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MAY/JUNE 2013 VOLUME 33, NUMBER 3

Clinical Supply Manufacturing Services

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PHARMACEUTICAL ENGINEERING®
(ISSN: 0273-8139) is published bimonthly by ISPE, 600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

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US Postmaster:
Send change of address to *Pharmaceutical Engineering*, 600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609.

Canada Postmaster:
Send change of address information and blocks of undeliverable copies to PO Box 122, Niagara Falls, ON L2E 6S8. Canada Post Agreement Number 40012899.

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table of contents

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MAY/JUNE 2013
VOLUME 33, NUMBER 3

also inside

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ISPE Members Making an Impact on Industry Issues Worldwide

ISPE President and CEO Nancy Berg discusses the impact that ISPE's new direction is making on individual Members, the companies they work for and regulatory and industry relationships around the world.

After attending an ISPE reception in Philadelphia last month, a Member from the ISPE Delaware Valley Chapter wrote to tell me that ISPE's new direction and vision are "coming to light." Alan told me that the reception was "a perfect example of how ISPE can offer a platform that not only brings together Members and their companies, but also connects them with regulators and regulatory issues." He recognizes that part of ISPE's role as the "industry-regulator connection" is to help ensure consistencies in the understanding of whatever technical or regulatory changes are moving forward.

Members like Alan understand how as a neutral association of *individuals*, ISPE is well positioned to be a leader and a facilitator because it is unencumbered by the politics associated with lobbying. Our new direction is indeed taking shape and today I would like to share examples of how ISPE Members are making an impact on the right issues worldwide.

ISPE's first Executive Forum (2-3 April, Philadelphia, PA-USA) brought together 75 senior leaders from major companies, contract manufacturers and suppliers who heard presentations by peers from the aerospace, defense, automotive and packaging industries on quality management, innovation and leadership. Other speakers included experts and renowned authors who shared views on continuous process improvement and lean leadership and discussed how other industries drive change and respond to government regulations. FDA's CDER Director, Dr. Janet Woodcock opened the meeting by challenging industry to (quantitatively) define *quality* and explained that FDA's new Office of Pharmaceutical Quality will be tasked with identifying new ways of measuring quality. As you may know, FDA has been soliciting industry views on whether common standards and metrics could enhance quality and ISPE has been involved in these discussions. Further dialog is planned during a Quality Metrics session at the ISPE-FDA Joint Conference (11-13 June, Baltimore, MD-USA).

Quality was clearly the theme of our first Executive Forum. Discussions comparing quality management, compliance and leadership in aerospace, automotive, beverage and other industries to the pharmaceutical industry drew candid questions and comments. While there are certainly differences in these industries, the role of leaders is the same whether the company manufacturers automobiles, jets or sterile injectables. Presenters described how great leadership can motivate employees toward a personal commitment to quality in *everything* they do and they emphasized the importance of leadership visibility, thoughtful questioning techniques, understanding processes and the importance of defining expectations for both quality and compliance. At the end of the day, delegates were in resounding agreement: *Quality cannot be a function or an initiative or even a competitive advantage; quality must be the imperative.*

At ISPE's Intensive Workshop on Aseptic Technology (5-6 March, Baltimore, MD-USA), participants heard case studies and discussed approaches to utilizing available technology and regulatory issues. Keynote presenter Rick Friedman, Associate Director, OMPQ, FDA/CDER, declared that "quality rests squarely with industry" and that "ISPE is the most prominent organization encouraging the move to more advanced technology in sterile operations." Friedman also shared his views on the importance of industry carefully monitoring complex and

Concludes on page 71.

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Establishing and Managing a Vendor Network for Clinical Supply Manufacturing Services

by Francis Dumont and Sandra Onorato

This article presents some essential operational and evaluation aspects of the Request for Information/Request for Proposal (RFI/RFP) process when conducted for the purpose of establishing a vendor network for clinical supply manufacturing services.

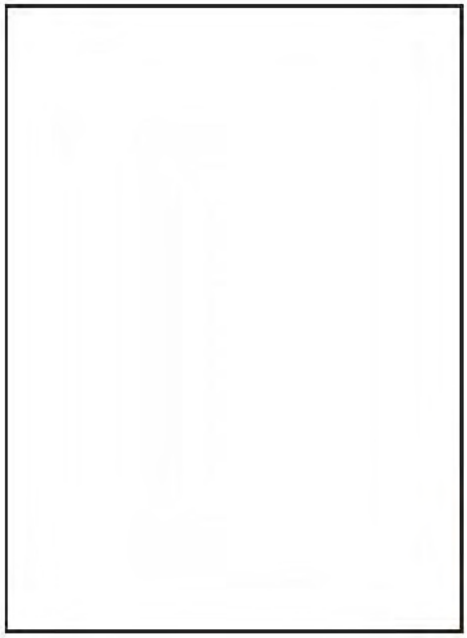
Note: Portions of this article are being reprinted with permission from Pharmaceutical Outsourcing.[1]

Introduction

The need to find cost-effective ways to operate is of paramount importance in face of the current economic challenges facing the Pharmaceutical Industry (Pharma). The industry is faced with the requirement for innovation, technical expertise, and high quality while at the same time needing to drive down costs against aggressive timelines. These same organizations are looked upon to enable the portfolio and constantly challenged with new, complex problems to solve. Additionally, Pharma has evolved to be global in reach across both clinical development and commercial product areas. The need to supply global clinical trials, while assuring global regulatory support, presents an added challenge to the industry during these cost sensitive times.

One way that Pharma has dealt with containing and reducing costs is through outsourcing. The fundamental technique for evaluating a pool of potential vendors against a block of work is through the Request for Information (RFI) and Request for Proposal (RFP) process. This is a well established process across all industries and is likely here to stay within Pharma, particularly during this period of focus on cost-effective sourcing. However, it is recognized that the process itself can be laborious and in order to be successful requires more effort and internal alignment than is typically considered or performed.[2] Nevertheless, the economic benefit obtained from using the process is too meaningful and measureable for RFIs and RFPs to disappear.[3] Numerous references and online aides regarding the basic concepts and processes of RFI/RFP are available, much of which are focused on the structure and content of these tools.[4,5] This article presents some essential operational and evaluation aspects of the RFI/RFP process when conducted for the purpose of establishing a vendor network for clinical supply manufacturing services. Based on Pfizer's experience across a number of projects, these essential aspects are focused on the following areas:[1]

- Establish and communicate realistic demand projections for the services under evaluation
- Assemble an appropriate team of Subject Matter Experts (SMEs)
- Identify key evaluation criteria at each step of the process
- Determine what measurement methods are appropriate as some may be more subjective than objective
- Make the RFI/RFP process work for both the buying organization and the service provider
- Evaluate output and document decisions based on that evaluation



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Sourcing professionals in Pharma should ask themselves the following questions:

- Do I have a clear understanding of what products/services I need to buy and how I want them to be provided?
- Do I know why I am using the current vendors in my network of service providers?
- Do I have the documentation to support the initial selection of these service providers?

Through the use of a well defined RFI/RFP process and by paying attention to some of the essential aspects discussed in this article, those questions can be answered affirmatively.

Once a vendor network for clinical supply manufacturing has been established, a practical approach to management needs to be put in place for that group of vendors. Careful consideration needs to be given to the type of work being conducted. This is not commercial manufacturing, where validated products are routinely made dozens or hundreds of times a year and metrics are easily captured. This article provides an overview of the collaborative approach developed by Pfizer for clinical services and includes the following aspects:

- Vendor segmentation to define management approach
- Assignment of a central point person, the Relationship Manager
- Engaging internal and external stakeholders
- Vendor Governance
- Performance Management
- Risk Assessment

Incorporation of the practices described in this article can help an organization successfully establish a vendor network to support clinical supply manufacturing and implement a practical approach to vendor management.

Establishing a Network

Establish and Communicate Demand

Better engagement by potential vendors on the RFI/RFP process can be expected when information is provided not only on the type of work within scope, but also the anticipated volume of that work in the foreseeable future. Due to the nature of Pharma work in the clinical development phase, it is often difficult to give definitive forecasts for manufacturing associated with that type of work. However, it is important that sponsors of this work, like Pfizer, invest the time required to gain a reasonable understanding of the expected and potential needs for both the immediate term and into the next year or two. There are many reasons to do this, including possibly leveraging volume-driven cost savings or influencing capital investments on the vendor side. Guaranteed spend/volume commitments can be used for price concessions, particularly if long term commitments can be established. Additionally, a realistic forecast can help determine a vendor's true ability to support the projected workload and what investments might be needed on their side to ensure continued productivity and efficiency.

It is also important to truly understand the intent of the sourcing exercise. Is it due to a large increase in the volume of work (e.g. capacity outsourcing)? Is there a need to explore cost savings against the current vendor network? Are external cost savings versus internal support being explored? Is there a need to access capabilities of the supply base not within internal competencies (e.g., competency outsourcing)? Typically, several of these drivers will be applicable, but an understanding of their relative importance helps to effectively design and execute the sourcing and selection process.

Giving potential vendors a view into projected needs and rationale for conducting the sourcing exercise is important for engagement. Vendors are inundated with RFI/RFP requests in the current environment that tend to go no further than the discussion stage, sending the message that many of these efforts are simply for benchmarking purposes. A well-stated and honest rationale for the sourcing project can help eliminate that fear.

Assemble Team of SMEs

The process for evaluating and on-boarding vendors for clinical supply manufacturing activities, including the RFI/RFP steps, is heavily reliant on a team effort within Pfizer. It is important to have a team lead that is responsible for the overall project, possesses a strong understanding of the work within scope, and has the authority to hold team members accountable for timelines and deliverables. While the mechanics of the RFI/RFP process and commercial assessment is typically led by a member of the Procurement organization, technical SMEs play a critical role on the team by being accountable for developing assessment tool criteria and evaluating technical and quality competencies based upon vendor responses. For clinical supply manufacturing projects at Pfizer, the team typically comprises members from Clinical Supply Sourcing, Quality, Analytical, Formulation Development, and Procurement. More frequently, a team member from the Environmental, Health, and Safety organization has been getting pulled into RFI/RFP discussions, particularly for projects that pose material handling challenges. For a large Pharma company that is well represented across all of these disciplines, it is reasonable to assemble this multi-functional team. Small, emerging companies often have sourcing professionals who need to source activities outside of their knowledge base. In those situations, it is highly advised that consultants be utilized to provide technical guidance in the areas that are lacking internal resources. A sourcing exercise conducted without the appropriate base

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of knowledge to evaluate potential vendors is a recipe for disaster, as it is easy to then overly influence selection based on cost criteria.

Identify Evaluation Criteria

Defining and implementing an evaluation process early on is key. Ideally, this would occur prior to receipt of RFI/RFP responses in order to reduce bias. Many approaches can be utilized to score response information; these can range from very simple to very complex methods. Potential evaluation options vary from simple yes/no responses to numeric values with category weightings. An example of a weighted scoring method used to evaluate service providers in the clinical supply manufacturing space is shown in Table A.

One important point to consider is the level of quality evaluation at this stage. It is certainly important to include quality criteria to ensure that the vendors being assessed have the appropriate regulatory and compliance history experience to support the desired work and meet the GMP requirements for the geographic areas where trials are planned. Regulatory agencies are continually increasing expectations that Pharma fully understand and are accountable for activities conducted at their outsourcing partners.[6,7] However, overly emphasizing those aspects at this early stage could prevent the buyer from evaluating some newly emerging potential partners that could bring significant value to a relationship. At the end of this process, a formal quality-driven audit will be the real opportunity to thoroughly test the quality, regulatory, and compliance aspects of the potential partner, including the identification of any showstoppers.

It is also important to provide RFI/RFP evaluators with a common set of criteria to score respondents (e.g., what warrants score of 5 vs. 1 for any particular category shown in Table A). Due diligence to this aspect is important to obtain a good comparison across potential service providers. Table B provides examples for a few of the areas evaluated in Table A. This scoring methodology provides a framework to compare vendors in an objective way and to help provide supporting rationale for sourcing decisions.

Buyer and Service Provider Interactions

A good communication plan when conducting an RFI/RFP exercise is essential to its success. While many of the recommendations provided here are based on common sense, they are worth repeating.

Considerations for Buyers

It is important for organizations initiating an RFI/RFP to

Category	Weight*	Vendor X*	Vendor Y*	Vendor Z*
1. Job Type Considerations	50%	4.4	4.7	1.7
A. Technical Capability to Perform Scope of Work	40%	5.0	5.0	2.0
B. Capability to Perform Work at Required Scale	30%	3.0	4.0	2.0
C. Projected Cycle Times	15%	3.0	5.0	1.0
D. Ability to Leverage API Mfg and/or Formulation Dev	10%	4.0	4.0	1.0
E. Scale-up and Commercial Launch Support	5%	4.0	4.0	1.0
2. Cost Considerations	20%	4.3	2.4	1.3
A. Job Type Costs – Costs to run typical jobs	80%	4.0	2.0	1.0
B. Pfizer-Specific Material Set-up Costs	10%	5.0	3.0	1.0
D. Analytical Testing Costs	10%	5.0	5.0	4.0
3. Quality Considerations	20%	4.4	3.4	1.6
A. Regulatory Audit Experience	60%	4.0	3.0	2.0
B. Completeness of Meeting EU Regulations	40%	5.0	4.0	1.0
4. Analytical Testing Considerations	10%	5.0	2.0	5.0
A. Analytical Testing Capabilities	100%	5.0	2.0	5.0
Total Score		4.4	3.6	2.1
*Weightings and score examples are for illustrative purposes only and not necessarily reflective of actual values used within Pfizer.				

Table A. Example scoring method.

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Aspect Evaluated	5* Excellent	4	3* Average	2	1* Poor
Technical Capability to Perform Scope of Work	All required job types fall within routine remit of facility		All required job types have experience base within facility, but may not be routine		Cannot perform all required job types
Projected Cycle Times	Projected cycle times are shortest of respondents		Projected cycle times are average compared to other respondents		Projected cycle times are significantly longer than most respondents
Job Type Costs – Costs to run typical jobs	Quoted cost is lowest of respondents		Quoted cost is average compared to other respondents		Quoted cost is significantly higher than most other respondents
Regulatory Audit Experience	Significant regulatory audit history with high positive outcome rate		Moderate regulatory audit history with mostly positive outcome rate		Limited regulatory audit history and/or unfavorable outcomes from audits
Analytical Testing Capabilities	Able to support critical test and 50% of all tests probed		Able to support critical test and 70% of all tests probed		Limited analytical support: cannot provide critical tests
*Criteria examples are for illustrative purposes only and not necessarily reflective of actual values within Pfizer.					

Table B. Scoring criteria.

have a well defined plan in place. When seeking a vendor network for clinical supply manufacturing, these aspects include having a well-written work scope document and clearly defining the information transfer process. Guidelines for response time and format of response need to be clearly set and communicated. It is also important to set realistic expectations regarding turnaround. While certain situations may warrant very aggressive timelines for turnaround of an RFI/RFP, organizations can expect better quality information and a wider base of service providers willing to participate when timelines are reasonable. It is also important to ensure that there are sufficient opportunities built into the process to allow time for the vendors to ask clarifying questions after any point of information transfer.

Perhaps the most important point for consideration is to provide feedback to RFI/RFP participants at the end of the process. This practice is a good professional courtesy and will help maintain credibility; it will also help assure active participation by the potential vendor pool in future projects.

Considerations for Service Providers

The key message for service providers of clinical supply manufacturing services is to treat the RFI/RFP process seriously if there is interest in the work and particularly if there is interest in working with the potential buyer. This includes effectively communicating whether or not participation is possible and desired. Formally recognizing and declining a request to participate in a sourcing exercise is better than no response at all. If participation is chosen, then delivering on the information transfers thoroughly and on time is a must. Doing otherwise can negatively impact the vendor's credibility with the buyer organization in both the short and long terms.[3]

Considerations for Both

The RFI/RFP process works best when both buyer and provider have a single primary contact in place to manage the communication flow. This helps to minimize confusion and assures compliance to timelines and associated commitments. The key contacts can also work together to facilitate clarification meetings and teleconferences as needed throughout the process.

Documented Output

The value of keeping detailed documentation of RFI/RFP efforts and other vendor evaluation exercises cannot be stressed enough. The data to support vendor selection and utilization decisions can be used for numerous purposes. Some practical examples based on experience include the following: (1) justifying approval of purchase orders, (2) demonstrating that a particular vendor recently "discovered" by a colleague has already been evaluated through a thorough process, (3) showing a new organizational leader that a defendable approach was utilized to establish a vendor network, and (4) providing a logical starting point when initiating the process for similar blocks of work or refreshing information on the current vendor pool.

The methods and tools used to document the identification and establishment of a vendor network through the RFI/RFP process can vary from the simple (e.g., retention of evaluation spreadsheets presented in Identify Evaluation Criteria section of this article) to the highly complex. A pragmatic approach to meet this objective generally entails assembling a presentation deck that includes background for RFI/RFP need, scope of work, explanation of how vendors were selected to participate in RFI/RFP, description of

evaluation criteria and scoring, and data that led to final vendor selection decisions.

Managing a Vendor Network

Vendor Segmentation

Appropriate segmentation of your vendor network is important to help determine the level of vendor management needed for that relationship. The resultant vendor management approach should then be variable and appropriate to the specific vendor relationship. Not all vendors need to receive the same level of operational, quality, procurement, and leadership oversight.

Figure 1. Vendor segmentation approach.

Pfizer Pharmaceutical Sciences developed a tiered approach to vendor classification as shown in Figure 1. These categories were defined based on both the value and risk associated with the work in scope, strategic value to the organization, frequency of work, and anticipated length of the relationship as shown in Table C. The level of quality, operational, and procurement oversight are commensurate to the tier rating and is also provided in Table C.

Relationship Manager

For vendors deemed as very important or critical to your business, it is recommended that a Relationship Manager be appointed. This individual is responsible for the overall health of the partnership. The Relationship Manager can work with his/her vendor counterpart to identify opportunities for maximizing current and future opportunities that drive mutual value and continuous improvement. A Relationship Manager also plays a key role in the following oversight activities:

Advocacy
- Provides a voice for the Vendor and is a resource for team members
- Helps ensure cultural compatibility

Communication
- Facilitates transparent and open lines of communication
- Establishes alignment on joint deliverables/commitments

Decision Making
- Ensures alignment of priorities and resources across parties
- Resolves disputes with mediation skills

Monitor and Feedback
- Drives performance management
- Performs regular risk assessments and addresses issues

Engaging Your Stakeholders

It is critical to engage internal stakeholders who have interests that will be affected by the vendor's performance. It is important for the overall health of the partnership to have everyone's interests represented and for all stakeholders to be aligned and working towards the same goals. In addition, value can only be derived from collaborative relationships that maximize joint outcomes internally and externally while supporting equitable business opportunities. Vendors support an outside organization's objectives while fulfilling their own interests in the growth and prosperity of their business. The closer the alignment is between organizations the healthier the collaboration will be. Key elements to consider for managing your stakeholder network include the following:

- Conduct a global evaluation of vendor capabilities, risk, and performance to set realistic expectations
- Ensure there is goal alignment to help manage multiple and conflicting priorities across groups
- Establish Service Level Agreements and collect the appropriate metrics
- Deliver a unified message and direction to set clear expectations
- Solicit feedback on stakeholder satisfaction to construct a productive environment
- Highlight accomplishments and how they can be applied more broadly

	Basic	Specialty	Collaborative	Strategic
Value/Risk of Work	Low risk purchases (e.g., readily available materials and components; routine services)	Project specific business value	Very important to business	Critical to meeting company objectives
Relationship	- Short term (i.e., transaction based)	- Short to mid term	- Mid to long term - Some strategic value - Continuous improvement on service, cost, quality is a focus	- Long term - High strategic value (e.g., multi disciplines, sites, programs, etc.) - Collaborative engagement with shared benefits
Relative use	Frequent and infrequent possible	Infrequent	Frequent	Frequent
QA Oversight*	Material Suppliers: QA assessment based on material type and intended use GMP and GMP/GCP Interface Contractors; As needed basis, short term focus during use	Material Suppliers: QA assessment based on material type and intended use GMP and GMP/GCP Interface Contractors; As needed basis, short term focus during use	GMP and GMP/GCP Interface Contractors; Proactive, ongoing Material Suppliers: QA assessment based on material type and intended use	GMP and GMP/GCP Interface Contractors; Proactive, ongoing
Operational Oversight	Tactical; sufficient to ensure terms of purchase agreement and applicable compliance requirements are met	Short term focus during supplier operations based on risk assessment	Proactive and ongoing relationship management *Level of review of tactical work is greater than for strategic supplier*	Proactive and ongoing relationship management
Procurement Oversight	Tactical only	Procurement Tier as applicable	Health Check (annual)	360 Survey; Health Checks

Table C. Vendor segmentation definitions and level of oversight.

- Practice proactive damage control when an undesirable event occurs

Vendor Governance

A robust governance framework that includes senior leader involvement is essential to a successful partnership. This should also include an escalation pathway for problem-resolution to course correct as needed. Defined teams responsible for the day to day interactions along with the Relationship Manager should actively monitor the agreed to standards for quality, performance, and cost and recalibrate when needed to ensure there is proper alignment.

Communication forums with defined frequency, governance topics, and attendees should be held with the vendor and be face to face where possible. Establishing a formal plan that provides channels for informal and formal communication and timely interaction is critical. The changing nature of business needs will require that relationships evolve and open communication will ensure they progress correctly. The governance structure can assist with monitoring vendor's investments and emerging capabilities to ensure that the direction of the business is supported.

Performance Management

A formalized performance management process that continuously maps the needs of the business and measures the vendor's ability to meet those needs is critical to vendor management. Effective performance monitoring provides the following:

- Increases the flow of communication between your organization and the vendor
- Allows for better insights into a vendor's performance
- Helps to identify, prevent, and mitigate supply risk
- Rationalizes vendors based upon performance information
- Weeds out low performers and high-risk vendors
- Provides opportunities for top performers to grow their business
- Assists with uncovering continuous improvement opportunities

In order to monitor performance, meaningful metrics based on performance expectations need to be established and should be site- and operations-based if a vendor has multiple locations and provides discreet services. Metrics can be rolled up further into a Vendor Scorecard for an overall score to capture the holistic value of the relationship. A balanced scorecard approach that integrates metrics for operations, quality, and value perspectives is recommended. An example is provided in Table D.

Risk Assessment

Periodic risk assessments based on the knowledge of activities, performance metrics, and information available at the time of the assessment are vital to managing your organization's risk and the health of the vendor relationship.

Once vendor risks are identified, a proper oversight plan is needed to address any potential adverse impacts. An effective mitigation plan requires close collaboration with the vendor and all the relevant stakeholders. Both organizations should work in partnership to develop and monitor mitigation plans to reduce identified risks to an acceptable level and track and address areas of non-compliance. Lastly, mitigation plans should be fair, reasonable, measurable, and fit for purpose. Parameters for evaluating, categorizing, and prioritizing risks should include the following:

- Risk likelihood (i.e., probability of risk occurrence)
- Risk consequence (i.e., impact and severity of risk occurrence)
- Thresholds to trigger management escalation and activities

For any given risk, techniques and methods should be explored to avoid, reduce, and control the probability of risk occurrence. However, some risks may be acceptable and simply monitored.

Supplier Name	
Scorecard Frequency	Monthly
Performance Period	Jan-13

Green - 90-100%
Yellow - 70-89%
Red - <70%

Monthly Rating	YTD Rating
100.0%	100.0%

Category	Metric	MONTH #	MONTH Total	MONTH Perf	MONTH Wgt*	MONTH Rating	2013YTD #	2013YTD Total	2013YTD Perf	2013YTD Wgt*	2013YTD Rating
Quality 30%	Substantiated Complaints	0	0	100%	6%	6.0%	0	0	100%	6%	6.0%
	Commitments completion on time	0	0	100%	3%	3.0%	0	0	100%	3%	3.0%
	Investigations & Deviations - no reportable events	0	0	100%	5%	5.0%	0	0	100%	5%	5.0%
	Investigations completion on time	0	0	100%	3%	3.0%	0	0	100%	3%	3.0%
	% CAPA completed on time	0	0	100%	3%	3.0%	0	0	100%	3%	3.0%
	Batch Record Conformance	0	0	100%	5%	5.0%	0	0	100%	5%	5.0%
	PharmSci Vendor QA Dashboard Rating	-		3.0	5%	5.0%	-		3.0	5%	5.0%
Operations 30%	On-time delivery performance	0	0	100%	7%	7.0%	0	0	100%	7%	7.0%
	Quantity Accuracy	0	0	100%	5%	5.0%	0	0	100%	5%	5.0%
	Quality Right First Time	0	0	100%	7%	7.0%	0	0	100%	7%	7.0%
	EH&S Rating	-		3.0	5%	5.0%	-		3.0	5%	5.0%
	Operations Survey	-		4.0	6%	6.0%	-		4.0	6%	6.0%
Technology 20%	Technology Survey	-		4.0	20%	20.0%	-		4.0	20%	20.0%
Value 20%	Overall Value Contribution (Survey)	-		4.0	20%	20.0%	-		4.0	20%	20.0%

* Weightings shown are for illustrative purposes only and not necessarily reflective of Pfizer process.

Table D. Example scorecard for vendor performance management.

Summary

Establishing and subsequently managing a vendor network for clinical supply manufacturing services poses many challenges to Pharma innovators. The RFI/RFP process provides tools that can guide much of this effort and lead to a fair, consistent, and well documented approach. The vendor management approach chosen can range from very simple to highly complex; a fit for purpose plan should be developed to address the needs of the organization and service provider. The application of aspects provided in this article can help both buyers and service providers get the most out of the RFI/RFP process and vendor management practices as they pertain to clinical supply manufacturing services.

Acknowledgments

We would like to thank the following colleagues for their review and feedback of content incorporated into this article: Kelli Boiselle, Kurt Speckhals, Paul Stuart, and Gerald Thompson.

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PHARMACEUTICAL ENGINEERING Interviews

Roger Nosal, Vice President, Global Chemistry, Manufacturing and Controls (GCMC), Pfizer

Roger Nosal is currently Vice President of Global Chemistry, Manufacturing and Controls (GCMC) at Pfizer. GCMC is responsible for the development, preparation, prosecution and defense of chemistry, manufacturing and control commitments and data for investigational, commercial and post approval regulatory submissions globally. Nosal currently leads the PhRMA LDKITT on Implementation of Quality by Design and has been instrumental in developing and establishing Pfizer's regulatory approach and position for application of QbD, including the introduction of Real Time Release testing (RTRt), Continuous Quality Verification (CQV), Continuous Processing and extension of QbD for development of analytical methods and stability protocols. He has 32 years of experience in the pharmaceutical industry at G.D. Searle, Monsanto, Pharmacia and Pfizer. During the last 19 years, Nosal has been responsible for developing and executing regulatory CMC strategies and approvals of global commercial applications for 49 new chemical, biological and device products and scores of investigational and post approval regulatory submissions. Prior to his tenure in regulatory, he served as a medicinal chemist during which he authored 24 patents for a diverse range of medicinal candidates (PAF antagonists, 5-HT3 antagonists and 5-HT4 agonists, COX-2 inhibitors, leukotriene agonists and antagonists, serotonin inhibitors) and as a process chemist, where among other projects, he focused on synthetic development and analytical control of derivatives of aspartame and manufacturing optimization of high order cuprate couplings for synthesis of prostaglandins.

What do you use for your elevator pitch/lay-persons definition of QbD?

QbD is fundamentally about developing process understanding and product knowledge to improve assurance of product quality. Conceptually, it describes a scientifically grounded approach for prospectively assessing risks, prioritizing experiments and developing a robust and holistic control strategy.

After several years leading industry toward adoption of QbD, what is the status of implementation of QbD at Pfizer?

The implementation of QbD is pervasive within Pfizer particularly during product development. Risk-based approaches are routinely used to assess manufacturing processes, prioritize experiments and determine criticality of product attributes and process variables.

Pfizer's "Right First Time" paradigm is largely based on principles of QbD.

Has participation in the pilot programs (FDA Pilot Program and the recent FDA/EMA Parallel Pilot Program) been successful for Pfizer and industry?

Participation in the FDA Pilot Program was successful for Pfizer and industry. Prior to the pilot program, QbD was primarily conceptual. Companies had adopted elements of QbD to assess the technical merits of process and product design, but had been reluctant to share the results from these approaches in regulatory submissions without assurance that regulatory review would not impact approval. The FDA Pilot Program provided a constructive opportunity to engage FDA

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on the technical and regulatory merits of the application of QbD. This pilot also began to address the possibility of offering regulatory flexibility where process understanding and product knowledge had been demonstrated to adequately reduce and mange risks.

As for the FDA/EMA Parallel Pilot, it is premature to judge its success as there have been limited examples; however, EMA and FDA regulators have claimed that the Parallel Pilot has been "extremely beneficial for regulators." Anecdotal comments from FDA, EMA and PMDA (Japan was invited to participate as an observer for the Pfizer candidate enrolled in the Parallel Pilot) suggest the interactions between the regulatory authorities were useful and insightful.

Have there been any specific hurdles with the implementation of QbD within Pfizer?

The most significant hurdles have been associated with the most recent QbD regulatory submissions where divergent perspectives between industry and regulatory authorities, primarily in the US and EU on definition and verification of design space, change management, level of detail in regulatory commitments, description of control strategy, consistency of submission content and alignment of inspections with regulatory review have become topics that warrant reconciliation.

What is your assessment of the regulatory receptivity toward QbD in regulatory submissions?

In general, regulators have been receptive to QbD in regulatory submissions. They recognize the value of increased process understanding and its impact on improving confidence in the quality of products. However, regulators have suggested, and industry has acknowledged, that industry needs to improve their stories particularly with respect to describing a comprehensive control strategy.

Is the adoption, implementation and regulatory acceptance of QbD transparent globally?

Not entirely. In several countries beyond US EU and Japan, i.e., Canada, Australia, New Zealand and China, QbD is transparent as QbD regulatory submissions have been approved in these countries. For many countries where a limited level of detail is not required, QbD is largely invisible, though the benefits of reduced level of regulatory commitments have been realized.

From Pfizer's perspective, what elements of QbD have been most successful to date and why?

The most successful elements of QbD for Pfizer have been the paradigm shift to a prospective, risk-based approach to developing process understanding and product knowledge. Pfizer has observed improved process understanding and capability, technical transfers and communication and integration of development and manufacturing operations. Pfizer has also realized reduced uncertainty, recalls, manufacturing anomalies, quality investigations and manufacturing problems with the adoption of QbD.

I also firmly believe that QbD increased the level and depth of communication between regulatory authorities and industry. While this required significant investment and effort, it improved mutual understanding and the opportunity to establish a reasonable risk-based and science based approach to continual improvement and technical innovation.

From Pfizer's perspective, what elements of QbD have not been successful to date and why not?

For EU and US regulators, the conspicuous disconnect between regulatory commitments and change management has been a significant surprise. There appear to be a misalignment within regulatory authorities on the connection between a company's Pharmaceutical Quality System and change management process and the regulatory commitments described in a regulatory submission. In addition, the apparent lack of comfort with risk associated with the establishment and verification of design space and decreased rather than increased confidence in quality despite the increase in process understanding and product knowledge in a QbD registration. To some extent QbD regulatory submissions have engendered increased numbers of queries and justification than traditional regulatory submissions and the respective regulatory relevance of many of those queries and increased expectations has been questionable.

What is the primary benefit of QbD to Pfizer? To Patients?

The primary benefit of QbD to Pfizer and patients is improved process understanding and product knowledge that translates to increased assurance of quality and reliability and consistency of supplies.

How does the PQLI Guide series support the movement toward embracing and utilizing QbD?

The PQLI Guide series translated the conceptual elements of QbD as described in ICH Q8(R), 9 and 10 into a practical demonstration of "how to" adopt, apply and integrate these concepts into a technical and regulatory strategy for designing and developing a product and associated manufacturing processes. The strength of the PQLI Guide series is that it was based on actual examples and experience from industry.

Is there anything else that you might want to say to our readers? Any last thoughts?

Recent examples of regulatory misalignment on fundamental aspects of QbD offer opportunities to improve consistency in regulatory expectations and establish relevant criteria for product lifecycle management. QbD also offers a scientific and risk based vernacular that can improve global harmonization of regulatory expectations.

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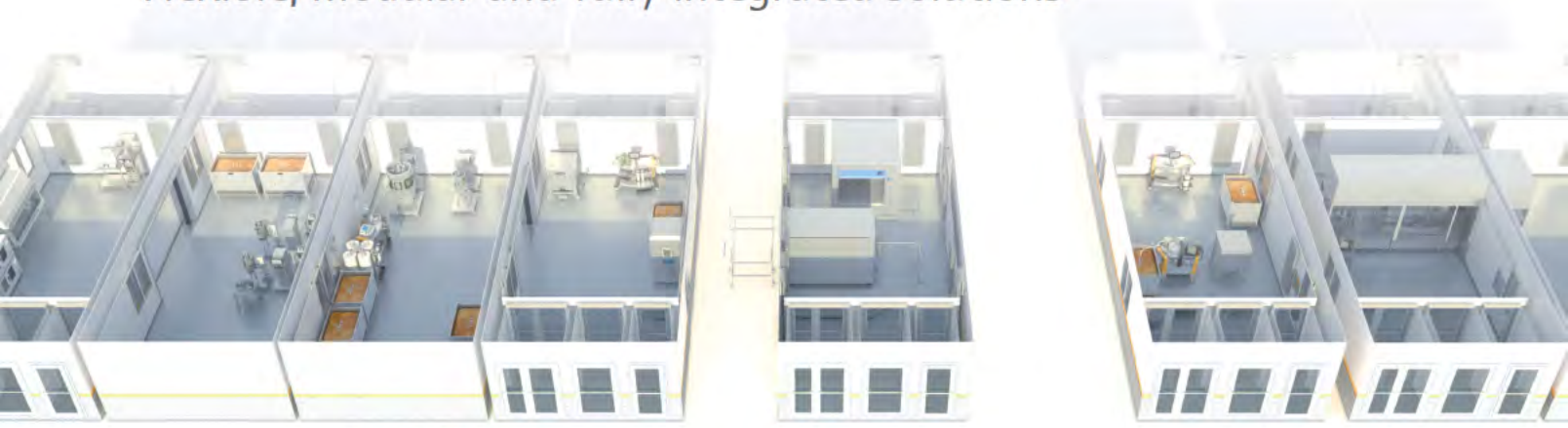

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An "Eco-Friendly" Assessment of Cleaning Agents in GMP Regulated Facilities

by Elizabeth Rivera

This article discusses cleaning agents used in GMP applications and relevant issues in minimizing pollution, reducing waste, managing personnel hazards, and complying with local regulations.

Introduction

There is a growing awareness and concern in today's society about the "long-term maintenance of biological diversity for human well-being," also known as environmental sustainability. This concern is growing due to a variety of factors, including global climate change, limited natural resources, human health issues, and increasing population, among others. This global issue has led to resurging demand for "green" chemistry solutions for cleaning and microbial control challenges.

The Origin of Green Chemistries

The "green chemistry" concept dates back to the mid 1990s when two chemists established 12 principles for designing chemical products and processes to reduce or eliminate the generation of hazardous waste.[1] These principles have been applied to various industrial processes, including pharmaceutical, medical device and cosmetic manufacturing, and other regulated industries.[2,3] The following discussion focuses specifically on cleaning chemistries.

The green chemistry concept focuses on the intrinsic hazard of a chemical or chemical process, and seeks to minimize that hazard to reduce personnel and environmental concerns. So, green chemistries can be viewed as risk mitigation tools.

The Meaning of "Green"

So what exactly does "green cleaning" mean? Does this term imply that the chemistry is safe for the environment; for humans and animals; in any concentration? Possibly. It also may mean that a product is made from plants and not petroleum. What about biodegradability? Recyclability?

In industry practice, "green" could mean any or all of those things and more. But a green formulation also must be effective and suitable for its intended use. A cleaning product that cannot efficiently clean (e.g., requires a high concentration or a very long contact time to be effective) is a potential waste of resources, and is the antithesis of environmentally sound.

The focus of this article is on cleaners as they relate to cleaning processes for GMP applications. A brief overview of several standards is presented to assist in understanding environmentally friendly cleaners. Next there is a discussion to answer some of the common concerns regarding current chemistries used for cleaning processing equipment in GMP regulated industries. The focus is given to relevant issues in minimizing pollution, reducing waste, managing personnel hazards, and complying with local regulations.

The Current State of GMP Cleaning

Cleaning procedures are required in current Good Manufacturing Practices (cGMPs) industries for maintaining safe and optimally performing manufacturing equipment and facilities. The use of cleaning products to effectively remove process residues, dust, allergens, and infectious agents may

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be crucial to preventing product contamination that could adversely affect patient safety. But the use of cleaning products also may present health and environmental concerns. They may contain chemicals associated with skin irritation and corrosion, inhalation risks, and other human and animal health problems.

Additionally, the concentrated forms of some cleaning products are environmentally hazardous, containing ingredients that must undergo significant treatment (e.g., pH adjustment) before they can be safely discharged. Since the use of some products creates potential handling, storage, and disposal issues for users, these use factors are increasingly becoming components of the selection criteria when new or current cleaning processes are being evaluated.

Beyond Consumer Endorsements

Definitions of green chemistries and processes rely primarily on local legislation; however, environmental organizations, public information, and company policies regarding the environment are also influences.

Green certification is also feasible for some categories of cleaners. Government agencies and non-profit organizations offer voluntary programs, such as the U.S. EPA Design for the Environment (DfE) and the Green Seal™. These are renowned programs dedicated to the development of green products standards; however, most of these programs focus primarily on household (consumer) and janitorial type cleaning products,[4-7] which may not be optimized for use in critical GMP cleaning.

The effectiveness of cleaning procedures used in GMP regulated facilities is affected by multiple factors like temperature, action, concentration, chemistry, and contact time. Other factors affecting cleaning are soil type and conditions, type of equipment surfaces, equipment design, and others.[8,9] Because of the many process variables and the critical nature of this cleaning, consumer-focused "green" guidance may not adequately address the effectiveness of cleaning products for GMP cleaning processes.

Another potentially problematic aspect of household and janitorial products is that because of their consumer focus, the formulations are regularly changed to maintain their "new and improved" status in the market. This may appeal to consumers, but it presents validation nightmares for GMP cleaning.

Moreover, voluntary programs may support the use of bio-based renewable ingredients that include plant, animal, and marine mass derived materials.[10,11] These types of ingredients may not be appropriate for GMP industries because they may pose risks associated with variable bioburden, prion contamination, and other related issues.[12-13] The variety of manufacturing equipment, complex soils, and unique applications in these highly regulated industries makes cleaning product selection even more difficult. For these reasons, each GMP regulated site might be best served by defining their own specific "green" goals.

However, some of the fundamental pollution prevention and hazard reduction principles might still be useful to GMP sites when they are developing an eco-friendly cleaning program. Table A provides a list of references.

This article does not intend to assess the requirements of any of the aforementioned standards or to establish criteria for green cleaning processes in the pharmaceutical and related industries. Rather this discussion addresses common issues regarding cleaning products and procedures used by GMP industry participants, and offers assistance in the selection of cleaning chemistries to ease major environmental and health concerns.

Minimizing Water and Air Pollution

The most controversial environmental problem related to formulated detergents is the surface active agents, or surfactants[14] used as ingredients. In the European Union, most of this concern has been alleviated by restricting the use of less biodegradable materials, such as tetrapropylbenzene sulfonate and certain alkyl phenol ethoxylates, through legislative ban or voluntary action. Even so, surfactants are

Name	Reference Standard (s)
Green Seal™	GS-37 Cleaning Products for Industrial and Institutional Use
United States (U.S.) Environmental Protection Agency (EPA) Design for the Environment	Standard for Safer Cleaning Products
Canada's Environmental Choice Program (EcoLogo®)	CCD-146 Hard Surface Cleaners
INFORM, Inc.	Cleaning for Health: Products and Practices for a Safer Indoor Environment
Consumer Specialty Product Association	Cleaning Products Compendium
ECOCERT® Group	Natural Cleaning Product Standard
EU Ecolabel	Commission decision on establishing ecological criteria for the award of the Ecolabel to all-purpose cleaners and sanitary cleaners
GREENGUARD®	Indoor Air Quality Standard for Cleaners and Cleaning Maintenance Systems

Table A. Green products voluntary programs.

still considered by many to be an environmental risk because they are in large-scale use by both industrial and consumer-focused manufacturers.

The overall biodegradability of surfactants has improved, in part due to legislation such as Detergent Regulation EC 648/2004, which demands stringent tests for biodegradability. This has led to the withdrawal of several surfactants from products sold in the European Union. In addition, the Organization for Economic Cooperation and Development (OECD) is developing standards for testing aquatic biodegradability of organic ingredients in products, and some have been adopted by several of the organizations listed in Table A.

Waste water regulations are often the starting point for determining the type of cleaning agent a facility should use. Local limits may be established for some chemical species and these must be addressed before implementing a cleaning procedure. For example, the general feeling in the late 1960s was that US lakes and streams were getting more polluted each day, and phosphate detergents were the primary reason. Furthermore, the presence of hypochlorite has been demonstrated to form trihalomethanes if the amount of chlorine and the nature of organic residues in the waste stream created the right conditions. Consequently, local authorities may establish limits for both phosphorus and chlorine, which necessitates limits on the amount of discharge from cleaning agents containing these materials.[15,16] Also there may be limitations on levels of mercury, lead, cadmium, and other heavy metals.

Chelating agents also may have potential environmental drawbacks. These are substances that improve the effectiveness of formulated cleaners by preventing free metal ions in solutions from interacting with surfactants. The most frequently used chelating agents are Ethylenediaminetetraacetic Acid (EDTA) and Nitrilotriacetic Acid (NTA). The first is biodegradable (but it does so slowly),[17,18] and the second is listed as a possible human carcinogen by the International Agency for Research on Cancer (IARC).[19]

There also has been resurging discussion about phosphates, because of the widespread use of Sodium Tripolyphosphate (STPP), which is a common ingredient used in the formulation of cleaning products. Since STPP is an inorganic substance, biodegradation studies are not applicable. However, STPP can be assimilated by algae and by microorganisms, thus ends up being assimilated into the natural phosphorus cycle. Restrictions in the use of certain chelating agents are in place or are evolving in some countries. For this reason, the industry continues to search for cost-effective alternatives.[20]

The pH of a formulation is another environmental factor to consider. Many municipalities have established pH restrictions in the discharge stream from industrial users. Facilities that use alkaline or acidic cleaning solutions must discharge the waste waters within acceptable discharge pH limits. If not controlled through neutralization prior to discharge, industrial users can incur substantial fines.

Cleaning agent suppliers should be able to supply charts or supplemental information to help these users establish neutralization processes. Usually, neutralization is done in specialized systems to allow mixing and temperature control. Most residues in GMP manufacturing are soluble in either a high or low pH cleaning solution. Neutralization of waste solution should not be performed in the cleaned vessel because a shift in pH may cause precipitation and re-deposition of residues onto vessel surfaces and consequently, more cleaning steps.

Water pollution concerns are also addressed by other tests to demonstrate that substances are not toxic to aquatic life. In some US states – California for example – acute aquatic toxicity would normally be determined using a fish 96-hour LC_{50} (lethal concentration) as required per California's Title 22 Code of Regulations. The Biological Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) of waste effluents are relevant in this regard. BOD is a measure of the content of biologically degradable substances in sewage, while COD is commonly used to indirectly measure the amount of organic compounds in water. Generally, it is desirable to send low level BOD and COD directly to the

municipal or plant wastewater system and divert high level BOD waste to a field recovery or holding tank. As in the case of LC_{50}, BOD and COD are often governed by regulatory agencies.

Phthalates are a class of widely used industrial compounds based on esters of phthalic anhydride. There are many phthalates with many uses, and just as many toxicological properties. Phthalates are used as emulsifying agents and suspending agents in a large variety of products, from enteric coatings of pharmaceutical pills and nutritional supplements to detergents and surfactants. Despite the variety of uses, phthalates are primarily linked to plasticizers in Polyvinyl Chloride (PVC) piping and packaging materials. Even so, there is a growing demand for phthalate-free products after a US bill was signed into law in 2008 banning the use of six types of phthalates in children's products.[21] The ban is permanent for the use of children's toys or childcare articles that contain more than 0.1% of di (2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or benzyl butyl phthalate (BBP). Environmentally conscious industries are demanding cleaning products with no hazardous phthalates and using phthalate-free PVC or stainless steel pipes in their GMP processes.

Certain Volatile Organic Compounds (VOC) released into the atmosphere may pose a threat to both air and water quality. VOCs are hydrocarbon compounds that have low boiling points, usually less than 100°C, therefore they evaporate readily. Since 1990, the US Clean Air Act requires abatement of a list of solvents that are hazardous air pollutants; a majority of these are toxic VOCs. Many VOCs can become a major concern for ground-water contamination because large environmental releases can be toxic to humans. Some VOC compounds can persist in ground water and migrate to drinking water supplies. Acetone, methanol, toluene, ethyl acetate, and other solvents are volatile organic compounds that are used in solvent-based cleaning processes in pharmaceutical production. While not all VOCs are hazardous air pollutants, handling large quantities for cleaning processes poses a concern because the spent solvents are not easily disposed of. They require solvent recovery, treatment, or incineration. For this reason there is a growing pressure in the pharmaceutical industry to move away from VOC solvent-based cleaning to aqueous-based chemistries or less hazardous solvents.

Ease of Disposal and Waste Reduction

The term "ease of disposal" is often applied only in reference to the cleaning agent in a GMP process; unfortunately, this is a gross oversimplification. The GMP industry deals with a wide range of process residues, including active ingredients and excipients, rouge and water scale build-up, and processing aids. Even when a cleaning agent is "eco-friendly," the spent solution may contain environmentally unfriendly residues like potent drugs and metal fines, among other things, that would not allow it to be disposed of directly into municipal sewers. Drug products manufactured at GMP sites are likely to be toxic in nature or otherwise bioactive and bioavailable (e.g., endocrine disruptors) and restrictions may be imposed on the amount of such residues that might end up in water effluents. This is where technologies like chemical and/or biological water treatment and stripping systems may need to be available on-site to ensure that waste streams meet required standards.[22]

Therefore, a spent solution's ease of disposal would not only depend on the cleaning agents, procedures, and tools that were used, but also on other residues collected in the spent solution. However, selecting a cleaning agent that poses minimal environmental impact should lessen the number of steps and resources necessary for water treatment.

Some residues may be easy to remove and some others can be tightly adhered to surfaces due to manufacturing steps that involve heat or steam. Complex residues like biopharmaceuticals may have an altered polymeric structure, which can make them more difficult to clean than their original state. Typically, parameters such as Time, Action, Chemistry, Concentration, and Temperature (TACCT) determine the cleanliness achieved by a process for a specific soil or group of soils.[23]

Choosing the right cleaning chemistry and parameters can help maximize productivity and reduce waste. Performing a laboratory simulation using representative materials of construction and manufacturing process soils is a good starting point to help determine the right cleaning chemistry and the optimum cleaning parameters. With this information in hand, a company can decide on the cleaning option that requires minimal raw material and utilities, and consequently produces less waste. Controlling these parameters effectively results not only in consistent cleaning performance, but also reduces waste by avoiding repeated cleaning steps due to unacceptable results.

Another way of reducing waste is by recycling and reducing packaging. Most packaging of cleaning products and tools are made of recyclable material. Plastics like High Density Polyethylene (HDPE), and Polypropylene (PP) are mostly recommended for liquid chemistries because of their excellent chemical resistance and recyclability. Cleaning agents that are offered in bulk sizes can accommodate large, industrial consumption, while also reducing the overall amount of packaging that must be dealt with. In addition, concentrated formulas can maximize the use of each unit container, which also reduces the number of empty containers.

Personnel Safety Management

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Bureau	Regulation	Description
U.S. Environmental Protection Agency	Toxic Substance Control Act	Lists ingredients used in non-exempt products.
U.S. Occupational Health and Safety Administration	Occupational Safety and Health Act	
Provides regulations and guidance for labeling, material safety data sheets, and hazard communication.		
Health Canada	Hazardous Products Act and the Controlled Products Regulations	Provides cautionary labeling of containers of controlled products, the provision of material safety data sheets, and worker education and training programs.
European Parliament	Regulation (EC) no. 648/2004 on Detergents	Controls the use of surfactants in cleaning products. Establishes biodegradability criteria for surfactants.
European Chemicals Agency	Registration, Evaluation Authorization and Restriction of Chemicals	Requires that all chemical manufacturers identify and manage risks linked to the substances they supply.

Table B. Regulations that impact cleaning agents.

example, packaging and delivery systems can be designed in such a way that they reduce operator exposure to the cleaning product.

Another great example is Clean-in-Place (CIP) systems, which allow for cleaning of a great deal of equipment without the added steps of dismantling it. This reduces operator exposure to potent drug residues and hazardous cleaners. It also minimizes the risk of damaging process equipment since the assembly and disassembly of the equipment is subject to human error. If not executed correctly, it can lead to malfunction or serious damage to the equipment, and can result in spills into the environment. Moreover, CIP systems may obviate the need for personnel to get inside the vessel to clean sharp parts like agitator blades or hard-to-clean locations, and reduce the added risk of personal injury.

A cleaning process in a facility also must consider the safety of the personnel who perform the procedures and who handle the chemistries. This is of special importance in manual cleaning processes where the personnel have a higher risk of exposure. In theory, a cleaning agent used in manual applications should not contain toxic VOCs or be corrosive to skin. Unfortunately, this may not always be feasible since the majority of organic residues are most efficiently cleaned with alkaline chemistries. Therefore, if cleaning agents that are corrosive to skin or are flammable are considered, proper Personal Protective Equipment (PPE) and training are essential.

Regulatory Compliance

In North America and Europe, cleaning agents are regulated by one or more agencies. Each agency has an impact on the type of cleaning agents that are available and on their applications. Table B offers a description of some global authorities and cites their reference guidance.

Even though biocidal agents are not within the scope of this article, it is worth mentioning them in this context. From a regulatory perspective, antimicrobial agents used in GMP facilities are often considered separately from cleaning agents. Overall, there is no widely accepted definition or criteria for "environmentally preferred" antimicrobial products. For example, "non-toxic" may be an unrealistic criterion for biocidal agents since, by definition, they must be effective at killing microorganisms, especially in highly regulated environments like aseptic GMP processing areas. Environmental and health impacts can be reduced by using proper application and worker protection techniques, making appropriate choices about which antimicrobial product is necessary under what circumstances, and substituting less toxic alternatives whenever feasible.

Conclusion

In the past, the topic of "green" in critical production industries has emphasized products rather than considering the whole picture, which also includes the processes. This focus on only one aspect of a complex process is not only limiting, but potentially harmful to personnel and the environment.

In the GMP industry, cleaning agents vary in type. They include formulated detergents, commodity chemicals, and solvents, and can be selected based on a variety of "green" criteria. When deciding on a cleaning process, the overall best approach takes into account performance, price, availability, regulatory requirements, and environmental impact.

As regulations continue to evolve and vary from region to region, being "green" may be "in the eyes of the beholder." GMP regulated sites should evaluate, define, and establish cleaning processes that best suit their individual cleaning and "greening" goals.

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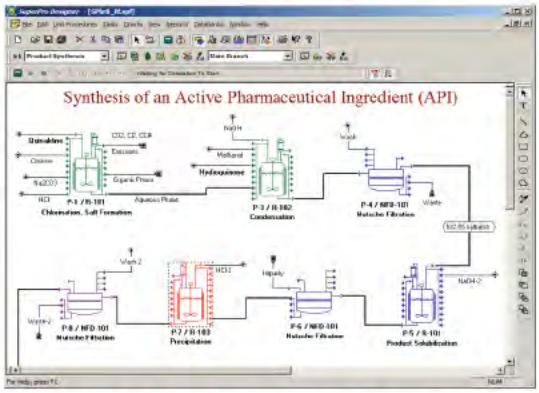

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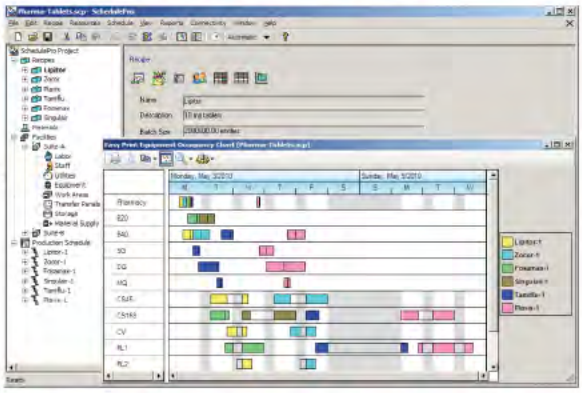

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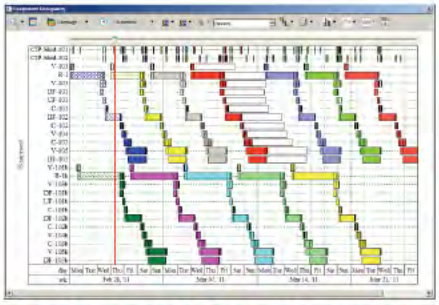

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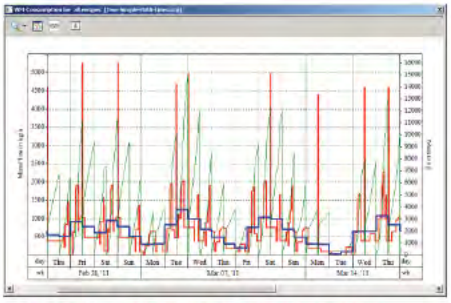

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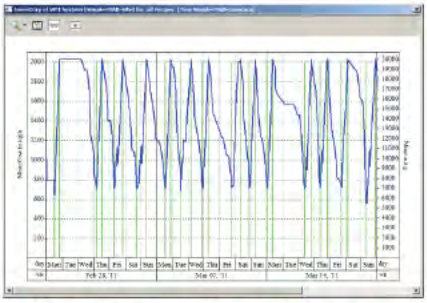

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Facility of the Future: Next Generation Biomanufacturing Forum

Part III: Identifying Facility Requirements Based on Specific Business Drivers and Uncertainties Using the Enabling Technologies

by Mark Witcher, PhD, Jeff Odum, CPIP, and Michael Zivitz

This article is the third of a three-part series focused on defining the facility of the future required for manufacturing biopharmaceuticals in the 21st Century.

Introduction

This article is the third in a three part series to define the Facility of the Future (FoF) required for manufacturing biopharmaceuticals in the 21st Century. The articles are the result of discussions and presentations made at the "NextGen Facility Forum" held at North Carolina State University in the Biomanufacturing Training and Education Center (BTEC) on 31 January 2012. The three articles summarize the topics discussed during the Forum.

The first article, "Part I: Why We Cannot Stay Here – The Challenges, Risks, and Business Drivers for Changing the Paradigm," elucidated why the biopharmaceutical manufacturing paradigm and the current generation of manufacturing facilities must change.[1] It summarizes the broad, industry-wide imperatives, challenges, business drivers, uncertainties, and risks discussed at the Forum.

The second article, "Part II: Tools for Change – Enabling Technologies and Business and Regulatory Approaches," summarized advances in biopharmaceutical technologies discussed at the Forum that impact most of the biopharmaceutical industry.[2] The advances provide important enablers that can be used to modify and, to some extent, control the drivers and uncertainties described in the first article.

In this third article, we will discuss this interaction between enabling technologies, drivers, and uncertainties shown in Figure 1. Although enablers, drivers, and uncertainties represent common challenges to the biomanufacturing industry, the resulting process and facility design will be the result of the application of these enabling technologies.

Planning New Facilities for the Future

Deciding what type of facility to build and when to build it is a challenging responsibility. The key to success in designing and building the Facility of the Future (FoF) is to deploy the right mix of enabling and traditional technologies. The discussion here will focus on selecting from the diverse mix of enabling technologies to mitigate the risks stemming from the project drivers and uncertainties shown in Figure 1.

To begin the process of developing FoF concepts, companies must be able to define and prioritize the business drivers, and make appropriate assumptions regarding uncertainties to reflect the most significant business issues to be solved, while characterizing the drivers in light of the environmental uncertainties. Another way to think about this is to ensure that there is clear alignment of the expected business outcomes for the program.

When the project is initiated, it is critical to have a clear consensus on the key assumptions that influence the success of the program. The following are examples of critical aspects (drivers and uncertainties) of the business decisions that must be established by making the appropriate assumptions before starting the capital project:

- **Location** – a critical look at the location where the project will be delivered will influence aspects of the engineering solutions, including Environment, Health, and Safety (EHS) requirements and infrastructure demands.
- **New Markets** – the markets the product will supply guide the quality requirements that, in turn, impact the project scope, cost, and schedule.
- **Capacity** – the team must establish a common understanding of the products and doses to be supplied in conjunction with the required flexibility of the facility and process.
- **Cost Structure** – the pricing structure and the capital impact on Cost of Goods Sold (COGS) must be established.
- **Regulatory (Quality, EHS, and Engineering)** – before initiation of FoF, engineering, clear quality and compliance expectations must be defined and aligned between all parties involved in the project.

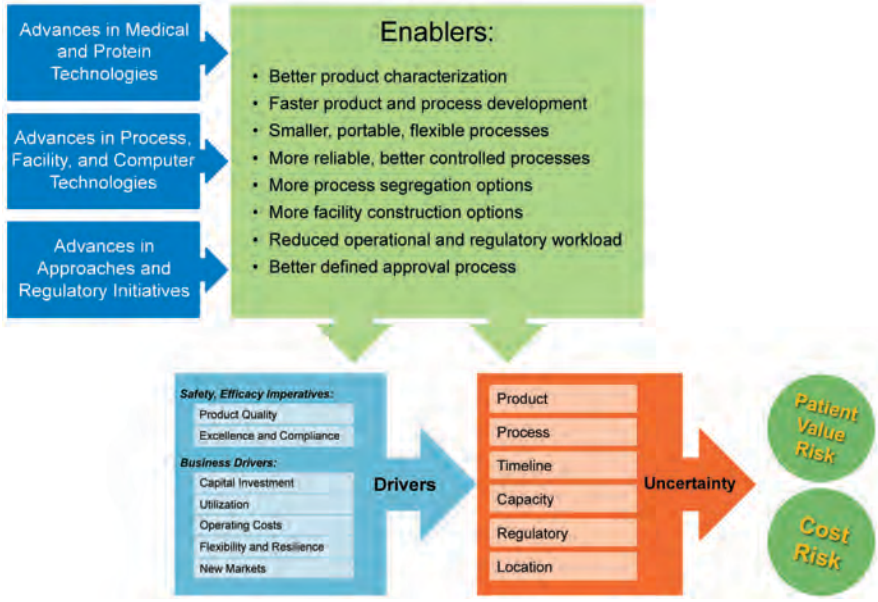

Figure 1. Drivers, uncertainties, and enablers.

biopharmaceutical industry. These differences may be seen through examples such as less (rather than more) automated facilities or more manual setups rather than the large and complex piping networks that were seen in traditional stainless steel facilities. Misalignment on the operational needs and expectations can result in companies building the wrong processes and facilities required for sustainability.

In order to develop and document a clear set of requirements for the expected business outcome, the regulatory basis, operational requirements, collaboration between

The imperative driver remains ensuring that the product that ultimately reaches the patient is safe and effective and that the safety of the employees and the environment (EHS) is not compromised. The path to meet this imperative may, however, be different than the traditional norms, e.g., in the case of new markets where EHS requirements are driven largely by local regulatory requirements and GMP requirements must be aligned to meet the regulatory requirements of the countries in which the product will be registered.

Finally, the operational philosophy to implement the enablers for the facility must be established. The likelihood is that the unique circumstances of the FoF will drive operational differences from the facilities and processes that have been traditionally developed for the

Step 1 – Establish Expected Business Requirements

- Identify new markets
- Identify products, processes, and capacity requirements
- Estimate COG and capital required

Step 2 – Set Regulatory Basis

- Identify regulatory requirements based on location
- Benchmark local GMP and EHS requirements
- Understand impact on existing company policies

Step 3 – Set Operational Philosophy

- Establish how facility will operate
- Adapt and improve from existing local operating philosophies
- Understand local operating philosophy and needs on design

Step 4 – Set Engineering Basis

- Align regulators, operating requirements with business requirements
- Design to meet project-specific requirements

Figure 2. Facility of the future design process.


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enterprise management, the engineering team, and the local operating management must be established. With this done, the engineering should begin with an innovative concept design effort.

This design process is shown in Figure 2. While this process is not unique to FoF projects, the assumptions for each of these steps may vary greatly from the assumptions that have traditionally been used by the biopharmaceutical industry.

Making appropriate assumptions which balance the risk and reward proposition with implementation will be a key differentiator in the future. Many companies struggle with these decisions and get caught in an indecision loop trying to balance the drivers against each other. The essence of failing to establish, align, and agree on a primary, or dominant driver, is an "indecision loop" shown in Figure 3.

These loops can have any number of driver elements. The enterprise gets caught, unable to decide which priority is dominant and which drivers need to be identified as subordinated assumptions in order to deal effectively with what is truly critical to success. Defining which driver is dominant establishes a clear set of priorities making the resulting decisions viable. The old clichés apply: "If everything is important, then nothing is important," and its first corollary, "If you deal with everything, then you wind up not dealing with anything." The failure to make timely decisions becomes a primary failure mode for some companies.

Indecision loops can be made more complex when elements of uncertainty are added. For example, the loop's complexity in Figure 3 can be increased by adding timeline and capacity uncertainties. The primary tool for minimizing the impact of uncertainties is to develop and reach a consensus on a carefully thought out and clearly stated set of business assumptions.

The balance of this paper will explore two sets of drivers. The first driver is the product safety and efficacy imperatives, including EHS considerations, shown in Figure 1. Basically, you have to make a safe and effective product; and you have to receive the required regulatory approvals to sell it. The second primary driver/uncertainty that will be discussed is the deployment of processes and facilities to new markets.

Figure 3. Indecision loop created by not establishing priorities among the various business drivers.

Enabler Impact on Product Safety and Efficacy Imperatives

Medical technology is rapidly advancing toward a better understanding of the Critical Quality Attributes (CQAs) required for safety and efficacy. Identifying and establishing appropriate product CQA requirements remains an area of very high uncertainty. Many product failures result from an incomplete understanding of the required CQAs for safety and efficacy. The CQAs are collectively combined into the product's Quality Target Product Profile (QTPP).

The first enabler, better product characterization, allows the product to be more clearly defined based on the medical needs of the patient population. This clearer definition provides the enterprise with more precise product and process development goals. The uncertainty with respect to the product's performance in clinical tests during clinical trials and the patient population after commercialization is reduced. In addition, the sensitivity of the CQAs on safety and efficacy can be better defined.

The second enabler, more reliable, better controlled processes, allows processes to better meet the QTPP requirements defined by the medical technology. With better targets and development methods, processes can be developed which reduce the uncertainty of the processes' ability to manufacture a safe and effective product.

The final enabler, better defined approval process, improves compliance by better aligning industry's understanding of regulators' expectations for achieving operational excellence. Operational excellence is the fundamental driver for both producing high quality product and efficiently meeting all necessary regulatory requirements.

With respect to specific application of the enablers to the imperatives shown in Figure 4, the following questions could be a starting point for identifying the best facility options to satisfy the imperatives:

- Does the facility provide an optimum environment (not too small or too large) to execute the process steps?
- Based on the manufacturing requirements, does the facility incorporate and support optimal segregation strategies for separating the products and processes manufactured in the facility?
- Does the facility design facilitate the use of existing and future advanced process control technologies?
- Is the process train designed for reliable operation given the operational design basis?
- Does the facility design meet current as well as likely future technology enablers and thus will be able to meet future regulatory expectations?

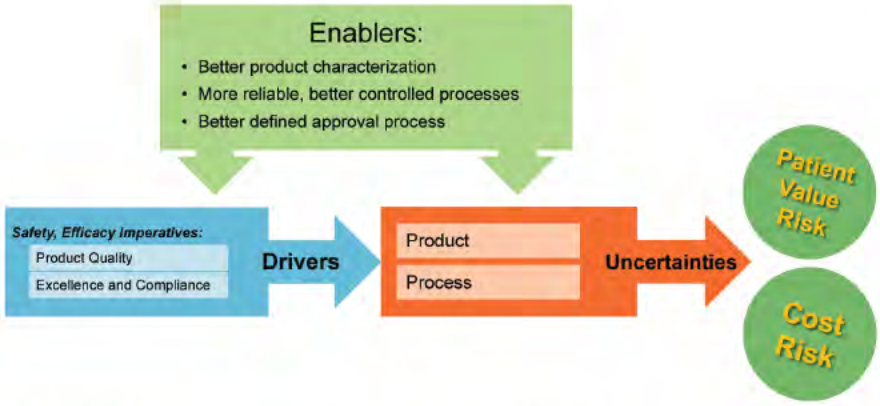

Figure 4. Relationship between enablers and safety and efficacy Imperatives and uncertainty.

- How can secondary business drivers be best satisfied while meeting the imperatives?
- How can the impact of the uncertainties be minimized?

Biopharmaceutical manufacturing runs the gamut from development facilities and pilot plants to commercial facilities producing product for sale. These companies vary widely from small biotech startups to large, integrated biopharmaceutical companies and Contract Manufacturing Organizations (CMOs). As mentioned, the unique circumstances of each company will help drive the critical-to-success factors for the program and, ultimately, the resulting engineering solutions.

With alignment on the imperative that the product must reach the patient and must be safe and effective and that the safety of the employees and the environment must not be compromised, the discussion will explore how this is done in the case of entering new markets. This case study will look at the unique challenges of a CMO; however, this example can also be applied to other business models in the industry.

The example is for illustration purposes and provides insights into several important primary drivers and how they interact with other possible secondary drivers. Priorities and approaches are management driven and can, and should, vary depending on the leadership team of each company. The example is based on a set of priorities set by a hypothetical leadership team and may be significantly different than what other leadership teams would do in the same situation.

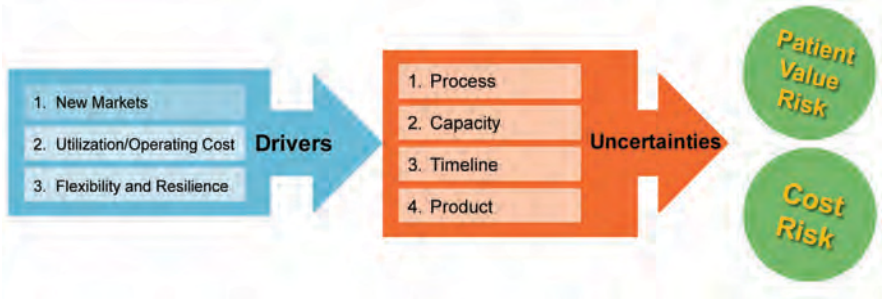

Figure 5. Business drivers and uncertainties for the example large CMO Enterprise.

Case Study: New Market Development

Identifying, creating, and developing new products and markets is an important driver for most companies as they look to meet unmet medical needs and generate new sources of revenue. For many, it is the reason they exist. New products can be found in both advances in medical technologies that identify new therapeutic targets, and in biosimilars and biobetters evolved from existing therapeutics. Expanding to new markets has traditionally been synonymous with emerging markets, but can also include competing and delivering existing products to traditional markets not yet tapped by the company. In the case of emerging markets, future facilities may need to be localized in order to allow market access. As mentioned in the first article in the series, many emerging market opportunities require smaller capacities and more flexibility to keep the facility fully utilized.

In this example, the enterprise is a large CMO needing to attract new customers with new products. As shown in Figure 5, the company sets new markets (new customers) as its priority business driver. Reaching new markets will require a competitive product pricing structure. As a result, the leadership ranks utilization/operating cost as its second most important driver because of its impact on Cost of Goods Sold (COGS). Because utilization has the single largest impact on operating costs, utilization is matched with operating cost. Underutilized facilities that are either not needed or not designed to do what they need to do are the root cause of many of the industry's manufacturing cost problems today.

The needs of the future remain the number one uncertainty for the industry and influence the considerations for our future facilities. As a result, a third associated driver, flexibility, is used to deal with new processes and to enable simpler future process improvements. In past facilities, flexibility came with a huge price tag and introduced significant complexity to the process train and facility design. New enabling technologies, such as single use systems, in conjunction with smaller batch sizes allow the use of movable equipment such that future facilities can be more flexible.

Designing the FoF to enable a higher utilization and flexibility will drive the following considerations:

- Development of a manufacturing platform that is adaptable and allows low capital unit operations changeovers either between product campaigns or even in the case of future introductions of new technology.
- Allows "scale-out" versus "scale-up" for unpredictable market requirements.
- Utilizes closed processing that allows flexible open plan layouts with the possibility for multiple products to be running in parallel.
- Provides a simpler and more reliable process.

The drivers coupled with the uncertainties are shown in Figure 5. The remaining drivers are subordinated and defined as assumptions.

The uncertainties are evaluated and ranked as shown in Figure 5. The process is the first uncertainty because the CMO has decided it wants to handle a broad range of customers with a broad range of processes. Capacity is viewed as the second primary uncertainty because the leadership team wants the enterprise to be able to run preclinical, clinical, and commercial manufacturing to attract and keep customers. Multiphase manufacturing, which minimizes tech transfer issues, is viewed as a critical CMO business development objective. Customer timelines are always an uncertainty. Dealing effectively with customer timelines is also viewed as a significant business development opportunity. Product uncertainty is viewed as an issue because the customer's durability as a client depends on the long term viability of the product. Thus, identifying and attracting customers with good products is important. The uncertainty of location and regulatory, although important, are regarded as secondary issues to be dealt with on case-by-case bases rather than considered in the facility design.

Evaluating the drivers with respect to the specific business model must be done by looking at the customer base. Because many diseases are being more precisely defined and subdivided into therapeutic families based on differences in patient populations, new products are likely to have smaller material requirements. As an example, breast cancer has been shown to have a number of subpopulations requiring different chemotherapy regimens for treatment.[3] Thus, one monoclonal antibody (mAb) may become many different mAbs depending on how the patient population is characterized and subdivided for treatment. In addition, biosimilars may require smaller processes as new generation manufacturing processes are developed and small niches are created and attacked in the market place. Thus, capacity flexibility as a driver may become very important to take advantage of new market opportunities.

With respect to addressing new market uncertainties, timeline pressures are likely to increase because of an increasing emphasis to get to the market quickly. Product development timelines are generally acknowledged to be too long and the pressure to speed up development to commercialization timelines is growing. Although the critical path timelines generally go through clinical trials and regulatory approvals, improvements in medical technology, adaptive clinical trial designs, and faster product and process development tools may place greater pressures on manufacturing timelines.

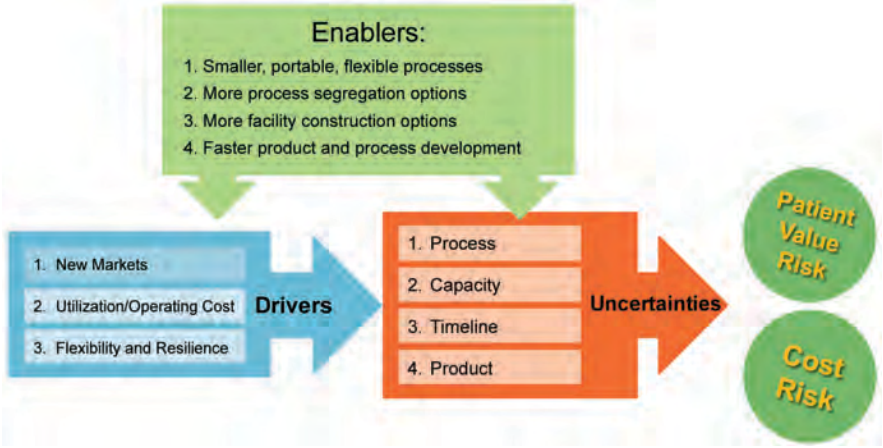

Figure 6. Impact of enablers on the business drivers and uncertainties for a large CMO enterprise example.

The relationship between the primary applicable enablers, new market business drivers, and uncertainties are shown in Figure 6. Four enabling technologies were identified by the leadership team as having a significant impact on the business model described in Figure 5. The enablers are ranked by the leadership team in the order of their perceived business impact.

Based on the previous discussion, the key to new markets appears to rely on the enterprise's ability to quickly run a broad portfolio of processes at a wide range of capacities. This is not true for all enterprises, but for the example being discussed, flexibility appears to be the real primary driver. Conceptually rearranging Figure 6, we get Figure 7 as being the real focus of the facility design issues.

How will the enterprise use the four enablers to design the best, most flexible facility to attract new customers? Enabler 1 (smaller, portable, flexible process) allows the operating process to be decoupled from the facility. Designing the process as an integral part of the facility is no longer necessary. The process uncertainty can be managed easily by configuring and moving the skid mounted unit operations into the facility without having to make facility changes. Upside capacity uncertainty becomes more manageable using the scale-out method of replicating the process to double the capacity. Downside capacity uncertainty is controlled by removing the process and installing another process from the customer scheduling queue. Timeline uncertainty is managed by being able to move processes in and out depending on balancing the various schedule requirements for the customer base. Simple facilities running portable processes also reduce capital cost requirements.

Enabler 2 (more process segregation options) provides a variety of facility design options. When combined with Enabler 1, closed Single Use System (SUS) processes can be installed in either large operating spaces (ballroom concepts) or small segregated spaces depending on the enterprise's facility control and process operating methods. Large operating spaces potentially reduce operating workload, while highly segregated spaces may increase the flexibility to rapidly add and remove processes from the facility. Each enterprise can use Enabler 2 to their advantage depending on anticipated business requirements.

Enabler 3 (more facility construction options) and the fact that SUS processes are decoupled from the facility by Enabler 1, make a wide variety of options for building manufacturing facilities available. When combined with the large single operating area option provided by Enabler 2, a very simple facility can be quickly constructed. Modular, design/build methods can be used to expand the facility very quickly if facility capacity becomes a problem. Using rapid design-build methods to scale-out processes provide for very rapid expansion of capacity. These simpler facility design, accelerated schedules, shorter lead time process systems, with plug-in installation can dramatically improve facility deployment

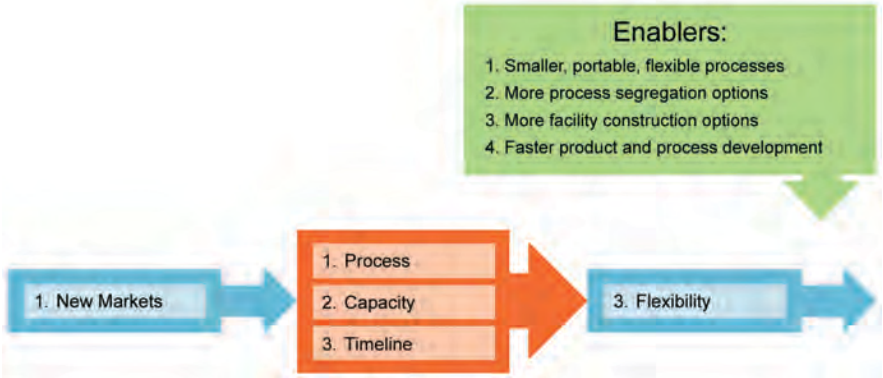

Figure 7. Enabler impact on facility flexibility.

schedules allowing companies more flexibility in executing business decisions about product and market needs.

Enabler 4 (faster product and process development) increases the emphasis on timeline uncertainties. If the same manufacturing facility can be used for preclinical through commercial manufacturing, then the development time to market can be decreased because tech transfer is no longer required. A seamless transition can be achieved as the process is scaled up and manufacturing requirements satisfied. An SUS, skid mounted process implementation facilitates moving the process to a second manufacturing facility constructed using Enabler 3 in any location simply by moving the skids, or their clones, with minimal revalidation requirements.

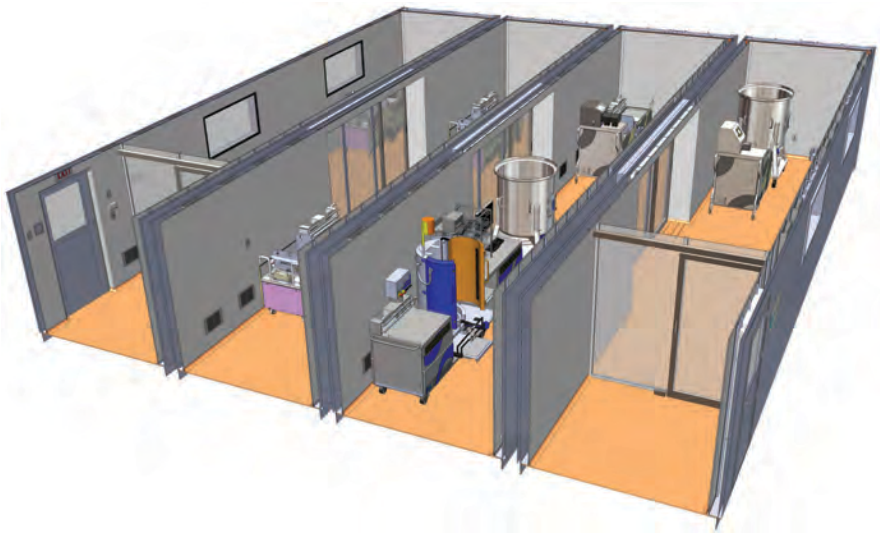

Figure 8. 200L Flexible mAb development facility concept *(image courtesy of Biologics Modular)*.

While the above example discusses one approach for a CMO business model, the following might be relevant questions for identifying the FoF for other enterprises seeking to address new markets as a primary driver.

- What will be the capacity requirements of the new products?
- What is the length of production commitments for new products?
- What is the scale of the new products?
- Which manufacturing requirements can be carried out in a single facility?
- Should multiphase manufacturing be considered or should the facility specialize in one type of manufacturing?
- Should the facility focus on one particular type of process (e.g., mAb) or should the facility be configured to handle a wide variety of process formats?
- What is the projected utilization of existing capacity?
- How important is the timeline?
- Should existing capacity be maintained and new capacity constructed?
- Should existing capacity be removed to make way for new process formats?
- How can SUS be best used to deal with the primary drivers?
- Will a scale-out or scale-up approach be the most appropriate for dealing with capacity related uncertainties?

Summary

The application of the identified enabling technologies to the business drivers in light of the uncertainties is very much dependent on the individual enterprises. An enterprise's manufacturing requirements can range from making a single product for early clinical testing to manufacturing a wide variety of different products over their entire development/commercialization lifecycle.

As the biopharmaceutical industry grows and the product mix becomes more complex, dealing with the business drivers and related uncertainties for defining, designing, and building new manufacturing facilities will be very difficult. Fortunately, the tools in the form of the enablers discussed are available to meet these challenges and continue to be enhanced by advances in technology and better business practices. This article provides a start in creating a framework that can be used to apply the enablers to solve industry's complex manufacturing business driver/uncertainty combinations.

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Effective Computerized System Compliance through Leveraging Supplier Effort

by Members of the ISPE GAMP® Leveraging Supplier Effort Special Interest Group

This article describes a controls framework that can be used to assess risks and determine a validation strategy that leverages supplier effort appropriately.

Introduction

Regulated customers face increasing pressure to utilize resources efficiently while ensuring effective compliance with global regulatory requirements in order to ensure patient safety, product quality, and data integrity. Effective and efficient compliance is established through process understanding, understanding of patient/product risk, adopting a scalable lifecycle approach, maximizing subject matter expertise, and avoiding duplication of effort. ISPE GAMP® 5 recognizes the key role of product and service providers in meeting these criteria.

Recognizing the capabilities, experience, and willingness of suppliers and integrating regulated customer and supplier resources provides an opportunity to utilize their combined knowledge, effort, and documentation to effectively achieve regulatory requirements. Leveraging supplier effort enables:

1. Targeting of internal resources on areas of greatest risk to patient safety, product quality, and data integrity
2. Minimizing duplication of effort between suppliers and regulated customers
3. Accessing subject matter expertise to ensure that solutions are fit for purpose and decisions are based on knowledge and quantifiable risk

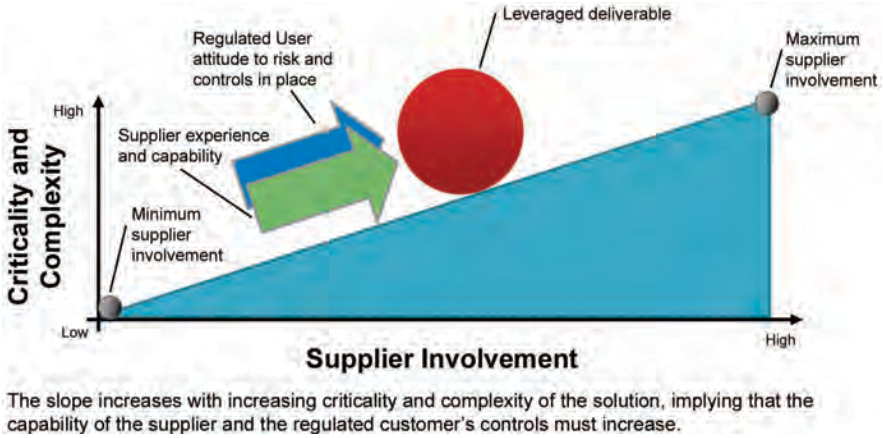
All of these objectives are in line with the GAMP® 5 principles to leverage supplier effort and to focus patient safety and product quality risks. Further, GAMP® 5 promotes the role of the subject matter expert in order to ensure that solutions are appropriately specified, implemented, and verified. Suppliers to the industry are a valuable source of such subject matter expertise.

Supplier assessment is a means by which regulated customers evaluate the effectiveness of product development and support systems to assist in planning system implementation, validation, and operational compliance requirements. Where the supplier's quality management system reflects pharmaceutical industry guidance, such as ISPE GAMP 5 or other cross industry standards/guidelines, such as ITIL®, COBIT®, TickIT®, etc., there is greater opportunity to leverage supplier effort. The extent of management and verification control applied by the regulated customer will be influenced by the outcome of the supplier assessment, the criticality of the business process, and the potential impact the supplier product or service has on patient safety, product quality, and data integrity.

This article does not set new expectations with respect to supplier quality practices; rather it presents an opportunity for regulated customers to establish risk-based controls that ensure mutual understanding of objectives and effective planning, management, and verification of supplier input to validation and operational compliance processes.

This article describes a controls framework that can be

used to assess risks and determine a validation strategy that leverages supplier effort appropriately. In designing the controls framework, it is recognized that there is no "one size fits all" solution to leveraging supplier effort. Suppliers, and indeed regulated customers, operate to different business drivers, standards, and tolerance of risk; the controls framework simply identifies potential controls that should be selected and adapted accordingly.



Figures 1. Determining the leverage position for a deliverable.

What is Leveraging?

In the context of this article, supplier means product suppliers, support organizations, service providers, and internal supply organizations, such as IT/engineering and similar organizations at any phase in the system lifecycle.

In the context of this article, leveraging is the utilization of supplier "artefacts" (supplier skills, knowledge, and documentation) in support of the regulated customer's compliance activities throughout the life of the computerized system (implementation and operation). Looking at the activities, knowledge, and responsibilities for both supplier and regulated customers, it becomes clear that there are two significant opportunities to leverage supplier effort.

First, duplication; there is overlap between the project activities of the supplier and regulated customers, in particular in the areas of planning, specification, testing, and support. An opportunity exists to remove duplication of effort and find more beneficial ways of verifying what has been done by others.

Second, skills and knowledge; with the experience of suppliers implementing similar solutions across a broad range of organizations, there is an opportunity to leverage such knowledge in support of effective decision making, solution development, project activities (e.g., requirements definition, risk assessment) and documentation creation.

It should be recognized that leveraging supplier effort does not, of course, affect the accountability for compliance. This always resides with the regulated customers. Leveraging cannot be undertaken blindly. It requires focused planning to assure the capability of the supplier and verification of any artefacts that may be leveraged. Supplier assessment for critical applications may become more intensive, in terms of verifying specific outputs of supplier quality management systems, rather than being a general appraisal. For example, where supplier testing is to be leveraged, the supplier assessment process may include a more comprehensive assessment of the effectiveness of critical function testing processes and documentation.

The Keys to Effective Leveraging

In order to leverage supplier effort, there needs to be a consistent understanding of expectation, capability, and risk between the regulated customers and supplier. Effort expended in the planning, evaluation, and specification phase will ensure that the benefits of consistent understanding are felt throughout project execution and operation.

The supplier influences the extent of leveraging through

Control Type	Objective of Control	Examples
Planning	Ensures the right activities are being undertaken and decisions being made at the right time by the right people	Ensure deliverables of different suppliers are synchronized Ensuring supplier and regulated customer's validation activities are integrated Addressing outcome of supplier assessment
Evaluation	Ensures that supplier knowledge, effort, and artefacts are only leveraged based on understanding of supplier capability and quality	Supplier Assessment Establishing mutual understanding of system requirements
Subject Matter Expertise Input	Ensures that people with appropriate expertise provide input into activities, deliverables, and decisions. Such people should have required experience, the authority to make decisions, and should be available to provide input and make decisions in a timely manner.	Ensure technical experts are engaged in design and design review Ensuring system requirements reflect current and/or planned business processes, are complete and accurate, and reflect experience of previous implementations Ensuring test teams understand business processes and good testing practice
Verification	Ensures activities and deliverables are confirmed as being fit for purpose	Review of design Ensures appropriate Testing of implemented solution Review of supplier test records

Table A. The controls framework recognizes that there are different types of control.

the effectiveness of their quality systems, experience, and capability. The regulated customer's attitude toward and ability to leverage is influenced by the criticality of their business processes, their attitude to risk, effectiveness of project management, and quality processes and internal skills and capability - *Figure 1*.

Controls Framework

Armed with a clear appreciation of the capability of both supplier and regulated customers, the project team will be ready to utilize a controls framework. The controls framework identifies typical controls that may be applied to ensure supplier activities, knowledge, and artefacts are appropriately leveraged. The identified controls ensure that supplier activities are appropriately planned, managed, and verified according to business process criticality, project/system complexity, and supplier capability - *Table A*.

The controls framework is intended as a guide only. An alternative set of controls may be appropriate, based on the characteristics of the supplier services being provided and regulated business operations being supported; however, the criticality of a system should not preclude leveraging; rather the controls applied need to be commensurate with risk. The controls framework encompasses three stages in the life of a computerized system, including planning, implementation, and operation.

Stage 1 – Planning

Development of the controls framework reinforced the fundamental importance of understanding project enablers and setting expectations, both within the regulated customers and with potential suppliers. Early planning and evaluation will determine the extent to which supplier knowledge, activity, and/or documentation can be leveraged. Activities such as supplier assessment, due diligence, project tendering, project/validation planning, contractual agreement, and previous experience shall determine:

- Willingness to cooperate and level of trust between parties
- Supplier capability, knowledge, and experience in the context of proposed project/service
- Mutual understanding of business processes/operations and risk
- Technical competency
- Effectiveness of quality systems
- Flexibility of supplier and regulated customer's quality systems in enabling (even encouraging) leveraging
- Quality of supplier deliverables
- Supplier longevity and client relationship
- Experience of previous projects/operations of similar characteristics
- Intellectual property considerations
- Degree of deviation from normal supplier practice

At the outset of any cooperative relationship, it is important to gain mutual understanding of:

- Project certainties and unknowns
- Supplier and regulated customer's roles and responsibilities
- Business process and user requirements, including deficiencies

Activity	Accountable Organization (Typical)	Opportunity for Supplier Input	Potential Regulated Company Controls (in addition to general controls)				Potential Risks and Considerations
			Planning	Evaluation	Subject Matter Expertise	Verification	
IMPLEMENTATION							
Validation Planning	Regulated Company	Input to Validation Plan, Integrates Supplier and Regulated activities Integrate Supplier Quality Plan and Regulated Company Validation Plan	Reference in contract documents Integrate quality/ validation activities into project plans Where supplier records are to be verified but not owned by the Regulated Company, controls need to be established to ensure integrity, access to and retention of such records for the required retention period	Evaluate previous examples Evaluate Supplier Quality Plans	Regulatory and Industry Knowledge	Review and approval (and ownership) of Validation Plan Review and Approve Supplier Quality Plan Define Verification Activities	Loss of knowledge within Regulated Company Regulated Company maintains overall Quality Assurance and Verification Accountability May necessitate increased number of supplier meetings/ verifications

Table B. Detail of the controls framework for validation planning.

- Quality systems and regulatory standards that will apply
- Controls that will be applied by both parties to manage the project/service, including verification controls
- Expectation of deliverables and ownership of deliverables
- Knowledge transfer requirements
- Ongoing support (including regulatory inspection)

Stage 2 – Implementation

The second stage of the controls framework examines controls from validation planning, through to completion of validation reporting. It is clear that some deliverables fall into natural groupings with a single set of requirements and controls; for example, the controls for each of the testing phases are likely to be similar. The supplier may be engaged to plan, specify, and execute tests with the regulated customers providing input, review, and oversight of testing.

Stage 3 – Operation

Activities during operation of the computerized system may provide opportunities for further leveraging of supplier knowledge and effort in areas such as change management, configuration management, repair, back up, and restoration and disaster recovery. Leveraging during the operational phase is likely to require greater integration between supplier and regulated customer's support organizations and quality systems. Establishment of service level agreements defining roles of supplier and regulated company organizations, service management controls, service performance expectations, and quality systems requirements are fundamental to service management.

In Table B, the traditional approach to validation planning is for the regulated customers to create, review, and approve the validation plan with the supplier, perhaps reviewing the validation plan initially during the tender process. In a leveraging model, the supplier may provide significant input into the validation plan, addressing system validation aspects; however, accountability for validation of the overall business process must remain with the regulated customer. Such an approach may ensure greater or clearer integration between the supplier and regulated customer's activities.

Secondly, the case of specification is described in Table C. Traditionally, the regulated customer develops the user requirements specification and issues this to the supplier for review and response during project tender processes and design processes. However, a supplier organization may have experience of previous implementations, skills in capturing and analyzing requirements from other customers, or tools for articulating and demonstrating requirements accurately and without ambiguity. Recognizing that a regulated company will require at least an initial understanding of

Activity	Accountable Organization (Typical)	Opportunity for Supplier Input	Potential Regulated Company Controls (in addition to general controls)				Potential Risks and Considerations
			Planning	Evaluation	Subject Matter Expertise	Verification	
IMPLEMENTATION							
Business Process Definition and Requirements	Regulated Company	Experience of previous implementations Skills in defining clear, complete, accurate requirements Technology experience	Reference in contract documents	Evaluate previous examples	Provide knowledge of "AS IS" processes Provide initial "TO BE" processes and requirements	Review and approval (and ownership) of Business Processes and Requirements	Loss of knowledge within Regulated Company Regulated Companies must own business processes and requirements and understand business/regulatory risks
Functional Specification	Supplier	Expertise in system implementation Create Functional Specification Provide Traceability to Business Processes and Requirements	Input Business Processes and Requirements		Input to Functional Specification	Review and approval of Functional Specification Review Traceability to Requirements	Typically a supplier led activity, limited opportunity for further leveraging
Detailed/System Design	Supplier	Expertise in system implementation Create Design Provide Traceability to Product or User Requirements	Input Business Processes and Requirements (if customizations required)		Provide business and IT input (if customizations required)	Testing based on Business Process and Functional Risk Assessment	Activity that is evaluated during supplier assessment, limited opportunity for further leveraging

Table C. Detail of the controls framework for specification.

their business processes and user requirements in order to effectively select a solution, leveraging supplier experience and expertise earlier in the ongoing development of user requirements could lead to a more effective solution with reduced risk for misunderstanding.

Other considerations are identified within the controls framework, providing additional experiences that should aid the reader in considering appropriate controls. For example, during the testing phase, "other considerations" for leveraging supplier test documentation would include the degree of customization required to implement business processes. An "out of the box" supplier test package would be less useful to the regulated customers when there is a high degree of system configuration and/or customization.

Practical Considerations

When using the controls framework:

- Greatest benefit may be achieved if both parties work to their own established QMS with no additional controls other than interfaces between supplier and regulated customer's QMSs.
- Suppliers will have certain strengths and weaknesses; therefore, it should not be assumed that all supplier knowledge, activities, and documentation can be leveraged.
- The extent of leveraging may change as more knowledge is developed during the delivery of the project or service.
- Where several suppliers are involved in a project, there will be a unique controls framework for each of them, given the nature of the relationship, experience, expertise, etc., between the regulated customers and each supplier.
- The ability to leverage from one supplier does not imply that knowledge, activity, or documentation can be leveraged from all suppliers.

ISPE Members can download the controls framework from the ISPE GAMP® COP website (www.ispe.org/gampcop).

During the creation of this article, a revised EU GMP Annex 11 was published. ISPE GAMP has published an interpretation of Annex 11, mapping requirements to GAMP 5. Annex 11 highlights key considerations for external and internal suppliers that are discussed in the interpretation article. Key highlights are found in Table D.

Regulations in the US, such as 21 CFR 211.34, recognize where consultants advising on manufacture, processing, packing, or holding of drug products are required to be sufficiently trained, experienced, and educated with records kept. FDA's General Principles of Software Validation (11 January 2002) make reference to regulated customers "assess[ing] the adequacy of the software developer's activities and determine[ing] what additional efforts are needed to establish that the software is validated for the device manufacturer's intended use." The manufacturer has latitude and flexibility in defining how validation will be accomplished. Supplier provision of information about their system's requirements, testing process, and results of their testing can be used by the regulated customers as the basis for their validation activities.

Topic	Key Considerations
Documentation	Agree with provision of documentation, this includes supplier and regulated customer's documentation, which should be highlighted in the validation plan or similar document (e.g., document management plan).
Risk Management	Where there is a large third party involvement, opportunities for sharing data, control information, quality standards and records, based on a justified and documented risk assessment, should be taken. Trust and confidence in suppliers will enable the leveraging of material and the avoidance of duplication of effort.
Compliance	Requirements for third party suppliers and service providers are extended to internal IT departments (as they are regarded as "analogous" to third party suppliers in this context).
Validation	Annex 11 requires "manufacturers," i.e., suppliers, to be able to justify their standards, protocols, acceptance criteria, procedures, and records based on their risk assessment. It would be sensible for each party to list and index such documents linked in the formal agreement or validation plan
Change Control and Deviations	Record keeping requirements during the project validation phase may (for complex projects) result in a high level of cooperation to enable review and transparency. The level of cooperation should be spelt out in the formal agreement between parties to the project. Section 4.2 concerns evidence, in support of fitness for purpose, that suppliers are required to provide.
Supplier Assessment	Section 4.5 specifically refers to the need for a formal assessment of the supplier, as a means of demonstrating that all reasonable steps have been taken by the regulated customers to ensure that the system has been developed in accordance with an appropriate QMS. It is likely to be to suppliers' advantage to demonstrate fitness for purpose in this regard.
Custom/ bespoke computerized systems	Section 4.6 requires the formal assessment and reporting of quality and performance measures for all the lifecycle stages of these systems. Where integrators and other contract staff are involved, then control, coordination, and cooperation are essential. The validation plan should make clear just how these aspects of the project will be covered. The formal agreement should cover data and knowledge sharing.
Testing	Section 4.7 provides an opportunity for the sharing and leveraging of supplier and customer knowledge and methodologies on evidence of appropriate test methods and scenarios. Automated testing tools and test environments are expected to have documented assessments for their adequacy. While these aspects would normally be covered by the validation document set, where such records reside primarily at the supplier, then original relevant information may need to be made accessible to the regulated customers as evidence in support of the specific compliance requirement.

Table D. Annex 11 highlights key considerations for external and internal suppliers.

Knowledge Transfer and Accountability

Leveraging supplier knowledge, effort, and documentation infers greater dependence upon suppliers. It is essential that regulated customers recognize and address key issues:

- Regulatory compliance is a sole accountability of the regulated customers
- Regulated customers must understand their business processes and business/ compliance risks
- Regulated customers must be able to defend their compliance position

- Business agility should not be constrained by supplier relationships

Conclusion

For both regulated customers and suppliers, adopting this approach to leveraging will enable:

- Understanding of project/service objectives
- Mutually agreed specification
- Understanding of roles and responsibilities
- Earlier realization of business benefits of the solution

Suppliers will further benefit from working to their own internal standards and tools. For the regulated customers, additional benefits of adopting this approach are:

- Access to expertise and experience
- Avoidance of duplication
- Focused use of internal resources in critical areas
- Managing the effect of losing internal knowledge through effective supplier relationship
- More effective solutions

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Commissioning and Qualification (Verification) in the Pharmaceutical Product Process Lifecycle

by David Dolgin

This article discusses the role of Commissioning and Qualification as "Stage 2a" of the Process Validation Lifecycle described in the US FDA's Guidance on Process Validation. It also explains how the concepts of Quality Risk Management and QbD are incorporated into facility and system verification efforts as detailed by two recently published ISPE Guides.

Background

In January 2011, the US FDA published an update on pharmaceutical process validation. Titled *Guidance for Industry – Process Validation: General Principles and Practices*, it represents the first update since 1987 to the agency's official guidance on the topic. Based on the principles of ICH Q8, Q9, and Q10 (*Pharmaceutical Development, Quality Risk Management,* and *Pharmaceutical Quality System,* respectively), this version of the process validation guidance aligns FDA's process validation expectations with the above ICH documents as well as with FDAs own 21st Century Risk-Based GMP initiative.

The FDA Process Validation Guidance (PVG) is structured on a lifecycle concept: The objective of "process validation" is a state of ongoing control of process variability. Process validation is not an event or task that can be completed, rather, it is a lifecycle of control across the entire product development and manufacturing product lifetime. One new aspect in this version of FDA guidance is the specific architecture that the agency applies to the lifecycle model described. It is a three-stage model that begins with process design and ends only with the discontinuation of manufacture. As shown in Figure 1, the stage traditionally containing the activities referred to as Commissioning and Qualification (C&Q) will be referred to as "Stage 2a" of the FDA Process Validation Lifecycle.

Figure 1 also depicts the inputs from the three ICH documents mentioned above and references a fourth industry standard: ASTM E2500-07, *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equip-*

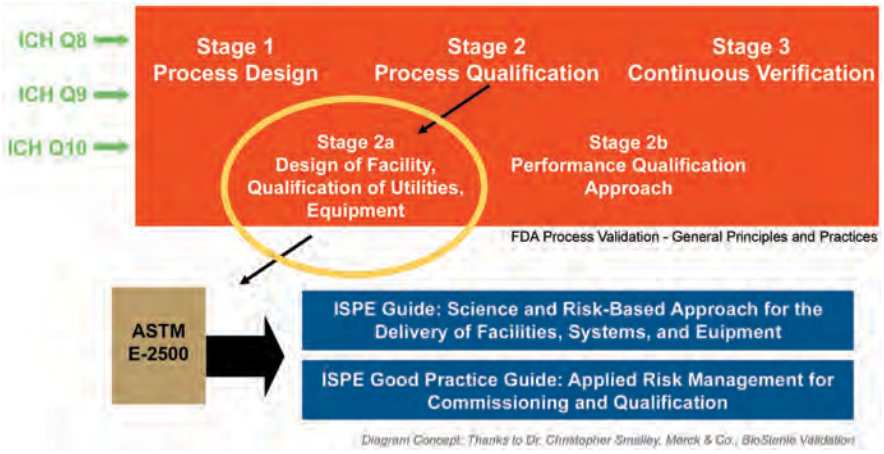

Figure 1. Where C&Q fits in the FDA process validation lifecycle.

ment. As will be discussed, ASTM E2500-07 is cited by the FDA PVG as guidance for activities that verify that facilities, systems, and equipment are fit for their intended use (sometimes referred to as "Qualification"). Lastly, Figure 1 identifies two relatively recent ISPE Guides that facilitate implementation of the ASTM. There is more information on those guides to follow in this article.

Quality by Design and Risk Assessment in the PVG Lifecycle

One of the fundamental principles of the PVG is that quality must be **designed** into a process from the beginning. It cannot be adequately ensured merely by inspection or sampling and testing. This truth applies equally to pharmaceutical manufacturing processes and to the equipment and facilities used to execute those processes. Facilities and systems must support the quality requirements of their associated processes in order to be deemed "suitable for intended use."

The key to defining facility and equipment quality requirements is based on the process knowledge gained during Stage 1 – Process Design. The PVG states, "This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes." Specifically, the PVG clarifies that the FDA expects manufacturers to:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

ASTM E2500-07

ISPE, beginning in 2005, with the encouragement of the FDA, began to act as a "change agent" by developing and championing a standard for a new and non-traditional approach to verify that equipment, facilities, and utilities were fit for their intended use. By 2007, ISPE had developed and submitted a draft to ASTM's Committee E55 on Manufacture of Pharmaceutical Products. The Committee approved ASTM E2500-07 in November of that year.

ASTM E2500-07 is the first guidance on system and facility verification with the status of a "consensus standard." Peer-reviewed and revision-controlled, the ASTM describes a risk- and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety. With its status as a "consensus standard," ASTM E2500-07 provides the FDA an approach to facility and system verification that the agency could officially recognize as an acceptable methodology.

Based on the framework of ICH Q8 and Q9, and ex-

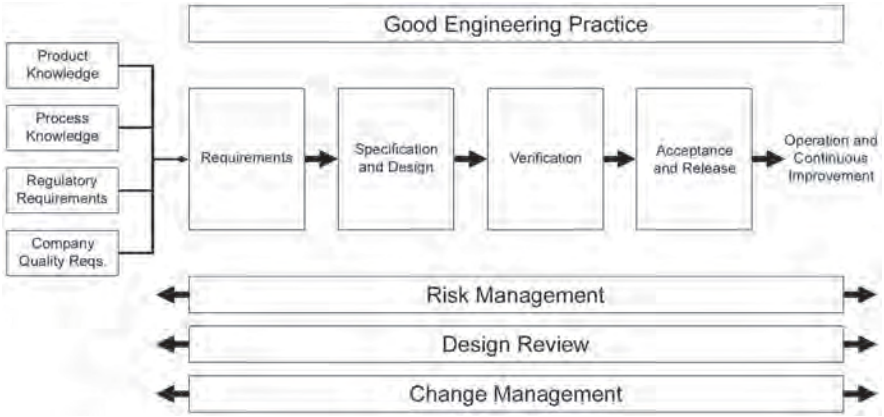

Figure 2. The specification, design, and verification process per ASTM E2500-07.

panding on principles and concepts introduced in the FDA initiative, *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach*, ASTM E2500-07 is intended to satisfy international regulatory expectations in ensuring that manufacturing systems and equipment are fit for intended use and to satisfy requirements for design, installation, operation, and performance. It describes a lifecycle approach of its own, beginning with the definition of requirements, followed by specification and design, verification (containing the elements of traditional C&Q), acceptance and release, and continuous improvement.

The FDA Process Validation Guidance references ASTM E2500-07 as "useful" in meeting the requirements under 21 CFR Part 211, Subpart C, of the cGMP regulations on *Buildings and Facilities*, and states, "It is essential that activities performed to assure proper facility design and commissioning precede Process Performance Qualification (PPQ-legacy process validation)."

Controlling variation in pharmaceutical manufacturing processes requires strategies that depend on specific aspects of facility and system design and function. These aspects, referred to as "critical aspects" by ASTM E2500-07, are the focus of risk-based verification activities described by the ASTM and elaborated on below. The identification of critical aspects of facilities and systems is accomplished primarily through multiple risk assessments as shown in Figures 3 and 4.

Figure 3. Levels of risk assessment.

The Product Process Risk Assessments shown in Figure 3 are an output of Stage 1 – Process Design, and apply to a given manufacturing process based on the chemistry and process-science specific to that process. Manufacturing risk assessments are site-specific, building on the Process Risk Assessments and taking into account sources of potential variability induced by local factors such as environment, available equipment, personnel, site experience, facility layout, etc.

Critical Aspects – Design-Based Control Strategies

ASTM E2500-07 contains the following definition of Critical Aspects: "Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding."

Manufacturing process risk assessments help inform the detailed designs of systems and facilities and can be used to identify Critical Aspects as a focus for design, testing, and verification documentation. Note that not all risk control strategies are matters of engineering design subject to verification (Qualification). The term "Critical Aspects" is used by the ASTM to indicate risk control design features and functions, not procedural controls or testing.

As indicated by Figure 4, Critical Aspects can be an output of a risk assessment. The specific type of assessment methodology is not as important as the identification of risks and their associated control strategies. Failure Modes, Effects, and Criticality Analysis (FMECA) is an example of a type of risk assessment method that does an excellent job of identifying specific risks/control, making it well suited for Critical Aspect identification. However, it is not the only option, and teams should select the best method based on each situation.

Applying ASTM E2500-07 to Stage 2a

Some of the key concepts that ASTM E2500-07 applies to facilities, equipment, and systems are analogous to process guidance in the PVG. For example:

- "Quality by design concepts should be applied to ensure that critical aspects are designed into systems during the specification and design process." (ASTM E2500-07, section 6.5.1)
- "Assurance that manufacturing systems are fit for intended use should not rely solely upon verification after installation but be achieved by a planned and structured

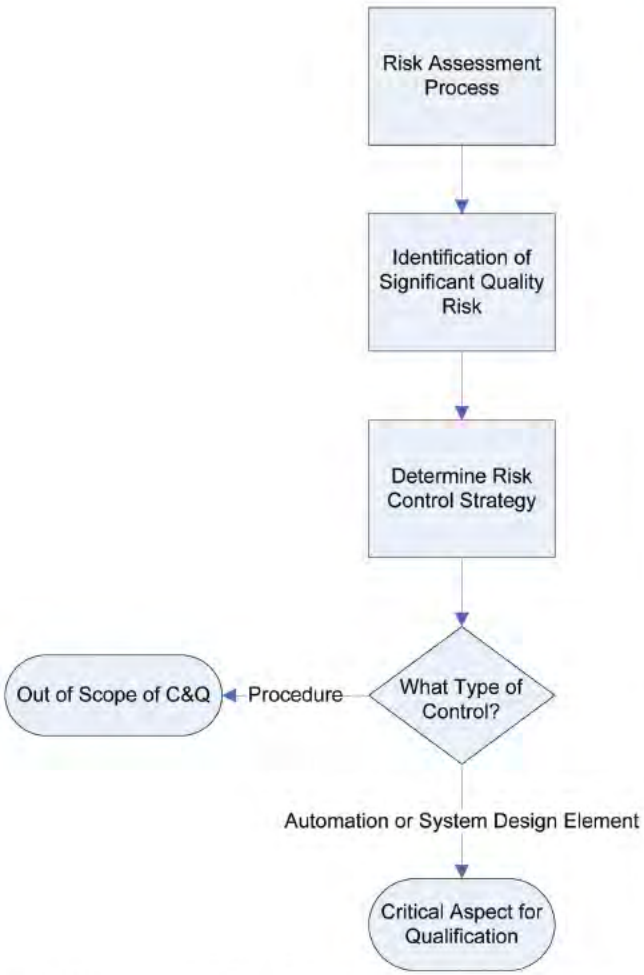

Figure 4. Identification of critical aspects through risk assessment.

verification approach applied throughout the system life cycle." (ASTM E2500-07, section 6.5.2)

To effectively apply QbD and Quality Risk Management to the design and delivery of manufacturing facilities, equipment, and systems, a foundational level of process knowledge regarding the intended use of said assets must be available. From their knowledge of the intended use of a given item, Subject Matter Experts (SMEs) in that application can define the appropriate quality requirements. According to ASTM E2500-07, specific requirements affecting product quality and patient safety should be based on:

- Product knowledge
- Process knowledge
- Regulatory requirements
- Company quality requirements

Product and process knowledge comes from Stage 1 – Process Design development along with relevant manufacturing

experience and history with the same or similar processes, thereby linking product and process requirements to the engineering designs of the facilities and systems that support those requirements.

ISPE Implementation Guidance

While ASTM E2500-07 provides the necessary high-level strategy for science- and risk-based verification that facilities and systems are fit for use, many companies are highly invested in C&Q methodologies and systems that significantly predate ICH Q9 and the ASTM. The mechanisms of IQ and OQ, along with associated rules for their use, are embedded in quality systems across the pharmaceutical industry, and these systems may not be easily adaptable to the ASTM approach. To meet the practical needs of firms wishing to update their C&Q systems to align with risk-based practices and to achieve the efficiencies of cost and time they can provide, ISPE published two new guidance documents in 2011 that provide options for the implementation of science- and risk-based verification:

Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment (FSE Guide) (published in June 2011)	Applied Risk Management for Commissioning and Qualification (ARM Guide) (published in October 2011)
• A pure ASTM E2500-07 approach • Direct implementation of ASTM • Verification terminology only • ASTM E2500 roles/ responsibilities in place for adopting organization	• A bridge document – how to transition from traditional approaches to a risk-based approach based on ASTM E2500-07 • Hybrid approaches, elements of both traditional and risk-based • Traditional C&Q terminology • Organizational transition based on maturity

Which Guide for My Company?

Although the topics are similar, they have different uses as summarized below:

FSE Guide for Organizations	ARM Guide for Organizations
• With new or flexible quality systems • Without significant legacy terminology and quality qystem mechanisms • Organizationally capable of Good Engineering Practices (GEPs) and risk assessments	• With established quality systems • With embedded terminology • Non-risk based cultures • Organizational maturity needs development

Summary

The FDA Process Validation Guidance establishes a three-stage lifecycle, where Stage 2 is bifurcated into two sub-stages, 2a and 2b, and where stage 2a is equivalent to the Commissioning and Qualification of equipment, systems, facilities, etc. The FDA guidance references ASTM E2500-07 as one of the sources for information on executing stage 2a.

ISPE has provided the community with two updated best practice guides facilitating the implementation of ASTM E2500-07 and/or risk-based approaches. Both were published in 2011. *Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment* describes a direct implementation of the ASTM and its terminology, and *Applied Risk Management for Commissioning and Qualification* provides transitional and hybrid approaches for adoption by established organizations and quality systems.

Both of these guides follow the concepts of ICH Q9 *Quality Risk Management* in its application by the ASTM, and support state-of-the-art verification approaches to assure that systems are fit for their intended use – the objective of Stage 2a of the FDA Process Validation Guidance.

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A Comparison of Process Validation Standards

by Jeff Boatman

This article presents a comparison between the Global Harmonization Task Force (GHTF) validation standard and the US Food and Drug Administration's (FDA's) process validation guidance.

Summary

Life science firms in the US are currently subject to two different process validation standards: the GHTF's *Process Validation Guidance* and the FDA's *Process Validation: General Principles and Practices*. These standards have considerable overlap, both officially and practically, across the drug and medical device industries. Previously, all FDA divisions followed a single guidance document, but that document has long since been superseded by new regulations and advances in validation science. This article examines the differences and similarities between the two guidance documents and concludes that any firm manufacturing product whose predicate regulations require process validation (drugs, devices, active pharmaceutical ingredients, biologics, or human-based tissues) should incorporate the philosophies and directives of both to meet Agency expectations and to assure the highest quality of their products.

This article does not examine requirements of the national compendia (e.g., the *United States Pharmacopeia*), whose validation requirements are much less prescriptive than FDA guidance documents; and did not include standards from industry groups such as ASTM. Note that while this article is specific to the regulatory requirements of the US FDA, the GHTF standard examined applies to Europe as well, and the new FDA guidance discussed in this article is under consideration by the European Medicines Agency as the possible basis for an E.U. equivalent,[1] currently in committee draft.[2]

Introduction

Process Validation: General Principles and Practices was finalized by the US Food and Drug Administration's Centers for Drug Evaluation and Research (CDER), Biologics Evaluation and Research (CBER), and Veterinary Medicine (CVM) in January 2011, nearly two years later than originally predicted by its authors.

Notably missing from the new guidance's authorship list is the Center for Devices and Radiological Health (CDRH), one of the main contributors to *Guideline on General Principles of Process Validation*, the 1987 document which was obsoleted by the 2011 guidance. At first glance, this seems an odd omission, as CDRH was an approver of the 1987 standard and has been instrumental in establishing the state of the art in life science validation practices in the years since.

Background

21 CFR 820.75 states *where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance*. This "fully verified" criterion is highly subjective on the part of an inspector; while some firms argue that because they 100% inspect product they therefore fully verify the output of their manufacturing process, an FDA inspector need not actually agree with that assertion. Although inspections and tests may be mitigations used to reduce the overall amount of formal validation required, CDRH generally demands validation of the overall manufacturing process. A review of the 1996 Preamble to the Quality System Regulation offers some insight:

One of the principles on which the quality systems regulation is based is that all processes require some degree of qualification, verification, or validation, and manufacturers should not rely solely on inspection and testing to ensure processes are adequate for their intended uses.

Since that time, the medical device industry has been subject to stringent, science- and statistics-based validation expectations. For example, the concept of ongoing process validation—i.e., that Performance Qualification (PQ) is not the end of validation, but merely the event that marks the start of commercial production—is a new concept in the 2011 guidance, but a longstanding expectation of medical device firms under the process trending requirements of 21 CFR 820.70 and 820.100. The new FDA document also relies heavily upon statistical analysis, control, and prediction, while statistical expectations are already built into the Quality System Regulation; and Statistical Process Control (SPC) and process capability tracking and trending (C_p/C_pK) are the norm at medical device manufacturers.

It might therefore seem mysterious that CDRH would not be a signatory to this seminal validation guidance. Prior to the finalization of the new guidance, the author discussed this with contacts within both CDRH and the Center for Drug Evaluation and Research (CDER), who confirmed that by mutual agreement, CDRH would instead utilize the Global Harmonization Task Force (GHTF) process validation standard, SG3/N99-10:2004, *Quality Management Systems – Process Validation Guidance*.[3] A clue to this internal discussion was present in the footnotes of FDA's *Inspection of Medical Device Firms*, which cited SG3/N99-10, and the January 2011 process validation guidance made it official by explicitly stating that device firms were to follow SG3/N99-10. That standard was updated in 2004 to reflect the new validation requirements of ISO13485:2003, *Medical Devices – Quality Management Systems*, which was itself updated to harmonize with the more general ISO9001:2000 standard. The FDA provided input into the 2003 ISO 13485 standard, so it is fitting that CDRH utilizes SG3/N99-10.

This article will examine the SG3/N99-10:2004 standard to evaluate how it compares to US medical device regulatory requirements, current best practices, and especially the new *Process Validation: General Principles and Practices*. This latter exercise may be of particular interest to combination product manufacturers and firms that produce or market both drugs and devices, and therefore may be subject to both CDRH and CDER and need to comply with the GHTF standard as well as the 2011 FDA guidance.

This analysis is not intended to be a tutorial on process validation or to analyze any validation document in detail. Except to highlight other FDA rules that further explain a requirement, comments are limited to only those instances where the GHTF validation standard appears to conflict

with or provides different expectations than FDA's process validation guidance and current industry best practices.

Operational Qualification (OQ)

A longstanding definition of OQ is "documented verification that all aspects of…equipment that can affect product quality operate as intended throughout all anticipated ranges."[4] Although OQ is not referenced by name in the FDA's process validation guidance, the new guidance incorporates that meaning, along with a somewhat controversial requirement that such verifications run at operating ranges for as long as would be necessary during routine production.[5]

By comparison, the GHTF standard defines OQ as "establishing by objective evidence process control limits and action levels which result in *product* that meets all predetermined requirements."[6] This appears to contradict other validation documents; typically, challenge of the overall process to ensure it consistently produces acceptable product is conducted only *after* qualifications have demonstrated that individual pieces of equipment operate properly throughout their specified ranges.[7] Indeed, equating validation to the successful manufacture of product meeting its specifications is a throwback to the original definition of *validation* in the 1978 drug GMPs;[8] that philosophy was abandoned when the FDA published the 1987 process validation guidance. This apparent contradiction suddenly makes sense if one equates "product" to "the output of the process."

21 CFR 820.3(r) defines *product* as "components, manufacturing materials, in-process devices, finished devices, and returned devices;" clearly these are the outputs of a rigorously defined process. The FDA guidance similarly defines *product* as "…human and animal drug and biological products, including active pharmaceutical ingredients…."[9] SG3/N99-10 does not define the term. Even if we use the conventional dictionary meaning (i.e., *product* equals the result of a process, but not necessarily the final product) this is hard to reconcile with "establishing action limits." Therefore, the GHTF document appears to use the term "OQ" differently, and in different sequence, than common US validation industry usage; but as this article will explain, this really is not an issue.

The FDA process validation guidances, both old and new, expect engineering studies to be performed to determine the critical processing parameters and their operational ranges that produce acceptable final product. Indeed, the 2011 guidance devotes an entire section to this practice and has specific expectations regarding its documentation.

The GHTF document also describes these activities, but assigns them to the OQ phase instead of an earlier, prevalidation phase.[10] The GHTF "OQ" is therefore more of an exploratory experiment than a rigorously defined protocol.

Reducing this to the absurd, a Combination Product manufacturer might have to perform process capability studies, execute an Installation Qualification, and then repeat the process capability study again as part of an OQ in order to satisfy all the relevant validation standards. The author concludes that there is no reason for a firm to change its current practice to match the GHTF standard, provided that operating and alert parameters are in fact being determined and documented, and equipment is being qualified as capable of meeting its process specifications at those limits. Whichever documentation approach a firm takes, they can be confident that they are following an FDA-endorsed best practice.

Note that the 2011 FDA guidance includes an expectation that such process development activities will be properly documented,[11] and medical device firms may consider that expectation the next time they are gearing up a production line. Although that guidance is not signed by CDRH, we will demonstrate later in this article why conformance may still be essential in order for a device manufacturer to meet CDRH and GHTF requirements.

Risk Management

Whether a firm produces drugs or devices, and whether performed during operational qualification or as part of pre-validation engineering studies, risk management and statistical tools are now mandatory. For medical devices, this has been a *de facto* requirement since CDRH formally adopted ISO 14971, *Application of Risk Management to Medical Devices*. The GHTF standard describes the use of Fault Tree Analysis (FTA) and process Failure Mode Effects Analysis (pFMEA) to determine which aspects of the process pose the greatest risk to product quality;[12] the new FDA guidance describes Design of Experiment (DoE) studies to identify relationships between control and component inputs and process output characteristics.[13] The FDA recommends a statistician or person trained in statistical process control develop the methods used in evaluating ongoing production trends;[14] GHTF recommends the use of sound statistics throughout the validation process,[15] for medical devices, both of these tie into the general regulatory requirement to maintain procedures for identifying statistical techniques.[16]

Experienced validation professionals have seen firsthand how all of these tools are essential for an efficient validation. Without DoE and pFMEA to flag the parameters most critical to product quality and identify those issues most likely to affect the process, validation coverage would have to be exhaustive. The use of "product tree" risk assessments to cross-check similar processes and materials can reduce the number of finished products whose processes must be validated from hundreds to a handful. And without proper and documented statistical strategies, confidence in results cannot be assured to a predetermined degree, violating the predicate "high degree of assurance" requirement in 820.75 and inviting an inspector to declare the entire validation effort null and void.

Therefore, the risk assessment and statistical requirements from both documents should be employed, not only to ensure compliance, but because in the long run these practices produce better products, reduce complaints—and inevitably save time and money.

Validation of Overall Process

As mentioned in the introduction to this article, the idea that an entire manufacturing process can avoid validation because the final finished device is 100% inspected is patently false. Confusingly, the flowchart included in the GHTF document for determining whether validation is required for a given process leans strongly toward product verification[17] ("Is Process Output Verifiable?" > "Is Verification Sufficient?").

Since SG3/N99-10 has been adopted by CDRH, one might conclude that CDRH is therefore backing away from its longstanding "fully verified" stance. However, this flowchart must be read in light of the validation examples that follow it.[18] Processes listed that may be subject to verification in lieu of validation include manual cutting operations; testing for color; visual inspection of circuit boards; and manufacturing of wiring harnesses. These are not comprehensive manufacturing processes, but are individual steps or sub-processes within the overall product manufacturing sequence; while verification may suffice for these individual steps, this in no way exempts the overall manufacturing process from validation. The GHTF document merely reinforces existing requirements in 820.75 and the QSR Preamble: while individual production steps may be exempted from validation based on risk (including the mitigation of verification), the overall manufacturing process must still be validated.

This is fully compatible with ISPE methodologies, in which system boundaries are defined; and within those boundaries, process components that have direct impact on product are subjected to risk assessment and validated on a sub-process level as appropriate.[19] The 2011 guidance does not explicitly address qualifications at the process-component level, except when the mitigation involves the use of process analytical technology;[20] but many device firms have adopted a "PQ/PPQ" strategy of performing PQ on individual processes and then an overall "PPQ" to make actual finished product. This strategy, originally suggested by the now-obsolete 1987 guidance, is certainly compliant; but is required by neither the FDA nor GHTF and may well be a waste of time and effort under current rules.

Software Implications

Both the GHTF standard and the 2011 FDA process validation guidance document explicitly exempt software validation from its scope, but do mention that software may be an integral part of a manufacturing process.[21] In many cases,

software that operates a manufacturing line is a standalone process deserving its own requirements, specifications, and validation, and the reader should refer to FDA's *General Principles of Software Validation*.

For instance, building management systems, and off-the-shelf programs that store labeling artwork and print and reconcile labels, have internal software processes that function independently of the equipment being monitored and operated; as such, they may warrant their own validation activity. At the opposite extreme, a simple Programmable Logic Controller (PLC) that was coded specifically to operate a heat sealer is arguably an integral part of that equipment. The exclusion of software validation from SG3/N99-10 does not itself prevent simple control software from being validated as part of an equipment OQ—but the code should be specified [21 CFR 820.70(g)] and if not contained in read-only firmware, maintained under change control [21 CFR 820.70(b),(i)]. Note that challenges of ladder logic as part of equipment qualifications, combined with code documentation and change control, also meet CDER requirements for such systems at drug firms.[22]

Determinations that software is, or is not, integral to equipment design should be described in validation plans or risk assessment documents, and should include or reference the software's 21 CFR 11 (electronic records) impact as well.[23] While no specific regulation requires separate validation efforts as a result of electronic record implications, many companies have a corporate policy regarding Part 11 (and for firms also operating under ISO13485 or the European Medicines Agency, E.U. Annex 11) and tie their validations of systems that process electronic records or electronic signatures back to that policy based on a separate computer system audit. Including a system's electronic records impact as part of an equipment assessment can assist in demonstrating compliance with the company's policy and highlight systems requiring special attention.

Number of Runs

The "classic" required number of production runs to support a performance qualification is three batches or lots. For example, the QSR preamble states:

> *While FDA believes that three production runs during process validation (process validation may be initiated before or during design transfer) is the accepted standard, FDA recognizes that all processes may not be defined in terms of lots or batches. The number three is, however, currently considered to be the acceptable standard.*

Three is the smallest possible number of runs that can identify a "trend," but there is scant scientific basis for arbitrarily picking three successful runs as a validation effort's acceptance criterion. On this issue, CDRH and CDER are now in complete agreement: the GHTF document states "challenges should be repeated enough times to assure that the results are meaningful and consistent,"[24] while the FDA guidance states "the number of samples should be adequate to provide sufficient statistical confidence of quality within a batch and between batches."[25] When questioned during an ISPE teleconference, the CDER representative stated that the number of runs had to be "enough to demonstrate consistency, but at least three."[26]

The author has confirmed with the FDA[27] certain special instances where a PQ could be performed with as little as a single confirming run; but these opportunities are most likely to appear at contract manufacturers whose "new" products are simply variants of products and processes for which extensive production and validation history already exist. The reader should further bear in mind that a "lot" is often defined by the firm in terms of financial impact or practicality, which may bear little relationship to validation. For example, declaring a "lot" to consist of 30 units because there are 30 rows to record serial numbers on a Device History Record or because the electronic batch record has a limit of 1,000 bottles of drug may result in tidy paperwork, but is a poor predictor of likely process variability. Validation plans and protocols should avoid dogmatic definitions of "batch," "lot," and "run" and rely instead upon risk assessments, and where appropriate, Analyses of Variance.

Historical Data

Basing validation and production sampling on historical parametric data is more efficient than reliance on attribute generalizations. Savvy manufacturing engineers know that by maintaining good records during process design activities, data from those studies can be analyzed to provide very efficient sampling plans and realistic acceptance criteria. For example, tight historical standard deviations encountered during process capability trials might statistically justify taking only 10 samples per run during PQ, while simply relying on a generic sampling plan such as Acceptance Quality Limits (AQL)[28] might require 50 samples. Likewise, establishing an acceptance criterion of "95% confidence that no more than 1 out of 1,000 units produced is defective" is far more meaningful than "inspect 50, pass on one defect, fail on two defects"—but the critical tail calculations required to make such an assertion demand reliable and representative historical parametric data.

Unfortunately, it is common industry practice to use generic AQL tables (or worse, unfounded guesses) as an acceptable, if inefficient, guideline. While AQL and similar sampling plans will continue for the purpose for which they were originally designed (i.e., sampling of product to test for go/no-go acceptance attributes), the era of using AQLs as a surrogate for sound statistical analyses may be coming to an

end. As expressed in both the FDA guidance and the GHTF document, there is a growing expectation at regulatory authorities that manufacturers demonstrate that they have a clear and in-depth understanding of their processes. One controversial provision of the FDA guidance is a recommendation of "...continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates."[29] The Parenteral Drug Association protested that this is an unwarranted expectation, stating in part "...a limited number of developmental batches would not be sufficient to develop a statistically sound rationale for commercial product distribution."[30] While CDRH has a longstanding expectation for firms to show thorough understanding and control over their processes,[31] their sibling Center, under such industry pressure, may ultimately relax some of these requirements. Even so, expect to see pharmaceutical firms coming under increased CDER and District Office scrutiny of their statistical controls, with SPC, C_pK, and analyses of variance among the likely candidates. The contra-wise argument is that it is acceptable for drug manufacturers to meet a lower validation standard than medical device firms, and with the 2011 guidance, CDER has made it clear that they strenuously disagree.

The above items make sound statistics during process capability, design of experiment studies, and good documentation of their results critically important. GHTF says "validation of a process can be partially based on accumulated historical manufacturing, testing, control, and other data related to a product or process... historical data is not feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis."[32] This means that for any data to be used in a validation exercise, it has to be properly recorded and stored in accordance with documented quality record procedures per 21 CFR 820.180. This mirrors CDRH constraints on the use of "retrospective" validation data, which in essence preclude the use of such data if not properly recorded or if the data and the system itself have not been maintained under rigorous change control.[33] As a practical matter, relying solely upon historical data to retrospectively "validate" a process is no longer permitted by either FDA division.

Ongoing Validation

As previously mentioned, ongoing monitoring of process variability and trending is a long-standing CDRH expectation. Any "Six-Sigma Green Belt" knows that a low C_pK means excessive waste, and CDRH inspectors are known to specifically check for C_pK metrics trending below 1.3. The GHTF document makes it explicit: "trends in the process should be monitored to ensure the process remains within the established parameters. When monitoring data on quality characteristics demonstrates a negative trend, the cause

should be investigated, corrective action may be taken and revalidation considered."[34]

What is really new is CDER's application of this strategy to drug firms as well: "…data collected should include relevant process trends…information collected should verify that the critical quality attributes are being controlled throughout the process."[35] While CDRH authority is explicit in 21 CFR 820.70 and 820.75, CDER argues that it has implied authority under the Annual Product Review clause of 21 CFR 211.180(e).[36] If that viewpoint ultimately prevails, it will no longer be acceptable for a firm to have one level of production surveillance for medical devices and another, lesser state of control for drugs. The author has seen device companies tell Agency inspectors that validating a given process to a high degree of confidence is impractical or impossible, only to be informed that their competitor is already doing it. Forewarned is forearmed: the QSR Preamble states "during inspections, FDA will assess whether a manufacturer has established procedures and followed requirements that are appropriate to a given device under the current state-of-the-art manufacturing for that specific device."

Finally, some pharmaceutical companies may attempt to revive a decades-old argument that manufacturing inefficiencies, such as scrapping batches or culling out product that fails to meet specifications, is a financial business risk that FDA has no authority over, and therefore they do not need to validate and/or monitor their processes. Such firms are advised to read another new FDA guidance explaining CDER's expectations of a drug manufacturer's quality systems, which concludes that quality must be built into product and processes through *Quality by Design*, and not established through subsequent inspection and test.[37] While guidance documents technically "do not establish legally enforceable responsibilities,"[38] this represents CDER's current thinking, and a drug firm will be hard-pressed to explain why their validations and ongoing monitoring should not meet the state of the art already employed by their sister device companies. Quality by Design, the concept that one must establish the expectations for a process in advance and then objectively prove that resulting products and processes meets those requirements (and not simply test product until it passes) is not merely an FDA philosophical expectation; it is United States federal case law.[39]

Conclusion

The good news is that a firm using risk assessment tools to perform and document process development; validating processes based on risk and sound statistical principles; and performing ongoing process monitoring using tools such as SPC swimlane charts, C_pK tracking, and determination of root and especially special cause of variation, is already meeting both the GHTF and FDA documents.

If your firm is not already doing this, GHTF SG3/N99-10 has an extensive appendix with an excellent explanation of these tools and their application. In particular, a company that produces combination products or both drugs and devices—especially within the same facility—should consider incorporating aspects of both SG3/N99-10 and *Process Validation: General Principles and Practices* as described in this article.

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About the Author

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Global Regulatory News

International

EMA and European Commission Renew Confidentiality Arrangement with Canada[1]

The European Medicines Agency (EMA) and the European Commission's Directorate General for Health and Consumers have renewed their confidentiality arrangement with the Health Products and Food Branch of Health Canada, the Canadian regulatory authority for medicines, for a further five-year period. The renewal builds on the success of the original 2007 confidentiality arrangement. It will allow the two parties to continue to exchange regulatory information related to the authorization and supervision of medicinal products for human and animal use for a further period of five years, with tacit renewal for subsequent five-year periods.

EMA and European Commission Renew Confidentiality Arrangement with Japan[2]

The EMA and the European Commission's Directorate General for Health Consumers have renewed their confidentiality agreement with the Japanese medicines regulatory authorities for a further five-year period. The renewal of this arrangement allows the Agency to continue the exchange of confidential information on the regulation of human medicines with Japan's Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency until February 2018, with the possibility of further extensions for five-year periods.

Middle East

Saudi Arabia

SFDA Launches Code of Ethics for Marketing of Pharmaceutical Products[3]

The Saudi Food and Drug Authority (SFDA) has launched the Saudi Code of Ethics for practicing pharmaceutical products marketing in the Kingdom. This code of ethics is considered a moral and ethical agreement for practicing pharmaceutical and drug marketing by all drug factories and organizations working in this field and practitioners in the healthcare sector, including physicians and pharmacists in the public or private sectors.

Asia/Pacific Rim

China

Chinese SFDA Issues Opinions on Drug Evaluation and Approval Reform and Drug Innovation[4]

The Chinese State Food and Drug Administration (SFDA) recently issued the Opinions on Deepening Drug Evaluation and Approval Reform and Further Encouraging Drug Innovation. Focusing on the aspects of changing the evaluation concept for innovative drugs, adjusting the evaluation strategy for generic drugs, strengthening quality management for drug clinical trials, and encouraging the research and development of children's drugs, the Opinions aims at deepening reform, encouraging innovation, and using the limited evaluation resources mainly for innovative drugs with clinical value and generic drugs urgently needed in clinical treatment.

Chinese SFDA Adopts Revised Good Supply Practice for Pharmaceutical Products[5]

The newly revised Good Supply Practice (GSP) for Pharmaceutical Products was recently adopted at the executive meeting of the Ministry of Health and officially issued. It will go into effect 1 June 2013. The revision of GSP is an action of China to adjust the policy for supervision of drug distribution. The revised GSP sets higher qualification requirements and higher standards for engaging in drug distribution. Compared with the current GSP, the newly revised GSP has higher requirements for quality management, which will effectively enhance the capability to control drug quality risk in the distribution process. The revised GSP comprises 187 articles in four chapters, including the General Provisions, Quality Management for Wholesale of Pharmaceutical Products, Quality Management for Retail of Pharmaceutical Products and Supplementary Provisions.

India

Slow Approvals Put India's Drug Trials Industry at Risk[6]

Slower government approval for testing new medicines is threatening India's aspirations to be a fast-growing, low-cost hub for clinical trials, and has prompted some drugs firms to shift operations elsewhere, adding to their costs.

Europe

European Union

New Members of EMA Management Board Appointed[7]

In December 2012, four new members were appointed to the Management Board of the European Medicines Agency (EMA); all are representatives from the doctor's and patient's organizations. Dutch citizen Wim Wientjes was elected as a representative from the umbrella organization International Diabetes Federation.

European Commission Publishes Draft Guidelines on Principles of Good Distribution Practices for Active Substances[8]

This new guideline covers manufacturing activities consisting of repackaging, re-labeling, or dividing up of active substances. It can be found at: http://ec.europa.eu/health/files/gmp/2013-02_gdp_for_api_cons.pdf.

EMA Revises Guidance to Include Orphan-Related Information[9]

The EMA has revised three guidance documents to include information related to orphan medicines. These documents provide guidance to applicants in relation to pre-authorization and post-authorization procedures and applications for marketing authorization of generic/hybrid medicinal products. The revision includes questions and answers related to medicines that have been designated as orphans or for indications in which there are already orphan medicines authorized. In the latter case, there is a need for assessment of similarity in comparison with the authorized orphan medicine and, where applicable, the assessment of any of the derogations in the Orphan Regulation.

Europe Split Over New Rules on Medical Devices[10]

EU health representatives are considering the introduction of two new pieces of legislation on the approval of medical devices. While stakeholders agree with the need to beef up patient safety with improved checks and changes to the system of Notified Bodies, whose job it is to review and approve products in each of the EU member companies, they could not come to a consensus on whether to insist devices should have EU premarket authorization.

Tackling Medication Errors: EMA Workshop Calls for Coordinated EU Approach[11]

A close collaboration between national patient safety authorities, national competent authorities, the EMA, and the European Commission is necessary to tackle the issue of medication errors causing harm in Europe. This collaboration should engage patients and healthcare professionals. This was the conclusion of the workshop on medication errors organized by the Agency from 28 February to 1 March 2013.

EMA Focuses on New Legislation, Increased Efficiency and Transparency in 2013 Work Program[12]

The EMA has published its work program for 2013. This year, the Agency's priorities are to:

- continue to ensure that assessment activities are conducted to the highest levels of quality and of regulatory and scientific consistency
- continue to implement the pharmacovigilance legislation, depending on resources
- continue to prepare for the implementation of the falsified-medicines legislation
- prepare for the outcome of the European Commission's impact assessment on revision of the veterinary-medicines legislation
- further develop the communication and transparency activities of the Agency

European Union Adopts Good Distribution Practice Guidelines[13]

The EU Commission's new guidelines on Good Distribution Practice of medicinal products for human use have been adopted and published. The guidelines will enter into force 8 September 2013. They can be found at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:068:0001:0014:EN:PDF.

EMA Updates Product-Information Template as Part of Pharmacovigilance Legislation[14]

As part of the implementation of the European Union (EU) pharmacovigilance legislation, the EMA has updated the product-information template to allow easy identification of human medicines that are subject to additional monitoring and to encourage adverse-reaction reporting for all medicines.

Great Britain

MHRA Publishes Annual Report on Regulation of Medicines Advertising[15]

The Medicines and Healthcare Products Regulatory Agency (MHRA) published an annual report, "Delivering high standards in medicines advertising regulation." This covers the year 2012. It provides details of the activities of the Advertising Standards Unit, including vetting of advertising and complaints investigated and the development of guidance with self regulatory bodies to promote high standards.

MHRA Looking to Appoint New Chief Executive[16]

The MHRA is looking to appoint a new Chief Executive who, in addition to leading the MHRA and working with the Department of Health, will be an ambassador representing the MHRA within Europe and wider global circles. The new Chief Executive will be accountable for ensuring the interests of the public are protected, and that a first class service is provided to agencies and the public.

MHRA Launches "Innovation Office" to Encourage Development of Novel Medical Products and Devices[17]

The MHRA is launching an "Innovation Office" to help organizations who are developing innovative medicines, medical devices, or using novel manufacturing processes to navigate

the regulatory processes in order to be able to progress their products or technologies. The main aim of the "Innovation Office" will be to promote early dialogue between innovative organizations and the MHRA to help facilitate their understanding of the regulatory considerations applicable to their innovation. For example, the MHRA can advise on the development of innovative products like advanced therapies, nanomedicines, and drug device combinations.

MHRA Marks First Ever Successful Prosecution under Good Laboratory Practice Regulations[18]

A man was found guilty at Edinburgh Sherriff's Court for altering preclinical trial data designed to support applications to perform clinical trials. Steven Eaton was prosecuted under the Good Laboratory Practice Regulations 1999 - the first time the MHRA has successfully used these regulations to bring a prosecution. Eaton is a former employee of Aptuit, a large research organization formerly based in Edinburgh.

Netherlands

Dutch MEB Releases Draft Strategic Business Plan for 2014-2018[19]

The Dutch Medicines Evaluation Board (MEB) released its draft Strategic Business Plan (SBP) 2014 – 2018. This SBP will determine the direction of the organization for the next five years and will form the basis of the annual plans by the MEB. The new SBP is partly a continuation of the strategy set out over the past years, but important sections will be intensified and new directions will be taken. The new SBP has been submitted to the Minister of Health, Welfare and Sport for final approval and will be presented at the MEB Day 5 June 2013.

North America

Canada

Information Available on Classification of Health Products at the Device-Drug Interface[20]

Products at the device-drug interface are products that do not readily fall within the definition of "device" or "drug" as set out in Health Canada's Food and Drugs Act, therefore present a challenge when determining which regulations apply. Health Canada's website provides information on how such products are classified. It can be found at: http://www.hc-sc.gc.ca/dhp-mps/dev-drug-instr-drogue/index-eng.php.

United States

Working with the US FDA Office of the Ombudsman[21]

Like many federal agencies, the FDA has a robust ombudsman program that addresses concerns and complaints from regulated industry and the public. At FDA, most product evaluation centers house their own ombudsman staff that address center specific issues. The FDA Office of the Ombudsman, as part of the Office of the Commissioner, provides this function for the agency as a whole. A new brochure, which can be found at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OC/ExecSec/UCM164330.pdf, provides guidance on working with the Office of the Ombudsman at FDA.

US FDA Names Kathleen Uhl Acting Director, Office of Generic Drugs[22]

The FDA has named Dr. Kathleen Uhl Acting Director of its Office of Generic Drugs as it initiates a nationwide search for a full-time replacement for Dr. Gregory Geba, who resigned in March.

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Second ISPE-FDA Event Attracts Top Names, Features Release of Drug Shortage Survey Results

ISPE will hold its second annual Redefining the "C" in CGMP conference 11 – 13 June 2013 in Baltimore, Maryland, USA. Themed "Ensuring a Reliable Supply of Quality Medicines," the event will feature strategic education on issues of interest to industry leaders and global regulatory officials focused on quality systems, processes, and technology utilization that drive quality enhancements that support a reliable drug supply.

"This event is where industry and regulators must come together to share their views on contemporary regulatory issues and solutions," said ISPE President and CEO Nancy Berg. "The sessions, case studies and workshops will be focused on how great companies are establishing and sustaining a culture of quality through contemporary quality management strategies, new methods and technologies, metrics and more effective approaches to integrating suppliers into quality systems."

The event will feature top speakers from the pharmaceutical industry and regulatory agencies, including:

- Howard Sklamberg, Director, Office of Compliance, US FDA
- Andy Skibo, Regional Vice President, Biologics-Supply, MedImmune/AstraZeneca
- Gerald Heddell, Director of Inspection, Enforcement and Standards, MHRA, UK
- John Pinion, Senior Vice President, Quality/Compliance, Genentech, Inc.
- Zena Kaufman, Senior Vice President, Global Quality, Hospira
- Cindy Salamon, Vice President, Global Quality Services, Bristol-Myers Squibb
- Carol Bye, Vice President, Pharmaceutical Sciences Quality Operations, Pfizer, Inc.

Education content will focus on providing attendees with new insights and executable action plans to help resolve challenges related to quality leadership, quality metrics, CMO quality management, flexible manufacturing and other hot topics related to product quality and patient safety.

The event will also feature the first public release of key data resulting from the ISPE Drug Shortage Survey, with an expert industry team providing commentary on the ISPE research, the impact of drug shortages, and potential solutions. A Meet the Press session will feature a joint regulatory and industry panel answering questions from recognized pharma media experts on strategies for industry and regulatory collaboration, as well as compliance and product quality issues.

Other Special Events include an Industry-Led Hot Topic Discussion Forum where participants will have an opportunity to interact directly with industry executives and have questions and concerns addressed, and a Breakfast with the Inspectors, where participants can meet and talk with pharmaceutical inspectors about their recent inspection observations and industry trends.

ISPE Releases New Guidance for Standardizing Use of Booklet Labels in Global Clinical Trials

The use of booklet labels in clinical trials is still growing; however, considerations of how to use booklet labels have become increasingly important in maintaining site and subject compliance.

The *ISPE Good Practice Guide: Booklet Labels*, published in March, aims to provide information and recommendations for the pharmaceutical industry on how to design and structure a booklet label, and how to standardize the use and application of booklet labels. This Guide is intended to support harmonization of labeling requirements and provides recommendations for the effective use of booklet labels to support investigational products across countries, trial programs, and/or protocols.

This Guide discusses the relevant GMP and GCP concerns related to the use of booklet labels for global clinical

Concludes on page 72.

Continued from page 8.

diverse supply chains and influencing a shift in employee skill sets to reap the benefits of modern technology." Friedman also mentioned that ISPE guidance documents are frequently cited in FDA inspector training. I think Members should interpret that statement as a very positive result of their work. Members who share their experiences by writing documents and articles make an impact well beyond ISPE and their companies—ISPE publications also support regulators who are equally challenged to remain current in a dynamic industry. I am proud to witness the increasing number of positive statements supporting the impact ISPE is making worldwide.

Active Members around the world are making an impact on key issues

Senior ISPE leaders are meeting to discuss progress on ISPE's drug shortages initiative, are engaged in dialog around quality metrics and reviewing the impact of new legislation such as the European Falsified Medicines Directive, the Food and Drug Administration Safety and Innovation Act (FDASIA) and other government directives. The increasing involvement of leaders throughout ISPE is an indication that your Society is addressing the right issues. Here are other great examples of Member projects underway.

Members involved in the GAMP Community of Practice (COP) are actively exploring how the GAMP methodology can be applied advantageously in other stages of the product lifecycle, and our Investigational Products (IP) COP and local ISPE European Affiliate Members are teaming on a new event entitled *Effective Approaches to Optimising Drug Supply and Ensuring Security: Best Practices in Both Investigational Products and Commercial Supply Chains* (13-14 June, Prague, Czech Republic). ISPE Members in China are also developing outstanding conferences and enhancing ISPE's relationship with the China Food and Drug Administration (CFDA), formerly SFDA, a newly constituted drug agency, and our Affiliate in Thailand is at work planning for its 10th anniversary celebration later this year.

Last but not least, Members and regulators are organizing the second ISPE-FDA joint conference entitled *CGMP: Assuring Reliable Supply of Quality Medicines* (11-14 June, Baltimore, MD-USA). Sessions at this meeting include PAI Readiness, Breakthrough Therapies, Quality Leadership of CMOs, CAPA, Flexible Manufacturing, PPPQMS, Quality Metrics and more. Delegates attending will hear from European regulators, co-sponsor FDA and during this meeting, ISPE will present results of the ISPE Drug Shortages Survey. The work done by ISPE Members such as gathering technical and trend intelligence and transforming that information into presentations and publications is part of what positions ISPE as the globally recognized leader in technical and regulatory advancement, education and the source of the most valuable networking throughout the pharmaceutical industry.

ISPE Releases New Guidance for Definition and Use of NIMPs in Clinical Trials

Currently, there are no complete regulations or practical guidelines for Non-Investigational Medicinal Products (NIMPs). As a result, pharmaceutical organizations may overcomplicate their clinical trials by submitting products as Investigational Medicinal Products (IMPs) when they could have been managed as NIMPs. Alternatively, organizations may file clinical trial products as NIMPs only to be denied approval by a health authority later in the process. The *ISPE Good Practice Guide: Harmonizing the Definition and Use of Non-Investigational Medicinal Products (NIMPs)* is intended to help alleviate regulatory and operational ambiguity.

The Guide summarizes current consensus on what the pharmaceutical industry and regulations/guidelines define as NIMPs. It aims to address regulatory, manufacturing, and clinical site aspects related to NIMPs. Development of the Guide followed an on-line survey with the goal of understanding how the pharmaceutical industry manages NIMPs. The Guide elaborates upon three key findings from that survey:

1. Which NIMP category is most often utilized?
2. Which NIMP category is most commonly challenged by the local competent authorities?
3. Which functional area of the clinical trial sponsor organization determines if a medicinal product should be categorized as IMP or as a NIMP?

The Guide provides an overview of regulatory requirements and incorporates practical operational guidance, based on industry experience, for the use of NIMPs. It is intended to provide support to personnel in clinical supplies, quality, or clinical operations who may have a need to include NIMPs within their clinical protocols.

Current approaches to supply chain management of NIMPs are considered in order to create guidance and schematics around:

- Sourcing strategies
- Approaches to packaging and labeling
- Recommendations for storage and distribution
- Approaches to clinical site re-imbursement
- Approaches to management of drug accountability, traceability, complaints, and recalls with reference to the original sourcing strategy

In addition, an appendix is provided that categorizes regions or countries according to regulations and practices related to NIMPs.

...Use of Booklet Labels in Global Clinical Trials

Continued from page 70.

trials and responds to the practical needs of users.

This Guide aims to help to ensure greater safety and compliance for subjects participating in clinical trials. Guidance is provided on the type of information that should be included within booklet labels.

This *ISPE Good Practice Guide: Booklet Labels* proposes a standard booklet label layout and using booklet labels in a standardized manner; helping to reduce or eliminate risks and concerns expressed by investigational sites and competent authorities.

Standardization of booklet labels can benefit the pharmaceutical industry by eliminating variability and reducing confusion amongst users. Similarly, standardization can help to reduce dispensing errors by sites and allow subjects and site personnel to become familiar with the label design, so they know where to look for pertinent information. Guidance is provided on the design of booklet labels for product pooling by recommending positioning of the trial identification in a manner that will make just-in-time labeling/identification of trial identification more feasible.

This Guide also includes recommendations to support eliminating use-by dates on labels when controlled using an Interactive Response Technology system. Special consideration is given to clinical trial materials labeled for multiple protocols, known as pooled products. The Guide also includes recommendations for booklet labels applied to IMP for use in hospitals (in-subject) and at-home treatments (out-subject).

This Guide is a result of a joint effort of representatives from the pharmaceutical industry and review by several pharmaceutical discussion groups. General support and professional insights have also been provided by representatives from the MHRA (UK).

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Concludes on page 74.

Continued from page 73.

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