	15	Boehringer Ingelheim GmbH	1,330,644,000
17	18	Takeda Chemical Industries Ltd.	1,127,902,691
18	19	Schering AG	1,045,506,000
19	20	Sankyo Co.	799,115,370
20	43	Allergan Inc.	763,500,000
21	21	Genentech Inc.	721,970,000
22	25	Fujisawa Pharmaceutical Co	678,603,023
23	22	Akzo Nobel NV	640,429,000
24	23	Yamanouchi Pharmaceutical Co.	637,670,475
25	24	Novo Nordisk AS	637,234,043

Table C. Top 25 companies ranked by healthcare R&D expenditure. (Source: Med Ad News, September 2004)

Research and Development (R&D) Challenges – Products in the Pipeline

To strengthen the pharmaceutical business and sustain growth, pharmaceutical companies are investing heavily in research and development. The US leads the world in investment of biopharmaceutical R&D. The US accounted for 85% of the total global spending for R&D, growing at a rate of 7% in 2003.

US pharmaceutical companies spent more than $40 billion on National Institutes of Health (NIH), and spent an additional $28 billion on research to develop new and better medicines. European research efforts were recently reduced due to government price controls and cost containment measures for therapeutics with the US being the main beneficiary of this shift in R&D expenditures. As a result of the new controls, according to the European Commission, the US pharmaceutical research companies should gain even more leadership in terms of generating new medicines and will continue to dominate the world market for prescription drugs.

Companies are supporting maturing pipelines with clinical programs in the areas of oncology, neuroscience, and diabetes and metabolic disease. Abbott delivered seven drug candidates from discovery to development in 2003 and has doubled the number of quality drug candidates generated by its discovery operations compared with just a few years ago. According to Med Ad News, Abbott's goal is to get nine candidates into clinical trials each year between 2003 and 2007. New Drug Approvals (NDAs) started to level off in the beginning of this decade; however, NDAs ramped up in 2004 to 92, and 2005 appears to be another winning year with 31 NDAs from January through 17 May 2005.

The biggest challenge faced by companies in research is in getting effective therapeutics to market as quickly as possible, scaling the processes up rapidly, and reducing R&D costs. Streamlining R&D processes as well as manufacturing transfer and scale-up practices will increase productivity. New innovative tools have the potential to reduce development costs substantially.

New tools are being developed for researchers to better evaluate new drug molecules as potential candi-

Rank 2003	Rank 2002	Company	% Growth in 2003
1	---	Schwarz Pharma AG	55.3%
2	2	Amgen Inc.	51.3%
3	16	Pfizer Inc.	39.6%
4	15	Chiron Corp.	38.4%
5	12	Serono SA	31.3%
6	6	Teva Pharmaceutical Industries Ltd.	30.1%
7	22	Genzyme Corp.	28.9%
8	3	Genentech Inc.	27.7%
9	5	Allergan Inc.	26.7%
10	---	Mylan Laboratories Inc./ King Pharmaceuticals Inc.	20.8%
11	8	Procter & Gamble Co.	20.6%
12	1	Forest Laboratories Inc.	19.3%
13	---	Watson Pharmaceuticals Inc.	19.2%
14	37	Novartis	19.1%
15	41	Bristol-Myers Squibb Co.	15.4%
16	13	Johnson & Johnson	15.3%
17	47	Eli Lilly and Co.	13.6%
18	20	Alcon Inc.	13.2%
19	22	Abbott Laboratories	11.3%
20	21	Bausch & Lomb Inc.	11.2%
21	18	Baxter International Inc.	9.9%
22	33	Wyeth	8.7%
23	25	Eisai Co.	8.0%

Table D. Fastest growing companies: growth in healthcare revenue. (Source: Med Ad News, September 2004)

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US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Continued from page 5.

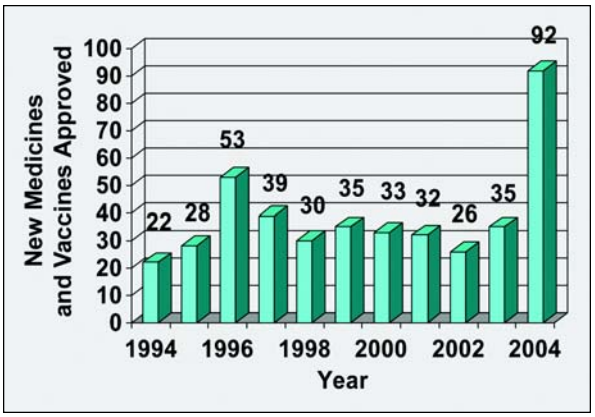

Figure 2. New Drug Approvals (NDAs). (Source PhRMA and Drugs.com)

dates. For example, early toxicity identification and elimination methods will increase efficiencies, and therefore, reduce costs so that energies can be focused on developing more promising biologics (non-toxic). Tools that eliminate toxic compounds and drug safety can be used early in the research process to improve patient safety while reducing costs associated with unproductive initiatives. Previously, animal models and other laboratory techniques were used, but today the focus is on computer-based predictive models using biomarkers (quantitative measures of biological effects that provide informative links between the drug's action and clinical effectiveness), knowledge management, and applying other new technologies to evaluate the efficacy.

Pharmaceutical Challenges – Increase Efficiencies and Reduce Costs

Traditional pharmaceutical companies need to consolidate resources and implement global standards and practices worldwide to improve productivity and efficiency. Larger companies are in the process of integrating functions that were previously separate, such as pharmaceutical research and development, and manufacturing operations into a single global structure with common goals and priorities.

The cost to bring a drug to market is estimated to be well more than $800 million to more than $1 billion with variations occurring from indication to indication and company to company. One fact is obvious, the numbers are very high. If costs keep rising, the possibilities for better-targeted medicines aimed at smaller patient groups will not be readily investigated because investors will not fund indications that will not be profitable. Traditional pharmaceutical companies will continue to invest in ways to operate more efficiently and compete on a global basis. Mergers and acquisitions will continue, but partnerships will be even more prevalent.

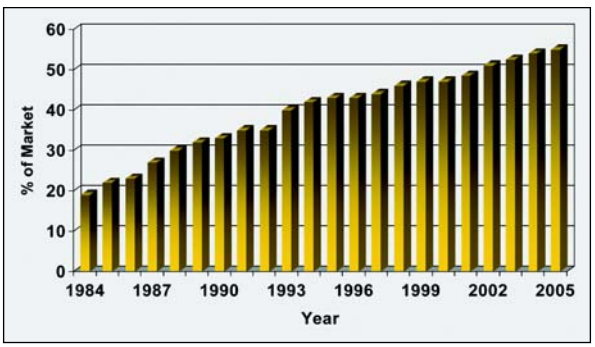

Figure 3. The generics share of the US prescription market continues to increase. (Source: PhRMA, New Medicines, New Hope)

Generic Challenges – Competition, Biogenerics, and Reducing Costs

Under the Hatch-Waxman law – which is the Drug Price Competition and Patent Term Restoration Act of 1984 – generic drugs are expedited by allowing the products to be approved without clinical trials, based on the safety and effectiveness data developed by the original innovator. In the US, the first company to file status for generic versions of drugs that have gone off-patent, has a 180-day period of exclusivity, meaning that only one generic firm, the first to file, can manufacture the product for the first six months after the patent expires. After this period, the drug price generally falls by as much as 80%. The firm must make profits immediately. In the US, the added challenge results from high labor costs compared to other parts of the world, making it difficult to compete globally after the six month exclusivity period. The challenge is to manufacture products as efficiently as possible while maintaining the highest possible quality.

The generic market share is still expanding quite rapidly at a rate of 14% annually. However, the competition for generics is increasing and speed to market is becoming more critical than ever. The first company to launch a generic version of the product tends to capture from 60% to 80% of the market. Globally, governments, health management companies, and insurance companies are encouraging the use of generics to cut healthcare costs. The generic market will continue to grow and help to reduce prescription drug costs in the US.

US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Biotechnology Challenges – Product Development, Clinical Trials, Biogenerics, and Regulatory Requirements

Thirteen of the 67 blockbuster drugs with annual sales more than $1 billion are biopharmaceuticals.[2] Biotech products accounted for approximately 27% of the active research and development pipeline and 10% of global sales in 2004. The US biotech industry is growing at a rapid pace – 17% for 2003 to 2004 – because research and development efforts attributed to strong US patent protection laws.

According to Cutting Edge Information, a business information company, conservative estimates predict that biogenerics will command more than $12 billion of the drug market by 2010.

A recent survey described in Biopharm International asked biopharmaceutical companies why the cost of development of biologics was so expensive. The top three answers were overcoming the technical challenges in product development, costs of clinical trials, and regulatory requirements. The survey also asked this same group how they would reduce costs while maintaining safety, quality, and efficacy of the new biopharmaceutical medicines. Two prominent strategies ranked highest: 1. using 'best practice skills to streamline product development to reduce time and costs,' and 2. developing 'new process technologies that increase productivity.' Thus, utilizing know-how to learn from past experience and utilizing innovative technologies and techniques seem to be the overall strategy for increasing bottom-line profits.

One major challenge to the biogeneric growth in the biotechnology industry is the outcome of the current debate for establishing the equivalency of biogenerics. Should a law be enacted that is similar to the Hatch-Waxman law for the generic manufacturing of biologics upon expiration of a patent? A new law would establish the criteria for bioequivalence and could affect the industry immensely since many of the biologics being sold today are already off-patent or will be in the near future. Proponents believe that biogenerics will reduce the cost of a biological drug, and opponents believe that it is more difficult if not impossible to establish bioequivalence for biogenetics.

According to Arthur Levinson, Ph.D., CEO, Genentech, "Genentech does not believe that the technology currently exists to prove a generic biotechnology product safe and effective outside of the new drug application and biologics license application process. Unlike traditional generics, we believe that differing cell lines and manufacturing processes mean that different manufacturers will make different protein products that are not substitutable."

In the meantime, Europe has already started manufacturing and selling biogenerics.

Contract Pharma Provider Challenges - Staffing, Commoditization, and Reducing Costs

Pharmaceutical companies will continue to rely on both research, clinical, and manufacturing contractors enabling them to focus resources and investments on cores specialties. It is now possible to outsource virtually every function involved in bringing a drug to market and pharmaceutical companies are starting to look at outsourcing as a long-term strategic measure rather than a temporary measure. As manufacturers focus on the process, the manufacturing contract business may slow a little, but research and clinical trial outsourcing will increase in an effort to reduce costs. Some of the challenges the contract provider faces include reducing costs, meeting GMPs as well as other global standards for quality and regulatory compliance, quick scale-up of processes, staffing, and commoditization. In the US, contract manufacturing is a $30 billion business. Pharmaceutical contract manufacturing is estimated to grow to $48 billion by 2008.

Previously, the pharmaceutical industry utilized Contract Resource Organizations (CROs) to get additional manpower when needed; however, contract ser-

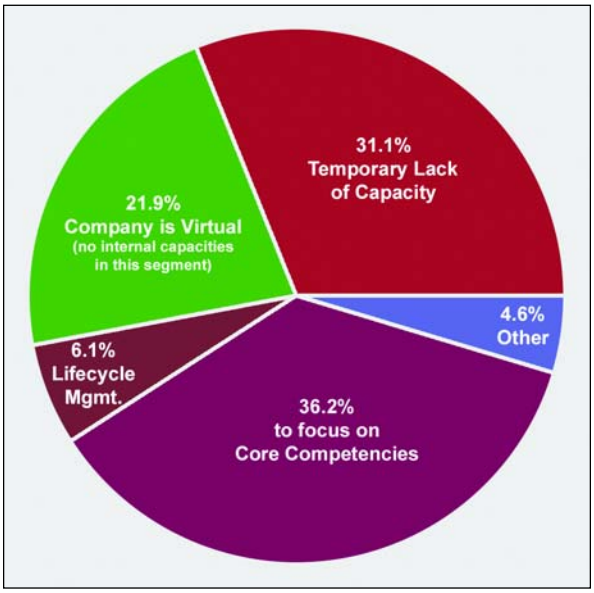

Figure 4. Top reasons for outsourcing. (Source: Contract Pharma, First Annual Outsourcing Survey 2005)

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US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Continued from page 7.

vices are becoming part of traditional pharmaceutical companies' strategy today. In a recent survey conducted by Contract Pharma, 68% of the pharmaceutical/biopharmaceutical outsourcers would describe their relationships with the contract manufacturer as a partnership with 54% stating that the reason for outsourcing was strategic. The number one reason for outsourcing was to focus on their core competencies (strategic), while the second reason cited was due to a temporary lack of capacity (tactical). When determining the outsource manufacturer, the number one reason cited was GMPs. This was followed by technology and third was (lowest) cost as the reason for choosing to outsource. Still, pharmaceutical industry customers are putting substantial pressure on contract providers to reduce their costs. Outsourcing has grown substantially over the past decade and has helped drug companies cut capital investment while preventing capacity bottlenecks, enabling the industry to focus on core competencies.

The US FDA, Regulatory Challenges, Government, and Legal Challenges

Patent Challenges

These are very challenging times for the US pharmaceutical industry with an outcome that will affect us all globally. The generics business will continue to grow and subsequently drive down prescription drug costs. Generic companies continue to debate pharmaceutical patents, and some branded pharmaceutical companies face a substantial amount of patent expirations. The industry continues to pour money into research and development, but only a few companies have been successful in filling their pipelines with innovative drugs and bringing new chemical entities that could turn into successful drugs to market. Even innovative biotechnology products will be impacted by patent expirations if the government establishes bioequivalence for generic biotechnology – which may happen in the next year or two.

Internationally, the US is working to strengthen the intellectual property protection of medicines. The World Trade Organization's (WTO) Trade-Related aspects of Intellectual Property (TRIPS) agreement established minimum international obligations for the patent protection of medicines. Additional work will continue in this area.

When ranking policy actions that would be the most beneficial in providing innovation incentives for intellectual property, two-thirds of executives polled by Ernst & Young say the most beneficial policy is appropriate market exclusivity for branded products.

Some of the patent challenges include the interpretation of the Food and Drug Administration exemption for studies "reasonably related" to a future drug application, and many of these issues are being debated as we write. The current US patent system provides the incentive necessary to continue the development of innovative and valuable research by granting the inventor exclusive rights to control the new product or technology. Patent concerns and legal debates will continue.

Food, Drug, and Cosmetic Act

The US Country Profile would not be complete without a discussion on the US Food and Drug Administration (FDA). FDA regulations are known around the world because any product that makes a medical claim and is shipped into the US must comply with the applicable Code of Federal Regulations (CFR). Since almost half of the therapeutics sold in the world are sold to the United States consumer, meeting US regulations becomes a priority for anyone interested in selling products to the US market. Additionally today, there is also an important initiative being undertaken to **harmonize global regulations**. The US FDA is working with other countries to accomplish this harmonization – which may take several years.

The FDA began when Congress enacted the Federal Food, Drug, and Cosmetic Act in 1937, which required companies to prove the safety of new drugs before putting them on the market. Cosmetics and therapeutic devices also were added to this Act, which has been updated to improve consumer protection. Over the years, Congress has continued to give the FDA new responsibilities. As a result, the FDA has an enormous range of responsibilities that include:

- Reviewing labeling, animal and human testing to assure product safety and efficacy of new products. The FDA tracks how they are manufactured and responds to reports of problems or newly identified risks.
- Ensuring the safety of marketed products by inspecting domestic and foreign manufacturers.
- Monitoring for risks using a scientific approach to ensure that regulatory decisions are sound and assess risk. The FDA initiates corrective actions and legal actions for dealing with problems.

Risk-Based Focus

The FDA uses science-based, efficient risk management in the following regulatory activities so that the Agency's limited resources can provide the most health

US Pharmaceutical Industry: Trends, Paradigms, and Challenges

promotion and protection at the least cost for the public:

- improve health through better information
- enable consumers to make smarter decisions by getting them better information to weigh the benefits and risks of FDA-regulated products
- improve patient and consumer safety
- seek continuous improvements in patient and consumer safety by reducing risks associated with FDA-regulated products
- protect the USA from terrorism
- strengthen the FDA's capability to identify, prepare for, and respond to terrorist threats and incidents
- develop more effective regulation through a stronger workforce
- ensure a world-class professional work- force, effective and efficient operations, and adequate resources to accomplish the Agency's mission
- establish science-based policies and standards
- issue final "Aseptic Processing Guidance"
- issue Process Analytical Technology (PAT) guidance for the pharmaceutical industry
- conduct comparability studies
- facilitate integrated quality systems orientation
- facilitate international cooperation (ICH, European Agencies)
- protect the public health
- 21 CFR Part 11 and Predicate Rules

Risk Assessment

Risk assessment is being used by the FDA and industry to identify, assess, prioritize, mitigate, and monitor the likelihood of the occurrence and impact of risks to product quality, patient safety, and record integrity. This approach is similar to the FDA's approach to the risk-based model that is being used to determine inspection sites (see risk-based model).

cGMPS for the 21st Century Initiative

The cGMPs for the 21st Century is an FDA initiative that was started in 2002 intended to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines.

Objectives of the 21st Century Initiative

- encourage the early adoption of new technological advances in the pharmaceutical industry
- facilitate industry application of modern quality management techniques (quality systems) to all aspects of production and QC
- encourage implementation of risk-based approaches that focus both industry and Agency attention on critical issues
- ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- enhance the consistency and coordination of FDA's drug quality regulatory program
- provide possible guiding principles for the restructuring of the FDA

As part of the FDA's 21st Century Initiative, one of the recent changes made is the FDA's acceptance of using new technologies and the drive to increase efficiencies as part of the PAT Initiative. The final PAT Guideline was issued by the Agency in September 2004. This Guideline is particularly exciting. Many companies have implemented or are implementing PAT type projects or solutions – some even prior to the FDA Guideline.

Process Analytical Technology (PAT)

FDA's focus on PAT is encouraging industry to invest in new technologies and improve product development and manufacturing efficiencies in terms of using more automation, advanced controls and optimization, new on-line sensors, and other exciting new technologies. Some of these technologies are already being used in other industries, but due to regulatory constraints, many of these techniques and technologies were not applied in the pharmaceutical industry. PAT should have a major impact on the industry in terms of innovative methodologies and technologies being used to increase efficiencies in the development and manufacturing areas. As the industry begins to see and measure the results of these initiatives deployment efforts for PAT solutions will increase dramatically. PAT should enable industry to reduce time to market, reduce the regulatory burden, increase efficiencies, decrease costs, and fundamentally change the way industry measures and tracks business performance.

Risk Ranking Model

As regulators and consumers intensify their scrutiny and global competition accelerates, pharmaceutical companies are being forced to adopt ever-more exacting measures to evaluate and manage risks. According

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to ARC's John Blanchard, "The FDA's new risk-based model has arrived, giving the industry additional incentive to develop enhanced process understanding, improve process control, and implement more extensive risk mitigation techniques." The new model takes into account potential product risks, potential processing risks, as well as risks the facility might pose. The results of the model are expected to be used to determine 50% of the sites to be inspected in each district in 2005.

Bioterrorism Act

The events of 11 September 2001 reinforced the need to enhance the security of the United States. Congress responded by passing the Public Health Security and Bioterrorism Preparedness and Response Act (the Bioterrorism Act), which President Bush signed into law 12 June 2002.

The FDA and Customs and Border Protection (CBP) Compliance Policy Guide (CPG) describes the strategy for maintaining an uninterrupted flow of food and drug imports while improving their safety in accordance with the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.The purpose of the Bioterrorism Act is to protect the health and safety from an intended or actual terrorist attack on the nation's food and drug supply. Provisions of the Bioterrorism Act include: national preparedness for bioterrorism and other public health emergencies, enhancing controls on dangerous biological agents and toxins, protecting safety and security of the food and drug supply, drinking water security and safety, and additional provisions.

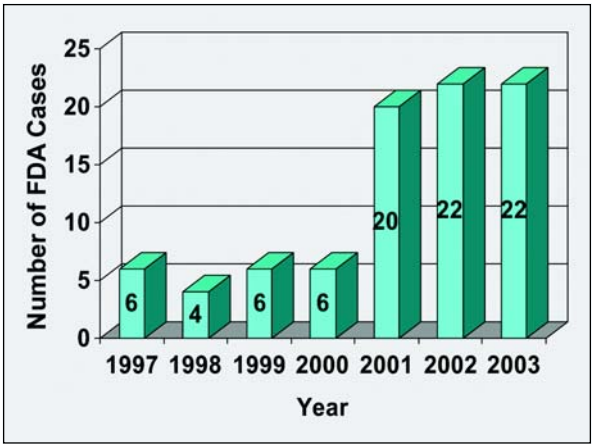

Figure 5. FDA open investigations for counterfeiting. (Source: Combating Counterfeit Drugs - A Report of the US FDA, February 2004)

The Act requests that the FDA receive a prior notification of all human and animal food, drinks, and dietary supplements imported to the US. It addresses threat assessments; technologies and procedures for securing food processing and manufacturing facilities and modes of transportation; response and notification procedures; and risk communications to the public. In order to protect the drug supply, the act requires yearly registration of all imported drugs. In addition to being registered yearly with a statement provided at the time of importation, all imported drugs must include the following information: that the 'article is intended to be processed into a drug, biological product, device, food, food additive, color additive, or dietary supplement that will be exported under the Public Health Safety Act.' The statement also requires name and place of business, US agent, name of importer, name of person who imports. Additional requirements include a certificate of analysis to identify the article, and information on the level, potency, identity, strength, quality, and purity of the drug.

Radiofrequency Identification (RFID) Challenges

RFID is a state-of-the-art technology that uses electronic tags on product packaging to allow manufacturers and distributors to more precisely keep track of drug products as they move through the supply chain. It is similar to the technology used for tollbooth and fuel purchasing passes.

Tracking and traceability will become more important as counterfeit drugs become more widespread, and the apprehension of counterfeit drugs will become more of an issue in this industry as additional cases are reported. There were 22 cases of counterfeit drugs reported in 2003 in the US - *Figure 5*. The industry will ramp up security and tracking systems rapidly in the next few years. Bioterrorism scares also have indicated a need for additional regulatory and company-wide security measures being implemented.

The FDA published a Compliance Policy Guide (CPG) on RFID in an effort to improve the safety and security of the nation's drug supply through the use of RFID technology.

The goal of this CPG is to facilitate the performance of RFID studies and allow industry to gain experience with the use of RFID. The FDA believes that use of RFID technology is critical to ensuring the long-term safety and integrity of the US drug supply. This Guide is part of the FDA's commitment to promote the use of RFID by the US drug supply chain by 2007.

US Pharmaceutical Industry: Trends, Paradigms, and Challenges

Re-Importation Challenges

Public pressure to control US pharmaceutical costs has recently focused the US government on re-importation proposals to reduce the cost of prescription drugs. The products may have been manufactured in the US or elsewhere; however, the current law does not allow for re-importation due to realistic health and safety issues. Some of the issues revolve around risks to the patient in terms of adulteration, contamination, or even counterfeit (or efficacy). Additionally, prescription drugs currently purchased over the Internet can pose the same threats. Although it appears to be politically appealing to amend our current laws, federal laws on drug imports and reimports reflect well documented concerns about the safety of imported drugs.

Conclusion

These are very challenging times for the US pharmaceutical industry. The complex environment is being driven by increased global market competition and consumer pressures to reduce healthcare costs, high labor costs, regulatory changes, and an increased need for life-saving and life-altering therapeutics. Pharmaceutical companies must maximize their portfolios' effectiveness while at the same time streamline operations.

The pharmaceutical industry will continue to look for ways to increase efficiencies and improve the bottom line. There does not seem to be any one action that would lead to overall healthcare cost reductions. Discussions on how to lower costs have revolved around improving the use of innovative technologies (see PAT), sharing know-how and knowledge bases, reducing the regulatory burden, and developing new therapeutics. Productivity enhancers include everything from increasing manufacturing performance to having better training for the workforce. Some state governments are trying to educate the local workforce to enhance productivity. For example, the state of North Carolina has established an ambitious biomanufacturing training program and the state of Massachusetts also has funded biotechnology training programs, as have several other states in the US.

Thoughts that will continue to preoccupy the industry include questions on what the US pharmaceutical market will be like in the future. The only thing that that we can write with certainty is that the US pharmaceutical industry will continue to be challenged over the next decade and beyond.

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About the US Food and Drug Administration (FDA)

Organization

The FDA's top official, Lester M. Crawford, DVM PhD, was appointed Commissioner of the FDA on 14 February 2005. Commissioner Crawford's job is to ensure that the Agency carries out its mission of protecting and advancing the public health.

The US FDA is responsible for protecting consumers by overseeing the safety and efficacy of all products with medical claims before they are sold in the US. The FDA regulates complex and sophisticated drugs, medical products, and other consumable products while protecting consumers. The FDA's mission is quoted below:

"FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, USA food supply, cosmetics, and products that emit radiation. FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and food more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and food to improve their health." (www.fda.gov)

At the heart of all FDA's regulatory activities is a judgment about whether a new product's benefits to users will outweigh its risks. The FDA uses science-based, efficient risk management to allow the Agency to protect the public at the lowest cost. While no regulated product is totally risk-free, it is important that the FDA evaluate each product individually and consider the risk against the potential benefit — especially for products used to treat serious, life-threatening conditions. In addition to prescription therapeutics, the FDA is responsible for regulating food, food additives, non-prescription pharmaceutical products (anything that makes a medical claim or is used in the prevention of a disease), biologics (vaccines, blood products, biotechnology products and gene therapy products), and medical devices (thermometers to pacemakers and dialysis machines).

Additionally, the FDA regulates drugs and devices used for animals, and veterinary medical devices for both pets and animals that produce food. Before manufacturers can market animal drugs (including drugs used in animal feeds), all of the regulated products must gain FDA approval by providing proof of their safety and effectiveness. The FDA monitors cosmetic products to be sure that they are safe and properly labeled. The Agency also oversees product labeling for food, drugs, and medical devices used by health professionals to ensure that the products have the information needed for proper use.

Most of the FDA's budget goes toward paying its highly skilled and internationally respected work force. The FDA employs some 9,000 science and public health professionals — including biologists, chemists, physicians, biomedical engineers, pharmacologists, veterinarians, toxicologists, and specialists in public health education and communication.

Structure

The FDA is a US Agency within the Department of Health and Human Services and is structured into eight centers/offices that include:

Center for Biologics Evaluation and Research (CBER) - CBER regulates biological products for disease prevention and treatment that are inherently more complex than chemically synthesized pharmaceuticals including:

- blood and blood products (plasma), blood-derived proteins including clotting factors for hemophilia, tests used to screen blood donors and devices used to make blood products
- vaccines and allergenic products
- protein-based drugs, such as monoclonal antibodies and cytokines that stimulate the immune system to fight cancer, and enzyme therapies that stop heart attacks

CBER also plays an integral role in several initiatives for protecting the US against bioterrorism.

Center for Drug Evaluation and Research (CDER) - CDER promotes and protects the public health by assuring that all prescription and over-the-counter drugs are safe and effective. CDER evaluates all new drugs before they are sold, and serves as a consumer watchdog for drugs on the market to be sure they continue to meet the highest standards.

Center for Devices and Radiological Health (CDHR) - CDHR ensures that new medical devices (pacemakers, contact lenses, hearing aids, etc.) are safe and effective before they are marketed.

Center for Food Safety and Applied Nutrition (CFSAN) - CFSAN has one of the Agency's biggest jobs: it is responsible for the safety of 80% of all food consumed in the US except for meat, poultry, and some egg products, which are regulated by the US Department of Agriculture.

Center for Veterinary Medicine (CVM) - CVM affects mil-

About the FDA

lions of consumers by helping to assure that animal feed products are safe. CVM also evaluates the safety and effectiveness of drugs used to treat pets and livestock.

National Center for Toxicological Research (NCTR) - The mission of NCTR is to conduct peer-reviewed scientific research that supports and anticipates the FDA's current and future regulatory needs. This involves fundamental and applied research specifically designed to define biological mechanisms of action underlying the toxicity of products regulated by the FDA. This research is aimed at understanding critical biological events in the expression of toxicity and at developing methods to improve assessment of human exposure, susceptibility, and risk.

Office of the Commissioner (OC) - OC is responsible for the efficient and effective implementation of the FDA mission. It is made up of several components and offices (Good Clinical Practice (GCP), Office of International Programs, Office of Orphan Products Development, etc.)

Office of Regulatory Affairs (ORA) - This is the lead office for all field activities of the FDA. ORA regulates the business establishments that annually produce, warehouse, import, and transport consumer goods. Highly trained staff ensures the implementation of the FDA's high public health standards such as GxPs.

The FDA's Web site is a great resource offering a wealth of information about all of the programs and product areas. For additional information about the FDA, visit www.fda.gov.

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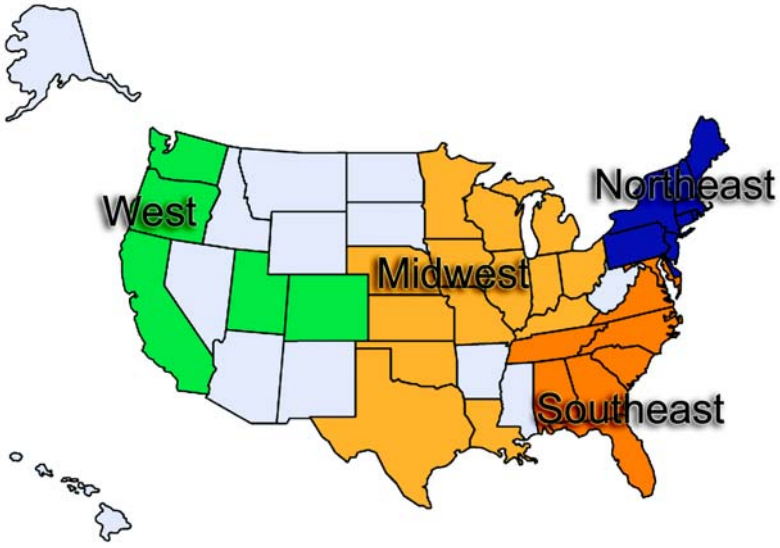
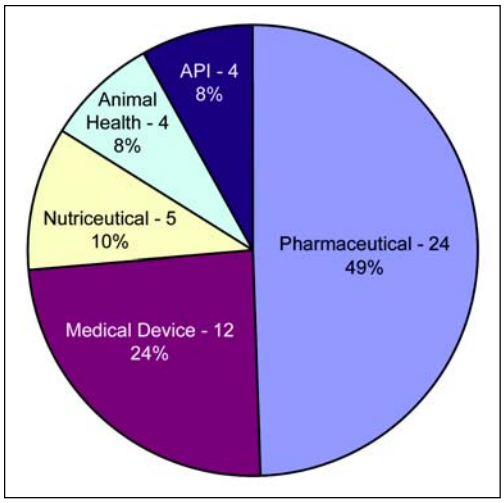


Midwest Overview

The Midwest Region encompasses the ISPE Great Lakes (Michigan, Illinois, Indiana, Ohio, Wisconsin), Midwest (Kansas, Nebraska, North Dakota, South Dakota, Minnesota, Iowa, Missouri), and South Central (Oklahoma, Texas, Louisiana) Chapters. The combined ISPE membership in this region is 2247, or approximately 20% of the total ISPE membership in the 15 state geography.

The companies with manufacturing capacity represented in this region include: Abbott, Alcon, Allergan, Baxter, Bayer, Ben Venue Labs, Bioport, Boston Scientific, Cambrex, Cardinal Health, Centocor, Colgate Oral Pharmaceuticals, Cook Group, Depuy, Dow, DSM Pharmaceutical, DPT Laboratories, Eli Lilly, Ethicon, Fort Dodge, Gerber, Guidant, Hospira, King Pharmaceutical, KV Pharmaceutical, Mallinckrodt, Mead Johnson, Medtronic, 3M, Nestle, Novartis, Perrigo, Pfizer, Protein Design Labs, Retractable Technologies, Roche Diagnostics, Ross Products, Roxane Labs, Serologics, Shaklee Technica, Solvay Pharmaceutical, Sovereign Pharmaceuticals, Stryker, Tanox Biosystems, Vetmedica, Zimmer, and ZRB Behring.

The breakdown of firms by category is as follows:



Visit the following Web sites to read more on the Midwest Region:

Biotechnology Industry Review

Interview with Tom Kowalski, President, Texas Healthcare and Bioscience Institute (THBI)

by Eric Unrau, Project Manager, CRB Consulting Engrs, Inc.

www.ispe.org/countryprofile

JETT Consortium

www.ispe.org/countryprofile

States Compete to Capture Bioscience Market

www.ispe.org/countryprofile

Overview of the ISPE Great Lakes Chapter

www.ispe.org/greatlakes or www.ispe.org/countryprofile

Overview of the ISPE Midwest Chapter

www.ispe.org/midwest or www.ispe.org/countryprofile

Overview of the ISPE South Central Chapter

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Issues and Opportunities in Contract Manufacturing

by Eric Unrau, Project Manager, CRB Consulting Engineers, Inc.

Overview

The market for Contract Manufacturing Organizations (CMOs) is estimated at $15 billion per year with an annual growth rate of 20%. Why so many opportunities and growth in contract manufacturing? Currently, the pharmaceutical industry outsources 30% of R&D and 40% of all manufacturing activities. Contract manufacturing ranges from simple packaging activities to the application of leading edge technologies - *Figure 1.*

Out of this $15 billion market, the largest percentage of contract manufacturing occurs in pharmaceutical chemicals, followed by solid dosage formulations. Packaging and biologics round out the market, but at significantly smaller capacities versus the other areas.

At face value, the concept of contract manufacturing is straight forward. However, typical relationships between the contract manufacturers and their customers (pharmaceutical companies for example) can be complex and multi-dimensional, taking years to develop into a full partnership in some cases. This is also a market that contains multiple segments, as shown in Figure 1, that are in flux as market pressures change continuously.

The opportunities for contract manufacturers in outsourcing come from four major areas:

- relative economics – cost savings through leveraging resources
- technology and skill availability – delivering value through specialized services
- start-up operations – creating a virtual company
- increasing pressure to increase efficiency and returns – market expectations

For DPT Labs, headquartered in San Antonio, Texas, the approach to the market needed to provide differentiation from other potential low cost competitor CMOs. DPT has focused on differentiation through providing specialized skills and products their competitors are unable to match. This creates more opportunities for partnership with their clients and reduces the chances that DPT will be viewed as a commodity – a difficult place to compete where often the only negotiating tool is price.

One area that is growing in the CMO business is the area of engineering support. Utilizing an in-house project engineering group can provide added value to clients when manufacturing challenges arise. For example, DPT has developed expertise in this group to assist clients in managing and launching novel processes. As they work with a number of their customers, they are finding that many innovations are coming from small companies that are in a mode of expansion. Some of these companies may not have the money or financing needed to open their own manufacturing facility, so they turn to CMOs for their increased manufacturing needs. These smaller companies' innovations often bring technology requirements that are outside the realm of the typical CMO operation, which is where DPT has been able to offer advantages to clients with their specialized services. These specialized services have even reached beyond engineering and into R&D. In addition to the engineering and R&D support, on the manufacturing side Speed-to-Market is key. Many companies have seasonal products (such as allergy medicines that are offered over the counter) where they need assistance quickly in bringing their formulations and manufacturing online fast. The ability of CMOs to respond quickly and provide that seasonal boost to manufacturing brings affordable capacity to their clients.

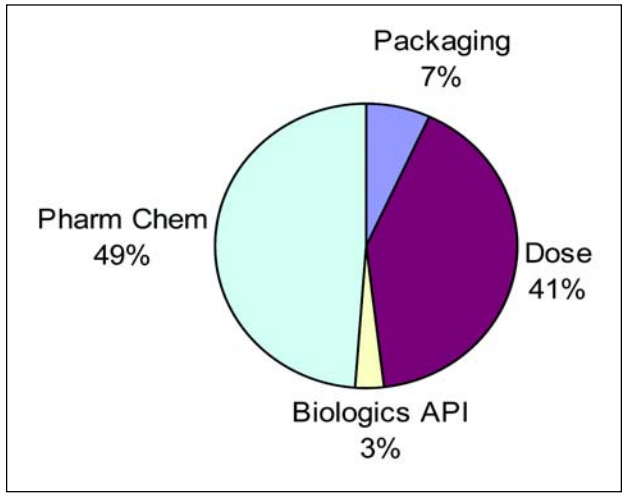

Figure 1. A breakdown of the annual $15 billion CMO market.

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Issues and Opportunities in Contract Manufacturing

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As a major part of DPT's business, they consider engineering services to be a "Focal Point of Success" in supporting their clients' multiple innovating delivery platforms, product scale-up issues, and integration with product development teams. This broad approach provides the users of CMOs more flexibility in their operations and planning.

CMO Challenges

What are some challenges for CMOs? In certain areas of the market today, such as solid dosage packaging for example, traditional manufacturers have excess capacity in-house creating pressure within these companies to keep their own plants running and reduce outsourcing. Economic pressures developing in other global regions, such as Asia – especially India, are creating a global competitive market.

In certain market segments, such as biologics and API, uncertain market conditions abound. Many CMOs are rethinking the strategies employed in these areas to increase their success. The failure of a multi-client business model and weakness in capacity availability has provided difficulties. Other issues including product failures, pipeline uncertainty, and the potential overhaul of the FDA approval process creates hurdles to success for CMOs in these markets. These areas also can add additional costs to CMOs in the regulatory demand for increased clinical and preclinical testing. When working with special or unique compounds, CMOs' risk goes up as they increase the cost of development, equipment and facilities requirements to support novel processes and complex formulations, as well as increased raw material costs.

For DPT, they focus on long-term relationships with their clients. They believe this approach provides them an improved chance for long-term growth and success. The longer term relationships also can assist both companies in weathering the changes that can occur in the marketplace.

In general, there continue to be other pressures facing the overall pharmaceutical market that can hold back growth in the CMO industry. These include continued pressure to hold down healthcare costs through drug re-importation, insurance company pressure to support the lowest cost therapy, and in some cases, dictated formulary pricing models. One area many companies are looking at currently is the occurrence of what seems to be a significant amount of blockbuster drugs falling out of favor with the FDA and the public. The concern is how this may affect CMOs' pipelines down the road.

CMO Opportunities

So what is coming down the pipe for CMOs? Some of CMOs' traditional advantages continue to be their ability to provide speed to market and manufacturing flexibility as well as their supply chain expertise in inventory management. The ability for fast decisions to take advantage of current market opportunities allows them to get increased savings for their clients, especially on the purchasing (raw materials) side of the business. These savings provide another advantage to their clients – freeing up assets and cash for more strategic investments.

Sterile product manufacturing is one area that required more evaluation for CMOs. This market can be broken into two main tiers: a larger segment where manufacturers are looking to provide millions of units to the market, and a smaller segment where more specialized manufacturing will produce smaller runs on products. The latter is where CMOs have found a need they can fill. Typically, companies looking for shorter and smaller runs of products have needed additional technical/engineering expertise in addition to the facility to manufacture smaller runs. CMOs who are equipped properly can offer both of these to provide added value.

One final area of potential growth is the area of supply chain support for their clients. CMOs are looking at how they can work with their customers in the areas of information infrastructure, managing costs and capital from raw materials through distribution, and creating the partnership to support immediate inventory replenishment models. Close collaboration and communication is needed to make these endeavors work.

Conclusion

Being successful means working closely and successfully with your clients. Customer service is a big metric, and one that is tied closely to information exchange with clients. By focusing on delivering value at multiple levels and creating the right relationship with their clients, the added value of specialized services have made some CMOs successful at what they do.

Acknowledgment

Special thanks to Mark Fite, VP Operations of DPT Labs and his presentation at the ISPE South Central Chapter Education Day in San Antonio, Texas on 7 April 2005.

Trends in the Animal Health Industry

by George Heidgerken, President and Damian Gerstner, Manager, Engineering, Boehringer Ingelheim Vetmedica, Inc.

The animal health industry provides medications, vaccines, anti-infectives, parasiticides, and medicated feed additives for a variety of species, including livestock (cattle, pigs, poultry, sheep) and companion animals (dogs, cats, horses). The $4.7 billion North American animal health industry is projected to have a real growth rate slightly higher than the global real growth rate - *Table A*.

	2001	2002	2003	2004	2005*	Growth*
North American Sales	4.138	4.180	4.475	4.700	5.010	2.0%
Global Sales	11.050	11.330	12.545	13.710	15.070	1.7%
(billion US $)					(* = Projected)	

Table A. North American real growth rate vs. the global real growth rate. (Source: Wood Mackenzie, LLC)

Recent US sales growth has been driven by parasite treatments within the companion animal segment. As the parasite treatment market has matured, there has been a notable shift toward medications that improve the quality of life for companion animals, and thus, improve the quality of life for their owners.

Within the livestock segment, the industry has been migrating away from products that treat diseased animals toward biological vaccines that prevent disease. This move has been in response to consumer concerns about misuse of antibiotics and other pharmaceutical treatments, and the potential impact on food residues and antibiotic resistance.

Animal health companies interact with and are regulated by the same regulatory agencies as human health companies. In addition, biological manufacturers within the animal health industry also are regulated by the US Department of Agriculture (USDA). Although USDA regulations and manufacturing inspections assure product quality, the USDA does not have formal requirements for Good Manufacturing Practices (GMPs). However, the USDA is increasingly collaborating with the US FDA to strengthen regulatory requirements for veterinary biological manufacturers.

With extremely few exceptions, the animal health industry GMPs are in lock step with human health GMPs. However, because animal health products typically do not have the profitability that human health products have, the cost of regulatory compliance becomes a significant factor in determining whether to bring new products to market or not. Ultimately, consumers will decide how much additional regulatory oversight they can afford for their pets.

Bovine Spongiform Encephalopathy (BSE or Mad Cow Disease) has made a huge impact on the animal health industry. Not only has BSE impact on biological manufacturing been similar to the effects on human health biologicals, but BSE impact on the food chain also causes disruptive factors. One outbreak of BSE can upset the economics of beef production instantly, which may make the use of normal production practices unprofitable. One result of financial losses due to an outbreak of BSE may be that producers no longer can afford to purchase cattle vaccines and medications. Cattle integrators will risk the chance of disease rather than incur the cost of the vaccines. From this author's perspective, the US needs to address the problem of BSE from a health safety and scientific viewpoint, rather than focusing on political solutions such as trade barriers. By understanding how BSE propagates and ultimately affects human health, we can focus on solutions that address the root cause.

Business consolidation affects the animal health industry in several ways. Food companies continue to consolidate regularly, becoming more vertically integrated along the meat production supply chain from the farm to the dinner table. This reduces the number of potential customers purchasing animal health products and increases the dependency/risk that animal health companies face with those customers that remain. Consolidation within the human health industry also greatly affects the animal health industry because animal health companies are often associated with, but usually a very small segment of, a human health company. Operating philosophies and capital allocated to animal health versus other business areas like human drugs can change drastically with a change in ownership. Finally, animal health distributors are consolidating often as they face the choice of reducing their costs or watch their customers leave to

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Trends in the Animal Health Industry

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purchase directly from animal health companies.

Although the US animal health market is growing at a slow rate, its size and business environment still provides the greatest opportunity for animal health manufacturers. US patent regulations give manufacturers the incentives they need to research and develop innovative products that improve meat production efficiency and improve the quality of life for companion animals and their owners.

Within this friendly, but very competitive US market place, the following critical success factors will determine which animal health companies are ultimately winners in the next decade:

Quality First

Manufacturers that continually improve quality can stay ahead of the regulatory curve and enjoy access to more markets.

Move Faster

Manufacturers must figure out how to innovate faster to bring products to market more quickly, without sacrificing quality.

Listen to Customers

Consumers are becoming more sophisticated in their tastes and preferences. If customers want more organic, chemical-free meat products or if they want their pet to have a high quality of life, then manufacturers must innovate to provide those solutions.

ISPE Affiliates and Chapters

ISPE Affiliates and Chapters vary in size, number, and nature of activities. Although each has a distinct character, all of them:

- promote and support educational programs designed to enhance professional performance
- foster and encourage favorable relations between its Members and related professionals
- collect and disseminate information for its Members
- establish pharmaceutical manufacturing as a profession, and educate and promote the valuable role of this profession within the industry

If you are already an ISPE member but do not belong to a local Affiliate or Chapter, you may join one by visiting the ISPE Web site **www.ispe.org** and indicating your choice on your Member Profile.

Northeast Overview

The Northeast Region of the United States as represented by ISPE is comprised of the following 10 northeastern states: Connecticut, Delaware, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. This region is supported by ISPE's New Jersey, Delaware Valley, New England, and Boston Area Chapters.

The Northeast Region of the United States is currently and has historically been the strongest geographical region in the world with regard to the pharmaceutical industry. Of the top 25 pharmaceutical companies globally, 80% have headquarters or major facilities in the Northeast Region. These companies generate 87% of global pharmaceutical sales and 86% of all research and development spending and they sell 82% of the top pharmaceutical products in the world.

Companies with headquarters in the region include Pfizer, Merck, Johnson & Johnson, Bristol-Myers Squibb, Wyeth, and Schering-Plough. Global companies with North American headquarters in the region include GlaxoSmithKline, Aventis, AstraZeneca, Novartis, Roche, Boehringer Ingelheim, Eisai, Novo Nordisk, and Teva. All of these companies have major research, development, and manufacturing facilities in the area as well. This is quite an array of companies to be concentrated in one geographical area making the Northeast Region a very important place in the pharmaceutical world.

While some of the manufacturing operations of these companies have moved from the region to the south and west, the area remains strong in its concentration of headquarters, administrative, and research and development campuses. Many large R&D facilities have been constructed on new and existing sites in the region in the past 10 years.

Bastions of the pharmaceutical industry are located primarily in the Philadelphia and New York metropolitan areas in a region stretching from northern Delaware to Connecticut. Like elsewhere in the country, the biotechnology industry is growing in the northeast with concentrations in the Boston and southern New England areas, northern New Jersey, and the greater Philadelphia metropolitan area.

Because of the concentration of pharmaceutical business in the region, there is also a high concentration of top quality support companies. Some of the largest construction companies in the world are located in the northeast and build for the pharmaceutical industry. Supporting them are architectural, engineering, and consulting firms that design, commission, and validate the facilities that they construct. Equipment manufacturers and vendors who make and sell everything from air handling equipment to scientific and manufacturing apparatus support this industry as well, and a plethora of satellite companies providing the industry with consumable supplies and other consulting and resource services are located here.

The region has a strong constituent of educational institutions including colleges, universities, and technical schools that feed professional talent into these allied industries. Their supporting strengths are generally in the sciences and engineering fields, but there are also strong medical schools and technical trade schools in this region as well. Historically, many of these institutions have sprung up around the industrial centers that they support. However, growth trends in biotechnology have shown that this industry has tended to germinate around its supporting scholastic institutions.

This region with its historical technical strength in the pharmaceutical industry has exported its products, businesses, and expertise throughout the country and the world. The northeastern United States has been and will continue to be the leading region in the world of pharmaceutical sciences.

Visit the following Web sites to read more on the Northeast Region:

Overview of the ISPE Boston Area Chapter
www.ispe.org/boston

Overview of the ISPE New England Chapter
www.ispe.org/newengland

Overview of the ISPE Delaware Valley Chapter
www.ispedvc.org

Overview of the ISPE New Jersey Chapter
www.ispe.org/newjersey

or www.ispe.org/countryprofile

History of Pharmaceutical and Biopharmaceutical Companies In New England

by Hank Moes, Consulting Director, Arion Water Inc. and James Blackwell, Consultant, BioProcess Technology Consultants

Pharmaceutical Company Locations

New England encompasses the states of Connecticut, Massachusetts, Maine, New Hampshire, and Vermont. The larger pharmaceutical companies are concentrated in Connecticut, including for example such companies as Bayer, Bristol-Myers Squibb, Boehringer Ingleheim, and Pfizer. These are all well-established companies whose facilities were built many years ago.

AstraZeneca, Novartis, and Bristol-Myers Squibb are the major pharmaceutical companies in Massachusetts. AstraZeneca has been around a long time since it was originally the Swedish company, Astra Pharmaceutical. Novartis is a relative newcomer.

Biopharmaceutical Company Locations

There are biopharmaceutical companies in almost every New England state, but the majority are located in the greater Boston area, which includes Worcester. Second place goes to Connecticut and Rhode Island. New Hampshire and Maine also have a number of companies.

The University and Medical Factor

The greater Boston area has one of the highest concentrations of biotechnology companies in the world. The reason, of course, is the presence of universities that specialize in the sciences as well as world-renowned medical research facilities and hospitals. Among universities, Harvard University and the Massachusetts Institute of Technology (MIT) are renowned, but Northeastern University, Tufts University, the University of Massachusetts, Boston College, Boston University, Brandeis University, and Worcester Polytechnic Institute (WPI) contribute to this vast knowledge base.

The Biotechnology History

The term "biotechnology" was probably coined in the 1970s, but biological processes in pharmaceutical companies were prevalent long before that. The majority of the biopharmaceutical companies in the Boston area were formed in the 1980s with additional companies in the 1990s. The major companies with capitalization of more than one billion are Abbott Laboratories' Bioresearch Center, Biogen-Idec, Wyeth Biopharma, Genzyme Corporation, Amgen (in Rhode Island), Serono, and Lonza Biologics (in New Hampshire). A brief descripion of these companies is located at **www.ispe.org/countryprofile**. This listing does not include Novartis and AstraZeneca.

The total number of biopharmaceutical companies in the area is more than 300. A listing and details of 325 companies can be found on the Web at www.massbio.org/directory/companies.

Biotechnology "Flavor"

New England is host to biotechnology firms of all sizes and flavors. Smaller firms are focused on leveraging new technologies, including stem cell research and gene therapy to develop products that meet unmet medical needs. These firms benefit from the close access to talent, research, venture capital, and new venture expertise, such as intellectual property law firms. Medium-sized firms typically have at least one product and have most of their production capacity in the state in which they reside. The larger firms typically have multiple products and operations around the world. The region is competing with other regions in the US and the rest of world to attract and maintain biotech manufacturing. Its attractions are its highly skilled workforce and proximity to research and development. The remainder of the discussion will focus on these larger firms.

Amgen is known for its oncology, immunology, and nephrology products. In Rhode Island, Amgen produces Enbrel for rheumatoid arthritis along with other products; Enbrel is a direct competitor to Abbott's Humira product. Abbott Laboratories is a multi-national, diversified healthcare company and produces Humira at its Worcester, Massachusetts production facility. Humira is a fully humanized monoclonal antibody for the treatment of rheumatoid arthritis. Biogen-Idec is known for its oncology and immunology products, most notably Avonex, Amevive, and Rituxan. While carving a niche in enzyme replacement therapy, most notably Cerezyme, Genzyme has been a diversified company for some time and has products for diagnostics, surgery and orthopedics, autologous cell therapy, and renal care, among others. Lonza Biologics is a CMO for biologics with small to large-scale cell culture manufacturing capabilities. Lonza has production agreements with many industry leaders. Wyeth Biopharma manufactures ReFacto Antihemophilic Factor, and BeneFix Coagulation Factor IX.

Mid-Atlantic and Southeast United States

Pharmaceutical and Biotechnology Manufacturing Growth

by Alan Jones, CRB Consulting Engineers and Builders and Jason Rifkin, President, Equilibrium Consulting, LLC

The Carolina South-Atlantic and Chesapeake Bay Area Chapters geographic region has been attractive to pharmaceutical and biotechnology manufacturers due to the low cost of labor, low taxes, good climate, access to research scientists, and a qualified labor pool.

Maryland

Maryland's pharmaceutical industry is predominately focused on R&D and early stage product development although manufacturing facilities are on the rise. Human Genome Sciences and MedImmune recently built corporate campuses that include pilot and scale-up manufacturing. Contract manufacturing organizations keep growing to meet the demands of the industry. These firms include Cambrex BioSciences, Chesapeake Biological Laboratories, and UPM Pharmaceuticals.

MedImmune plans to continue this trend with a manufacturing expansion in Frederick, Maryland. The recent approval of $5.6 billion for Project BioShield also will likely lead to an increasing number of companies relocating to the Washington, DC area. One example of this is BioPort's recent entrance into Maryland where they plan to expand their Anthrax Vaccine production capabilities.

Virginia

Eli Lilly & Co. is building an insulin fill/finish manufacturing facility on 120-acres in Manassas. The location is projected to employ more than 700 employees with an average annual salary of $44,000. Pat McGarrah, General Manager of the Lilly Prince William site, says a highly skilled workforce and high quality of life were the primary deciding factors for the location.

North Carolina

In North Carolina, the Research Triangle Park (RTP) near Raleigh-Durham has a large concentration of manufacturers located within 100 miles of RTP. From 1990 to 2000, more than 42 new companies have established facilities in RTP. New construction and expansion has totaled more than five million square feet. Some of the larger pharmaceutical manufacturers in the RTP area include BiogenIdec, Diosynth Biotechnology, and Eisai Pharmaceuticals - *Figure 1*.

Figure 1. Eisai Pharmaceuticals.

Merck and Co. is building a new 272,000 square foot vaccine manufacturing facility to be located in Durham. Talecris Biotherapeutics launched its new worldwide therapeutic proteins business on 1 April 2005 after acquiring the contributed assets of Bayer's plasma business, including the state-of-the-art production fa-

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Visit the following Web sites to read more on the Southeast Region:

Balancing Cost and Operating Paradigms are Key Facility Issues for Burgeoning Life Science Companies in Today' Market

by Ken Berkman, Executive Vice President, Scheer Partners, Inc. and Jason Rifkin, President, Equilibrium Consulting, LLC

www.ispe.org/countryprofile

Overview of the ISPE Carolina-South Atlantic Chapter

www.ispe.org/carolina-southatlantic
or www.ispe.org/countryprofile

Overview of the ISPE Chesapeake Bay Area Chapter

www.ispe.org/chesapeakebayarea
or www.ispe.org/countryprofile

Pharmaceutical and Biotechnology Manufacturing Growth

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Figure 2. Talecris Biotherapeutics.

cility in Clayton - *Figure 2*.

Wyeth Vaccines, located in Sanford, also has seen phenomenal growth in both its workforce and site layout - *Figure 3*. The Sanford site is the exclusive producer of HibTITER, a conjugated vaccine that has been effective against haemophilus influenza b (Hib) and is licensed for use in more than 60 countries worldwide. The site has more than doubled in size to more than 1,100 employees since 2001 creating not only jobs for the surrounding communities, but also opening unlimited professional development for current staff.

Other large manufacturers in North Carolina include: Novo Nordisk Biochem, Novo Nordisk Pharmaceutical Industries, Inc., Banner Pharmacaps, Baxter Healthcare IV Systems, GlaxoSmithKline, EON Pharma, Purdue Pharmaceuticals, Merck (two Facilities), AKZO Nobel, and Cardinal Health Sterile Technologies.

Several contract manufacturing firms have recently expanded to meet improved customer demand. DSM Pharmaceuticals in Greenville formulates pharmaceutical products into various dosage forms and recently expanded its fill/finish operations - *Figure 4*. DSM

Figure 3. Wyeth Vaccines.

Figure 4. DSM Pharmaceuticals.

Pharmaceutical Products focuses on the development, scale-up, and custom manufacture of pharmaceuticals. It acts as a customer-oriented and reliable partner supplying the pharmaceutical industry with a sophisticated range of chemical intermediates, biotech-based drugs, and dosage formulations such as orals, topicals, and steriles. They recently expanded their fill/finish operations to include sterile product manufacturing capacity to 410,000 square feet with more than 3,700 square feet of lyophilization capacity and innovative aseptic liquid filling suites.

South Carolina

Martek Bioscience, Inc., located in Kingstree, recently expanded. They are "an innovator in the research and development of products derived from microalgae." Martek has developed and patented two fermentable strains of microalgae which produce oils rich in docosahexaenoic acid, DHA. In a similar manner, another patented process was developed for a fungus that produces an oil rich in arachidonic acid, ARA. Both DHA and ARA are found in breast milk and are important nutrients in infant development. Thus, the two oils are used in infant formulas, while the DHA-rich oil also can be used in supplements and functional foods for older children and adults. Martek also makes and sells a series of proprietary and nonproprietary fluorescent markers. These products have applications in drug discovery (high-throughput screening), DNA microarray detection and flow cytometry." Martek's key markets include: infant formula, nutritional supplements and functional foods, life science, and drug discovery.

Other key manufacturers in South Carolina include: Bausch and Lomb (Figure 5), Roche Carolina, Pfizer Capsugel, GlaxoSmithKline, Holopack International, Perrigo Company, Leiner Health Products, Pharmaceutical Associates, and Irix Pharmaceuticals.

Georgia

Georgia has a robust manufacturing base with several renovations and expansions to the Northeast of Atlanta. Elan Holdings, Inc. (Figure 6) and Merial are both located in Gainesville while Merial also has manufacturing facilities in Athens. Solvay Pharmaceuticals' North American Headquarters is also in Georgia. Merck has had a manufacturing facility in Albany for many years. Augusta is home to Monsanto and UCB Bioproducts manufacturing operations. Mikart, a recognized leader in providing formulation development, contract manufacturing, and packaging services to the pharmaceutical industry, has state-of-the-art facilities in Atlanta.

Pharmaceutical and Biotechnology Manufacturing Growth

Figure 5. Bausch and Lomb.

Florida

Florida has rapidly grown its pharmaceutical manufacturing business over the last 15 years and they now have more than 4,000 employees involved in pharma/bio manufacturing. A majority of the companies are clustered in the South Florida area.

Among biotechnology companies in South Florida is Goodwin Biotechnology, Inc. (GBI). GBI is a Contract Manufacturing Organization (CMO) specializing in the production of biologics for toxicology studies and Phase I, II, and III Clinical Trials. GBI has been in business as a CMO longer than any existing competitor and has historically specialized in mammalian cell culture. Recently, GBI was acquired by Wallace Pharmaceuticals Pvt. Ltd., an India-based multi-specialty pharmaceutical company. GBI has received a significant capital infusion in connection with this transaction, and is expanding into 200L mammalian stirred tanks and microbial fermentation. GBI's business is growing rapidly, and the Wallace organization is eager to participate both in the growth of biotechnology in the US in general and specifically, South Florida's biotech growth as a result of the Scripps transaction.

A recent accomplishment for the state was the commitment by North American Biologics Inc. (NABI) to build a state of the art vaccine production facility for StaphVAX, an investigational vaccine to prevent life threatening S. aureus infections. This will be the first commercial vaccine facility in the state. The facility is located in Boca Raton.

Andrx Corporation is located in South Florida and per their Web site, Andrx "develops, manufactures, and commercializes generic versions of controlled-release, niche, and immediate-release pharmaceutical products, including oral contraceptives; and distributes pharmaceuticals, primarily generics, which have been commercialized by others, as well as their own, primarily to independent pharmacies, pharmacy chains, pharmacy buying groups, and physicians' offices."

IVAX Pharmaceuticals, headquartered in Miami, has experienced considerable growth the last few years - *Figure 7*. IVAX was recently recognized as a leading US generic company moving up to a #5 ranking based on dispensing 84 million prescriptions in 2004. IVAX ranked #1 in terms of absolute total prescription growth with 14.8 million prescriptions. For the total pharmaceutical industry (brand and generic), IVAX now ranks as the 11th largest pharmaceutical company in the US, and the fastest growing among the Top 20 Pharmaceutical firms.

Figure 6. Elan Holdings, Inc.

Figure 7. IVAX Pharmaceuticals.

Aphton Corporation in Miami currently has several drugs in Phase II and III Clinical Trails. They also have alliances with Aventis Pasteur, GlaxoSmith Kline, and Schering Plough.

Tennessee

The Eastern part of Tennessee has two large pharmaceutical manufacturing facilities in GlaxoSmithKline and King Pharmaceuticals. King is headquartered in Bristol.

It is evident that the Southeast and Mid-Atlantic regions will continue to compete for new manufacturing facilities due to the large capital investments in academic research facilities and worker training programs currently being implemented to introduce current Good Manufacturing Practices to the existing labor pool.

We hope you have time to visit our region in the future and that this article enlightens your knowledge of the pharmaceutical and biotechnology manufacturing industry in the Mid-Atlantic and Southeast Region of the United States.

Interview with Dr. Leslie Alexandre

conducted by Jeffery N. Odum, Principal, NCBioSource

Dr. Leslie Alexandre is President and Chief Executive Officer of the North Carolina Biotechnology Center, a private, non-profit corporation established by the North Carolina General Assembly in 1984. The mission of the Biotechnology Center is to provide long-term economic and societal benefits to North Carolina by supporting biotechnology research, business, and education statewide.

Before joining the Biotechnology Center in August 2002, Dr. Alexandre was assistant director for industrial relations in the Office of Technology and Industrial Relations of the National Cancer Institute (NCI) in Bethesda, Maryland. She was responsible for building relationships with the private sector on behalf of NCI and facilitating the development of scientific collaborations with industry to accelerate the progress of cancer research.

Looking at the biotech industry in the southeast, where do you see the greatest changes over the past five years?

I do not think of biotechnology as an industry per se, but rather as a collection of scientific tools and technologies that use living cells and their molecules to make products and solve problems in many different industries. Over the past several years, the southeast has witnessed tremendous growth in the importance of biotechnology as an engine for economic development at the state and local level, as well as regionally. Five years ago, the southeast was not viewed as a major force in terms of attracting investment or intellectual "capital" for biotechnology companies. There also was not broad recognition of the large and growing concentration of manufacturing and support companies within the region. Today, that has changed dramatically as major biotechnology companies such as BiogenIdec have located in the southeast, and many "home grown" companies have not only become viable, but have successfully launched products to the marketplace. In addition, we are seeing broad diversification in the application of biotechnology to multiple industries in the southeast – perhaps more so than in any other region. In North Carolina, for example, not only do you find lots of biopharmaceutical companies, you also find many companies focused on industrial, agriculture, forestry, and marine biotechnology applications.

Now looking ahead to the next five years, what trends do you foresee for biotechnology companies in the southeast?

I believe that the growth of biotechnology companies in the region will be even more dramatic over the next five years. Helping to fuel this growth will be a concerted push by states to transition their economies from those dependent on brawn to those dependent on brains, related efforts by state and local economic developers to stem the transfer of jobs overseas, the continued commercial successes of "home grown" southeastern-based companies, and the exciting advances in the sciences coming out of the region's major universities. In addition, I believe you will see a large increase in the number of pharmaceutical and biotechnology companies that choose to manufacture in the southeast. With their business friendly environments, low cost of doing business and seasoned manufacturing workforce – not to mention low cost of living and high quality of life – southeastern states are well positioned to attract biotechnology and other life science companies that wish to do at least some of their product manufacturing in the US.

What issues do you see as being potential roadblocks to continued growth?

While the future of biotechnology in the southeast looks extremely bright, there are some critical issues that must be addressed. One is expanding access to investment capital throughout the region. Unlike the more abundant supplies of investment capital found in the San Francisco Bay area and the metro-Boston area, there are currently only a few large pools of venture capital within our region. Part of our challenge stems from the fact that the southeast is still relatively unknown with respect to biotechnology. We have not yet created any big, household name companies, such as an Amgen or a Genentech. Those companies and a few others in California, Massachusetts, and a handful of other states provided phenomenal returns to their early investors and motivated substantial additional biotechnology investing in their regions.

Expectation management is another big challenge economic developers in the southeast will face, particularly in those states that currently lack a large concentration or "cluster" of biotechnology companies. I see some such states

Interview with Dr. Leslie Alexandre

committing enormous sums of taxpayer dollars to initiatives aimed at stimulating biotechnology research and commercialization with the ultimate goal of creating large numbers of high paying biotechnology jobs in the near future. What we have learned in North Carolina is that it takes decades, not years, to create a sustainable biotechnology cluster and it takes the involvement and full cooperation of a huge constellation of partner organizations in the public and private sector. Research cannot be rushed, nor can the process of moving a new therapeutic agent from the bench to the bedside. I fear that substantial taxpayer dollars will be wasted in those states that have come most recently to biotechnology as a form of economic development and lack the critical ingredients required for success. In all likelihood, those will be the states that can least afford wasted expenditures.

More than 20 years ago, North Carolina was fortunate to have extraordinarily visionary leaders who recognized that the new science of biotechnology would one day yield tremendous commercial opportunity. To help catalyze the development of biotechnology, the General Assembly proceeded to create and fund every year since then, the North Carolina Biotechnology Center. Today, we are the third leading state for biotechnology with nearly 200 biotechnology and related life science companies employing nearly 40,000 workers in clean, safe high paying jobs.

Do you see challenges on the regulatory front that the industry must address in order for the growth to continue?

Protection of the consumer will always be a top priority. But there also must be a focus on the business needs of the companies that manufacture human therapeutic products. Answering the question of how to ensure both safety and compliance in an affordable and timely manner will be critical to patients and companies alike.

As the industry becomes more global, we must also look for ways to expand the concept of harmonization. More products manufactured in the southeast and throughout the United States are being targeted for global markets. We need to focus on ways to improve communication within the regulatory framework under which we must operate. If we continue to have a fragmented regulatory landscape, it will be especially difficult for smaller companies to succeed. Professional organizations such as ISPE will play a critical role in this area. Being able to look at the substance of issues and propose solutions that are focused on the needs of the industry is something that is critical. Having worked on Capitol Hill, I have seen first hand how important it is to have strong professional organizations become involved in providing information and helping simplify issues to make them clear and straight-forward to lawmakers and their staffs. That way, legislative and regulatory issues can be resolved much easier.

If you had to pick a few "hot buttons" for the southeast to focus on in the coming years, what would they be?

Again, access to investment capital is critical. Without plentiful venture capital, we will not be able to keep pace with other regions. We also must continue to grow the talent pool of entrepreneurs and executive leadership and find new venues for nurturing young companies in supportive environments until they are ready to stand independently. That may require greater involvement by the universities and companies from which new technologies are spinning out. And finally, as I said earlier, the region needs more "home runs." More home-grown success stories that become visible will do great things to fuel the growth engine of biotechnology in the southeast.

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For more information, please contact the Center at Tel: 1-919/541-9366.

West Overview

The West Region of the United States as represented by ISPE is comprised of the 11 western most states of: Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Wyoming, and Washington.

This region is supported by ISPE's Rocky Mountain, Pacific Northwest, and three California Chapters including the San Francisco/Bay Area, Greater Los Angeles Area, and San Diego Chapters.

The Western Region hosts the headquarters of two of the largest biotech/pharmaceutical companies in the world: Amgen and Genentech. It hosts a myriad of others including, but not limited to: Abbott, Abgenix, Allergan, Alza, Baxter, Bayer, B Braun, Berlex, BiogenIdec, Biomarin, Biosite, Cardinal Health, Cephalon, Chiron, Gambro BCT, Gen-Probe, Icos, Medtronic, Nektar, Novartis, NPS Pharmaceuticals, QLT, Roche, Sandoz, Watson Laboratories, and Zymogenetics.

Two of the major draws the west has for the pharmaceutical industry are university collaboration and the quantity and quality of local support companies. Bioscience parks have been erected by many universities in the region and these universities are working with local companies to develop the products and technologies of the future. The region produces a large quantity of PhD level academicians and attracts even more with its climate, salary scale, and quality of life. In addition, local support companies make the region very attractive for manufacturers. Venture capital, experienced and highly skilled construction companies, equipment and product manufacturers, validation and QA/QC companies, certified inspectors, and others compliment the well educated talent base and draw employers and employees alike.

The pharmaceutical industry in California is concentrated in San Francisco, Los Angeles, and San Diego. All of these locales boast significant bioscience parks and centers. The Northwest, Rocky Mountain, and Southwest areas are up-and-coming pharmaceutical centers where university collaboration, an educated talent base, and tax incentives offer a compelling draw for both existing residents and potential companies.

California alone is home to more than 4,000 bioscience companies that employ more than 150,000 people. Academic institutions in California like USC, Scripps, Stanford, Cal Poly Pomona, Cal State Fullerton, and the Universities of California at Berkeley, Los Angeles (UCLA), Irvine (UCI), and San Diego (UCSD) play a vital role in the development of new technologies and bioscience parks in affiliation with their local pharmaceutical communities.

The Pacific Northwest has experienced a 20% increase in pharmaceutical employment over the last 10 years with more than 30,000 people now working in the industry. Nearly two-thirds of these people are employed at companies of less than 50 employees. These include many significant start-up companies with technologies that have been developed in collaboration with local institutions like the University of Washington, Washington State University, Fred Hutchinson Cancer Research Center, University of Oregon, and Oregon State University.

The Rocky Mountain area is comprised of Utah and Colorado and has more than 800 registered companies and 30,000 employees in the pharmaceutical industry. The University of Colorado,

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Visit the following Web sites to read more on the West Region:

Amgen
by Michelle M. Gonzalez, Principal Corp. Eng., Amgen, Inc.
www.ispe.org/countryprofile

Overview of the ISPE Greater Los Angeles Area Chapter
www.ispe.org/greaterla or www.ispe.org/countryprofile

Overview of the ISPE Pacific Northwest Chapter
www.ispe.org/pacificnorthwest or www.ispe.org/countryprofile

Overview of the ISPE Rocky Mountain Chapter
www.ispe.org/rockymountain or www.ispe.org/countryprofile

Overview of the ISPE San Diego Chapter
www.ispe.org/sandiego or www.ispe.org/countryprofile

Overview of the ISPE San Francisco/Bay Area Chapter
www.ispe.org/sanfrancisco or www.ispe.org/countryprofile

The Life Sciences Industry in Washington State

by Kevin Brettmann, Director of Life Sciences, JE Dunn Construction and Pam Love, Director of Mktg. and Member Services, Washington Biotechnology and Biomedical Association

The boom you hear from the Pacific Northwest isn't just the sonic boom of a Boeing jet any more. Businesses based on new technology and upscale taste - Microsoft, Amazon.com, Starbucks, and Nordstrom - have infused the region with wealth and entrepreneurial energy.

Although yet a small portion of the overall state economy, biotechnology is among the most dynamic growth sectors in the state, experiencing a 20 percent increase in employment in the last 10 years, more than the state's overall job growth during the same period. More than 20,000 people are employed in biotechnology here, nearly two-thirds of them in smaller companies of less than 50 employees. More than three-fourths of Washington biotechnology firms are not publicly traded, but the state is home to some larger companies. Amgen's significant R&D unit (formerly Immunex), is in Seattle; ICOS employs nearly 700 in Bothell, and Seattle also is home to Dendreon, Corixa, and Rosetta Inpharmatics, a division of Merck.

There are several important reasons for the industry's growth in Washington State: excellent research institutions, access to capital, a high quality of life, and several business initiatives that have created a friendly climate for start-ups. Industry leaders are unanimous in crediting the University of Washington, Washington State University, and the Fred Hutchinson Cancer Research Center, as the technology foundation for Washington's biotechnology industry. More than one-half of biotechnology firms in the state are either founded on technologies developed at these institutions or have ongoing collaborative relationships as an important component of their business operation. Battelle Pacific Northwest National Laboratory in Richland is also an important research partner with many of the state's biotechnology companies.

Several institutions are in place to encourage entrepreneurship: the Washington Technology Center (WTC) is the state-funded enterprise that supports commercially promising research and technology development of direct benefit to the economic vitality of Washington State. WTC provides grants to professors to encourage them to team up with entrepreneurs. A private economic development group, the Alliance of Angels, nurtures the growth of technology-based businesses in Washington State and improves the interactions among angel investors and emerging local technology companies seeking funding. The Washington Biotechnology and Biomedical Association (WBBA) is at the center of networking events and political advocacy for the industry.

Washington has no corporate or personal income tax. Capital investments for qualified high technology firms (including biotechnology and medical devices) are exempt from the state sales tax. Firms that are manufacturing in the state that have repair and replacement costs have those costs exempted as well. Washington has a tax credit for businesses that locate in distressed areas although the biotechnology hotbeds of the state, King and Snohomish counties, do not qualify as distressed.

A major expense for most businesses is the Business and Occupancy (B&O) tax on gross receipts. However, qualified high technology firms, including those in the biosciences, receive a credit against B&O taxes (up to $2 million per year) for their research and development expenditures. Another organization, the Washington Biotechnology Foundation (WBF), provides the tools to teachers to foster awareness of biotechnology in the classroom. WBF provides resources and training for teachers, including workshops, seminars, biotechnology lessons, and opportunities to meet and learn from biotechnology professionals.

Washington is rich in education and training opportunities for people seeking careers in all levels of biotechnology. Washington State University in Pullman is one of nine campuses across the country chosen for a National Institutes of Health graduate training program in the science and applications of protein chemistry. In addition to UW's Department of Molecular Biotechnology, which attracts students internationally, UW is a leading center for training in virtual reality software development with many exciting implications for biotechnology.

Many of the state's community colleges and four-year colleges have programs that prepare students for

Concludes on page 32.

The Life Sciences Industry in the Rocky Mountain Region

The life sciences industry is thriving in the Rocky Mountain Region. Manufacturing companies, research and development enterprises, research facilities (institutes, universities, hospitals, and laboratories), and supporting companies have established themselves from the Canadian border to the Mexican border along the Rocky Mountains. The majority of these life sciences entities are clustered in the greater Denver area in Colorado and in the greater Salt Lake City area in Utah. In those two states, there are more than 800 registered life science companies in all. Estimates from 2003 show these two states contain nearly 30,000 workers in the life sciences industry. Industry sectors in the Rocky Mountain region include: aerospace, animal biotechnology, bioinformatics, biotechnology, pharmaceutical, medical device, diagnostics, plant and agricultural biotechnology, nanotechnology, photonics, and nutraceuticals. Fueling these sectors is a strong research base in the area with numerous institutes, universities, and research centers that annually receive more than $300 million for life science research. Helping drive the expansion of the industry to the area are the many quality of life factors, favorable tax environment, and a high concentration of 'High Tech' workers in the area.

Colorado's Life Sciences Industry

Colorado's state government has identified the life sciences industry as a key to its future economic success and is in the process of making the state an even more attractive location for companies. Currently, the state has more than 600 registered companies, employing nearly 17,000 workers with the majority of these in medical device, biotechnology, and pharmaceutical sectors. There are several representatives from established companies, including Amgen, Novartis, Roche, Baxa Corporation, Medtronic, COBE Cardiovascular, Gambro BCT, and Cargill. There are numerous universities, research and development enterprises, and institutes fueling the life sciences industry. These include the University of Colorado, Eleanor Roosevelt Institute, and the Division of Vector-Borne Infectious Diseases. Colorado also is home to the Fitzsimmons "Life Science City." This $4.3 billion 'square mile of life sciences,' located in the Denver metro area, is the largest medical-related redevelopment effort in the country. The investment in this "biopark" is a major step forward for Colorado and the life sciences industry and represents a major hub for the industry in the Rocky Mountain region and the United States.

In addition to this positive-life science environment, Colorado boasts one of the highest concentrations of 'high tech' workers in the US, a state cabinet technology position, and a top five rating for 'tax-friendly' states. These factors along with the investments in infrastructure mentioned above as well as other factors such as quality of life make it an attractive location for the life sciences industry.

Colorado's current challenge to expand the industry includes the lack of notoriety in the industry over other areas such as Boston and California, and the fact that the industry hasn't reached a 'critical mass' of companies. However, with all the positive attributes found in the state, it is just a matter of time until it becomes a national hub for the industry.

Utah's Life Sciences Industry

Utah has been a growing player in the life sciences industry since the early 1980s when the University of Utah successfully implanted an artificial heart into a human. Prior to that milestone, the medical device market in Utah had exploded with the invention of disposable medical devices by newly founded Deseret Pharmaceuticals in 1956. For the state of Utah, this growth in the medical device industry was bolstered with the development of Ballard Medical Products a few years later and the Sorenson Family of medical science companies.

Since this time, Utah has begun to build a reputation as a medical products and biotechnology center with up and coming biotech companies spinning off from the University of Utah and Utah State University making national newspaper headlines. Currently, Utah is home to more than 150 life science companies primarily in the medical device and biotechnology sectors. Utah has major biomedical devices and supply companies, two world-class biopharmaceutical companies, a national drug delivery company, and a worldwide leader in biological products. With industry leaders that include Cephalon, Myriad Genetics, Abbott Critical Care Systems, NPS Pharmaceuticals, and Watson Laboratories, as well as associated partnerships with most of the leading pharmaceutical companies, Utah is positioning itself to continue significant expansion in the bio-

The Life Sciences Industry in the Rocky Mountain Region

sciences market.

Utah's state universities have major genetic medicine and biotech/agricultural resources, as well as significant research capabilities in bioinformatics and scientific imaging. The education system in Utah is committed to facilitate the growth of biotechnology throughout the state. The University of Utah, Brigham Young University, and Utah State University are all active in research and development in the bioscience arena as well as facilitating the transfer of university developed technologies to the marketplace. The Huntsman Cancer Institute in collaboration with the University of Utah has discovered more gene-related diseases than any other university. This adds to the potential of university spin-offs in genetic medicine.

Utah's overall culture provides a unique asset to biotech and also may be attractive to companies looking at moving there. The altruistic culture in Utah encourages many to participate in cancer research, genetic testing, and associated genealogical disclosure. This culture combined with the quality of life; educational excellence, and long-term commitment of the high-tech workforce helps facilitate the process in seeing a new drug through the subsequent years of clinical trials. Local government does not play a huge part in the development of Utah's life sciences industry; however, revolutionary efforts by Utah's Senator Orrin Hatch to make the FDA more efficient coupled with his efforts to fund research for pediatric AIDS have contributed to this states' technical growth.

Attracting venture capital funding is an ongoing challenge for Utah. Utah based biotechnology companies have had to rely primarily on business partnerships with higher profile companies to receive funding. Utah will need a stronger financial and legal infrastructure, including legal services, venture capital firms, and investment banks that specialize in biotechnology - all of which are key to the successful development of any related high tech industry. The last challenge left to overcome is the successful marketing of Utah as a strong option for life science companies. Although Utah companies do a good job of marketing, the world does not know that they are there, and Utah is still not seen as a primary place to invest in biotechnology.

A Brief History of Biotechnology in Northern California

by BayBio

A university researcher and a venture capitalist formed the world's first biotechnology company, locating it in 3,000 square feet of industrial space in South San Francisco. Genentech, founded in 1976 by University of California, San Francisco biochemist Herb Boyer and Robert Swanson, was one of the first of many successful Bay Area biotechnology companies to come.

Genentech followed the direct entrepreneurial lead of pioneering Northern California companies like Cetus Corp, a biological engineering company – the first ever – founded in Berkeley in 1971, and Palo Alto-based Syntex Corporation, founded in 1964. Syntex, led by Alejandro Zafferoni (later a founder of a number of biotech companies), was the first pharmaceutical company to form since World War II.

Much of the work in biotechnology's early years was done by a handful of brilliant investigators and scientists at world-class research institutes – Stanford University, UCSF, and UC Berkeley. Charged by the federal government in the early 1970s to fight a war on cancer, researchers guided by their interest in pushing the frontiers of genetic engineering built more than science. They founded an industry that revolves around the Bay Area.

The Foundations

The research institutions created the technology, tools, and intellectual climate necessary to build a new industry. The Bay Area in the 1960s was percolating innovation and discovery in many quarters, including science. Since the mid-1950s, Stanford University, UCSF, and UC Berkeley had produced Nobel Laureates in chemistry, physics, and biology. In the early 1970s, that tradition of rigorous scientific innovation continued as UC Berkeley biochemist Bruce Ames devised a method, now a standard for researchers, to detect genetic mutations in bacteria. Stanford University's Leonard Herzenberg developed rapid cell-sorters, speeding up research.

In 1973, Boyer, Stanford geneticist Stanley Cohen, and Stanford biochemist Paul Berg isolated many of the genetic engineering methods used. Berg linked two genes from different viruses together, and Cohen and Boyer demonstrated that cloning DNA was possible. Cohen and Boyer then proved that they could splice genes into bacteria, using microbes to churn out human hormones, growth factors, and other medically important chemicals. In just a few short months, these complementary discoveries became the intellectual basis of biotechnology.

With the new genetic tools came new fear. Researchers sought to understand the dangers and possibilities that genetic engineering offered. Unsure of the dangers and the regulatory climate they might face, Berg and others in 1974 called for a worldwide discussion on issues of gene splicing and safety. In 1975 at Asilomar Conference Center in Pacific Grove, 140 prominent researchers and academicians debated their opinions about gene-splicing. Within a year, the National Institutes of Health would issue guidelines based upon the conference's recommendations. Swanson and Boyer then founded Genentech, which would win the race to produce the first human proteins using biotech techniques, including insulin (FDA approved in 1982) and the human growth hormone (FDA approved in 1985). Other discoveries were leading to new companies: UCSF's William Rutter and two university researchers co-founded Chiron Corporation to find vaccines for hepatitis B. In 1979, the J. David Gladstone Cardiovascular Institute began research at UCSF.

As science pushed forward, questions regarding patentable science would dominate the 1980s. "If companies and universities poured millions into research without patent protection, innovation would be dampened," recalled Dr. George Rathmann, founder of Amgen, and Chairman of Sunnyvale-based Hyseq at a recent Bay Area Bioscience Center forum, Bay BioNEST. In 1980, the Supreme Court agreed that life forms could be patented. Patents in hand, biotech companies were ready to face Wall Street. Genentech became the first of many companies to go public, generating $35 million in its initial public offering. A rash of additional public offerings followed as companies attempted to duplicate Genentech's success. Cetus followed in 1981 with a $107 million IPO. Scios, Amgen, Chiron, Xoma, and others would follow in the next five years.

A Brief History of Biotechnology in Northern California

Into the 1980s

During its first decade, biotech in Northern California experienced tremendous growth. From 1964 through 1977, 84 companies were founded. By 1987, the Bay Area's biotechnology industry had grown to 112 companies, supporting 19,400 jobs and total sales of $2 billion. Throughout the remainder of the 1980s, that growth continued, and between 1987-1990, 81 new companies formed. In 1989, Stanford opened the $100 million Beckman center for medicine and molecular biology, headed by Nobel Laureate Paul Berg.

An early focus of genetic engineering was agriculture. And again, Northern California was, and is, at the forefront of agricultural biotech, and can lay claim to ownership of the first agricultural biotech, International Plant Research Institute. In 1986, UC Davis founded its program for biotechnology in agriculture. Early in biotech's history, researchers focused their efforts on helping food crops resist frost and pests and Bay Area researchers responded as UC Berkeley professor Steven Lindow and Advanced Genetic Sciences created and developed ice-inhibiting bacteria, the first release of a bio-engineered organism in 1987. Calgene worked on testing of a genetically engineered tomato, later approved in 1994. Groundbreaking agricultural engineering work, begun in Northern California, continues in earnest.

Beyond business success, university researchers and biotechnology institutions are working to cure diseases. Early on, research that led to biotech had an anti-cancer goal, but came to include therapies for nearly every disease. The relatively new disease, AIDS was no different, and research began to try and understand the disease immediately. Northern California research led the way as UCSF researchers isolated the HIV virus in 1983. Chiron cloned the virus in 1984, and in 1986, blood screening and diagnostic tests were made available worldwide.

The regulatory climate in the 1980s was evolving as well. The federal government and industry worked to coordinate oversight of genetic engineering. In the early 1990s, an effort by the Clinton administration to reform the nation's healthcare system also impacted biotech's prospects by threatening to intervene in pharmaceutical pricing, and thus reduce the chances of recouping development costs. Because the industry is new, government oversight and regulatory frameworks have shifted frequently.

From the 1990s to Tomorrow

Silicon Valley fueled innovation to accelerate the pace of discovery. An entire industry of tool-makers and testing-equipment manufacturers developed as the need for new instruments pushed technology, led by research done at Stanford University, Applied Biosystems' early DNA synthesizers, and Bio-Rad Laboratories. Cetus Corp. developed PCR, a chain reaction allowing researchers to generate billions of gene sequence copies in only hours netting Kary Mullis the Nobel Prize in 1993. Later, tool companies would take techniques learned in the development of silicon chips for high tech and apply them toward biotech. The new tools would be necessary for the next big revolution, and the next decade of discovery. The much-publicized Human Genome Project, begun in 1990, led to a new basis of drug research and development, from viral replication of proteins to gene-based discovery and treatment of diseases. Again, Northern California research was at the forefront, as Lawrence Livermore and Lawrence Berkeley Labs headed up the Western Facility in Walnut Creek, playing a key role in the genome. Northern California also built on its rich legacy of world-leading research as UCSF would herald two more Nobel Prizes, one for Michael Bishop, current chancellor.

With the maturation of a number of early biotech companies, many invested heavily in production facilities. Chiron, Bio-Rad, Genentech, Genencor, and Bayer in Berkeley built or expanded research and production facilities in the Bay Area. And, just over 20 years after Genentech's founding, the company began marketing the first genetically engineered monoclonal antibodies aimed at fighting cancer, Rituxan.

Bay Area research universities are currently gearing up for the next wave of research. UC Berkeley unveiled its life sciences initiative. UCSF is expanding into its Mission Bay Campus, which will allow the university to perform more research projects for the NIH, and is building QB3, a joint research program between UC Berkeley, UCSF, and UC Santa Cruz. Stanford University has established BioX at the Clark Center, a multi-disciplinary program to assist in the discovery and understanding of science and medicine, and UC Berkeley is undergoing a similar transformation, expanding its college of engineering.

San Diego Regional Profile

The history of biotechnology in San Diego began with two pioneers, Howard Birndorf and Ivor Royston, and the founding of Hybritech in the late 1970s. Initially researchers at UCSD, their use of monoclonal antibodies revolutionized the tedious process of diagnosing disease. They, along with the others at Hybritech, ended up founding many of the biotech companies in San Diego. The two are commonly known as the fathers of San Diego's biotechnology industry.

Today, the biotechnology industry in the San Diego area is all-encompassing and includes pharmaceuticals, medical devices, biotechnology, bio informatics, bio-argriculture, and environmental biotechnology.

San Diego is one of the top bioscience centers in the country for NIH funding and is regularly listed as one of the big nine. The area boasts roughly 625 bioscience companies and employs approximately 23,000 people. As a region, these numbers compete with many states and even some countries.

La Jolla and the nearby Sorrento Valley host prominent bioscience parks with the who's who of bioscience residents. Pfizer, Novartis, Gen-Probe, Skyepharma, La Jolla Pharmaceuticals, Cardinal Health, Invitrogen, Diversa, Merck, Elan, Tannox, and Amlyin all call the area home. San Diego is aggressive in courting large pharmaceuticals as well. An example of this is the addition of pharmaceutical giant BiogenIdec in the northern San Diego area.

Biogen Idec was created by the merger of Biogen, Inc. of Massachusetts, and Idec Pharmaceuticals, Inc. of San Diego in November 2003. BiogenIdec, now headquartered in Cambridge, Massachusetts, is the third largest biotechnology company in the world. The company employs 4,000 people worldwide. It currently has approximately 20 products either in clinical trials or on the market. Biogen Idec maintains a large R&D facility in San Diego.

Genentech has recently come into the San Diego marketplace with the purchase of a 90,000 liter biotech manufacturing facility in Oceanside, California that had formerly belonged to BiogenIdec. This $380 million facility is the largest manufacturing commitment to the San Diego area.

The San Diego area has many draws for bioscience companies. Among these are a highly educated talent base, local university support, tax incentives, plus incredible weather. In addition, San Diego has a large number of support companies, including a number of contractors and vendors with extensive pharmaceutical experience and expertise.

West Overview

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Eleanor Roosevelt Institute, Division of Vector-Borne Infectious Diseases, University of Utah, Brigham Young University, and Utah State are the major education centers that feed the pharmaceutical industry in the region. Colorado has the largest medical-related redevelopment effort in the country with a $4.3 billion "square mile of life sciences." Utah's stronghold was the early emergence of the medical device industry beginning in the early 1950s and the successful implant of an artificial heart by the University of Utah in 1980.

The Life Sciences Industry in Washington State

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careers in the biotechnology industry. In Ellensurg, Central Washington University is home to the oldest biotechnology-training programs on the west coast.

In addition to the educational opportunities, the quality of life in Washington helps attract talent. The natural attractions include three national parks, both the Cascade and Olympic mountain ranges within 90 minutes of Seattle, miles of public beaches, and nearly every form of outdoor recreation one can imagine. Seattle itself is home to professional sports teams, a ballet, opera, and dozens of professional theater companies.

Wherever you go among biotechnology professionals in Washington, you find connections. More than a dozen biotechnology firms trace their roots to the University of Washington, including Cell Therapeutics, Corixa, and ZymoGenetics.

At the confluence of Microsoft and a bioscience cluster, genomics and bioinformatics firms are bound to be born and flourish. Geospiza, Rosetta Inpharmatics (a division of Merck), VizX Labs, and the Institute for Systems Biology, founded by Dr. Leroy Hood, are some of these. On the device side, strong ultrasound research at the UW has resulted in nationally-known device companies such as Philips Ultrasound North America (formerly ATL), SonoSite, and Siemens Medical Solutions Ultrasound.