PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

JULY/AUGUST 2013 VOLUME 33, NUMBER 4

Compliant Cloud Computing

Manufacturing Execution Systems

Software Development

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addresses

ISPE Global Headquarters
600 N. Westshore Blvd.
Suite 900
Tampa, Florida 33609 USA
Tel +1-813-960-2105
Fax +1-813-264-2816

ISPE Asia Pacific Office
20 Bendemeer Road
#04-02 Cyberhub
Singapore 339914
Tel +65-6496-5502
Fax +65-6496-5599

ISPE China Office
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road
Shanghai 200041, China
Tel +86-21-5116-0265
Fax +86-21-5116-0260

ISPE European Office
Avenue de Tervueren, 300
1150 Brussels, Belgium
Tel +32-2-743-4422
Fax +32-2-743-1550

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When Annex 11 – the part of the EU pharmaceutical regulations covering computerized systems – was revised in 2011, the reason for the change given by the regulators was the increased use of computerized systems and the increased complexity of these systems. And as we all know, there are few areas of the pharmaceutical and life science industries that are not affected by and dependent on computer systems and automated processes.

Throughout the product life cycle, the challenge to the industry is how best to adopt innovative and effective technologies for process control and information management, while remaining compliant with regulatory requirements, and safeguarding product quality and patient safety.

In this issue, Lopez reviews the current requirements applicable to computer systems in the pharmaceutical manufacturing environment and how these have developed and changed over a quarter of a century.

While that article focuses on regulatory activities, Clark and Wyn describe how ISPE and the GAMP Community of Practice (COP) have also played a major role in defining, refining, and sharing good practices through a series of guidance documents. *GAMP 21 Years Later* presents an overview of the history and achievements of the GAMP COP and shows the results of a truly international and collaborative effort.

One GAMP application area central to manufacturing is the increasing adoption of Manufacturing Execution Systems (MES) as the basis of strategic initiative for integrating manufacturing and IT, and bringing benefit through improved quality and production efficiencies. The potential advantages and how they may be achieved is well documented in the GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach. In this issue, Savage presents the findings of a study of how MES is increasingly being adopted by the pharmaceutical industry, and how companies are gaining a competitive advantage by doing so.

One current challenge for Information Technology (IT) practitioners is how to achieve the potential benefits associated with cloud computing, while achieving a level of control, security, and integrity required for regulated processes, data and records. A risk management approach for cloud computing is required. The article by Stokes explains what cloud computing is, how it differs from traditional IT outsourcing, and how the specific risks associated with cloud computing's essential characteristics can be understood, assessed, and mitigated.

Another author addresses how to exploit the benefits of the latest software development models, methods, and tools, while still achieving the level of transparency and documented evidence traditionally expected by regulators. An in-depth article by Stafford presents new insights into software design, including a potentially more efficient way to implement software without undermining regulatory expectations.

I hope you find this issue of *Pharmaceutical Engineering* informative as well as thought provoking. I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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Members Are the Strength of ISPE

ISPE President and CEO Nancy Berg discusses the importance of active participation in the Society and how it leads to the development of pivotal events, initiatives, and publications that are shaping the industry and strengthening regulatory relationships.

I recently met with Members of ISPE's European Strategic Forum to discuss our regional strategies and to gather their views on how to enhance the value of ISPE. It was not surprising when these Members identified *networking* as the most significant ISPE Member benefit. Whether linking industry professionals with common work challenges, connecting professionals and companies to practical guidance, or engaging industry and global regulators in dialogue, the value of ISPE has always been in relationships and connections. People are the strength of ISPE.

In this issue of *Pharmaceutical Engineering*, many of the articles are focused on GAMP®. With this as our theme, we have the opportunity to recognize the long-standing Members of ISPE GAMP who keep this group relevant – on the edge of technology, and a source of valuable Member networking. GAMP began as a small group of people who recognized the value in working together to help industry meet evolving regulatory expectations for computerized system compliance and validation and is now one of the largest ISPE Global Communities of Practice (COPs). GAMP's success is a testament to what can be achieved when a committed group of people with common interests leverage their knowledge and energies to make a difference. Today, GAMP Guidance Documents are available in multiple languages, and through successful GAMP conferences and workshops, ISPE has trained thousands of people on GAMP methodology worldwide. Manufacturing companies, suppliers, and regulatory agencies recognize ISPE and GAMP as the world's authority on the subject.

The Society's long-standing relationships with regulatory colleagues are also valued and this month we are recognizing the nearly 700 regulators who are Members of ISPE, supporting work on mutual goals. Our regulatory Members participate in committees, throughout the COP network, and as advisors and speakers at ISPE events. Last month, key European regulators supported ISPE's conferences in Prague, Czech Republic and for the second year, ISPE and FDA collaborated in organizing a successful CGMP Conference, "Ensuring a Reliable Supply of Quality Medicines," in Baltimore, MD USA. During both conferences (which took place just days before this issue of *Pharmaceutical Engineering* went to press), ISPE announced the results of its Drug Shortages Survey and led delegates in discussions on key survey findings related to the quality system, leadership, and corporate governance, as well as regulatory relationships. By now Members will have received a copy of The Report on ISPE Drug Shortages Survey, which is available to download on ISPE's website (www.ispe.org/drug-shortages-initiative). During the Baltimore program, ISPE conference speakers led discussions on industry "hot topics" and facilitated industry's first workshop discussions on metrics. Another dynamic session addressed manufacturing issues associated with breakthrough therapies and ISPE's Product Quality Lifecycle Initiative (PQLI®) just released its latest guide entitled, *Part 4 – Process Performance and Product Quality Monitoring System*.

We continue to develop ISPE's new alliance with PMMI and Pharma EXPO--ISPE's new trade show and conference. Supplier Members and exhibitor customers should have received detailed information on how to get involved in this new event, which will debut 2-5 November 2014 in Chicago. Pharma EXPO offers supplier Members and exhibitors an opportunity to connect with pharmaceutical, medical device, and nutraceutical manufacturers from around the world. This new show will reflect the *pharmaceutical lifecycle*, presenting visitors the opportunity to see and compare the latest in world class equipment and technology.

I encourage you to become active in your Society and to share in the benefits resulting from participation in this remarkable group. Getting involved will introduce you to a large global network of people with similar backgrounds and interests who are working toward the same goals. Won't you join us?

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Compliant Cloud Computing – Managing the Risks

by David Stokes

This article presents pharmaceutical business process owners with an explanation of what cloud computing is, how it differs from traditional Information Technology (IT) outsourcing, and how the specific risks associated with cloud computing's essential characteristics can be understood, assessed, and mitigated.

With an increase in reported security breaches from large, well known Information Technology (IT) companies, the pharmaceutical industry has understandable concerns about information system security and the outsourcing of Information System (IS) services.

This has led to a situation where the pharmaceutical industry has been slower than other non-regulated industries to adopt cloud computing, often because of a false belief that cloud computing is synonymous with IT outsourcing. As explained in this article, while cloud computing may involve outsourcing (and many of the outsourcing risks are discussed), this is not always the case.

So that non-technical business process owners can better consider the risks, the first part of the article clearly defines how mature consumers and providers are defining cloud computing and discusses the essential characteristics that define cloud computing and the relationship between cloud computing and outsourcing.

The second part of the article then considers the risks of cloud computing in the specific context of the pharmaceutical industry, and how these risks can best be mitigated, either by moving to an in-house (on-premise) cloud computing model or private cloud model, or by choosing not to move essential services to the cloud.

It concludes by stating that in most cases the cost advantages of cloud computing can be realized and risks mitigated by a careful assessment of cloud providers, leveraging a better understanding of what cloud computing actually is.

The Path to Cloud Computing

Pharmaceutical companies have been increasingly moving toward the outsourcing of non-core services for many years and this has certainly included the use of hosted and managed IT services provided by external third party organizations. Cloud computing is undoubtedly the biggest paradigm change in the world of computing in the last decade and is the latest development in this trend.

The technology that underlies cloud computing introduces a number of new opportunities into the outsourcing model which are extremely attractive to many businesses. However, these same technologies also bring additional risks which pharmaceutical companies must understand and mitigate to be able to successfully leverage cloud computing to the fullest extent possible.

In the early years of cloud computing, there was (and to some extent still is) a good deal of confusion as to what cloud computing is – and what it isn't. To a large extent, this was driven by vendors understandably using differing terminology, telling prospective users that they didn't need to understand the technology and in some cases overusing the phrase "cloud computing" by using it to refer to services that are not – at least by current definitions – in the cloud.

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This made it very difficult to understand the model and manage the risks. This has been one of the main reasons why pharmaceutical companies (and organizations in other life sciences sectors) have been relatively slow to embrace the paradigm change.

The IT industry has now started to develop useful consensus guidance and adopt standard terminology which makes it easier for non-specialists to understand cloud computing. This in turn means that it is now easier for a wider range of stakeholders in the pharmaceutical industry to understand what is different about cloud computing, to understand the risks to their business processes and their data, and to develop appropriate strategies to mitigate risk and to move – at least to some extent – into the cloud.

What's Different About the Cloud?

As mentioned above, pharmaceutical companies have been moving to an outsourced computing services model for many years – well before the cloud was developed. Therefore, it is important to understand what is different about cloud computing, which risks are shared with other outsourced computing models, and which risks are unique to cloud computing.

To do that, it is important to understand what is different about cloud computing, and to define and comprehend a consistent set of terminology. The IT industry is now adopting a set of definitions developed by the US National Institute of Standards and Technology (NIST), known as NIST SP 800-145 "The NIST Definition of Cloud Computing."[1] Partly through the work of the ISPE GAMP® Community of Practice (COP), these definitions are being leveraged to provide guidance to the pharmaceutical industry using terminology that can be understood not only by IT subject matter experts but by all by business, financial, and QA stakeholders.

As a result, this article uses the terminology from NIST SP 800-145 and from the GAMP® Guide[2] and GAMP® Good Practice Guides[3] to provide (or reference) a consistent set of definitions and models which stakeholders can use when developing a cloud strategy or when looking to move specific IT platforms or applications into the cloud.

In order to understand what is different about the cloud, it is important to understand how cloud computing is defined. Under NIST SP 800-145, cloud computing is defined as *"... a model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g., networks, servers, storage, applications, and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction."*

There are different models for implementing cloud computing (discussed below), but there are also five essential characteristics which should be fulfilled if a service is considered to be cloud computing. These are defined in NIST SP 800-145 as shown in Table A, but the terms used are not always easily understandable to the non-IT stakeholder and certainly aren't written in terms that are relevant to the pharmaceutical industry.

It is worth thinking about these essential characteristics in terms of risk to patient safety, pharmaceutical product quality, and data integrity in order to understand what is different about cloud computing and what risks need to be assessed and mitigated.

On-Demand Self-Service

It can certainly be useful for "consumers" to be able to quickly set up new computing services on-demand. Compared to the time required to source, install, and qualify in-house infrastructure in the regulated company's own data center, the ability to quickly leverage new processing and storage capacity can massively enhance the responsiveness of the IT organization to meet business needs.

In a similar way, the ability to purchase the functionality of a software application, such as a Clinical Trial Manage-

On-Demand Self-Service:	A consumer can unilaterally provision computing capabilities, such as server time and network storage, as needed automatically without requiring human interaction with each service provider.
Broad Network Access:	Capabilities are available over the network and accessed through standard mechanisms that promote use by heterogeneous thin or thick client platforms (e.g., mobile phones, tablets, laptops, and workstations).
Resource Pooling:	The provider's computing resources are pooled to serve multiple consumers using a multi-tenant model with different physical and virtual resources dynamically assigned and reassigned according to consumer demand. There is a sense of location independence in that the customer generally has no control or knowledge over the exact location of the provided resources but may be able to specify location at a higher level of abstraction (e.g., country, state, or datacenter). Examples of resources include storage, processing, memory, and network bandwidth.
Rapid Elasticity:	Capabilities can be elastically provisioned and released, in some cases, automatically, to scale rapidly outward and inward commensurate with demand. To the consumer, the capabilities available for provisioning often appear to be unlimited and can be appropriated in any quantity at any time.
Measured Service:	Cloud systems automatically control and optimize resource use by leveraging a metering capability, at some level of abstraction appropriate to the type of service (e.g., storage, processing, bandwidth, and active user accounts). Resource usage can be monitored, controlled, and reported, providing transparency for both the provider and consumer of the utilized service.

Table A. NIST definition of cloud essential characteristics.

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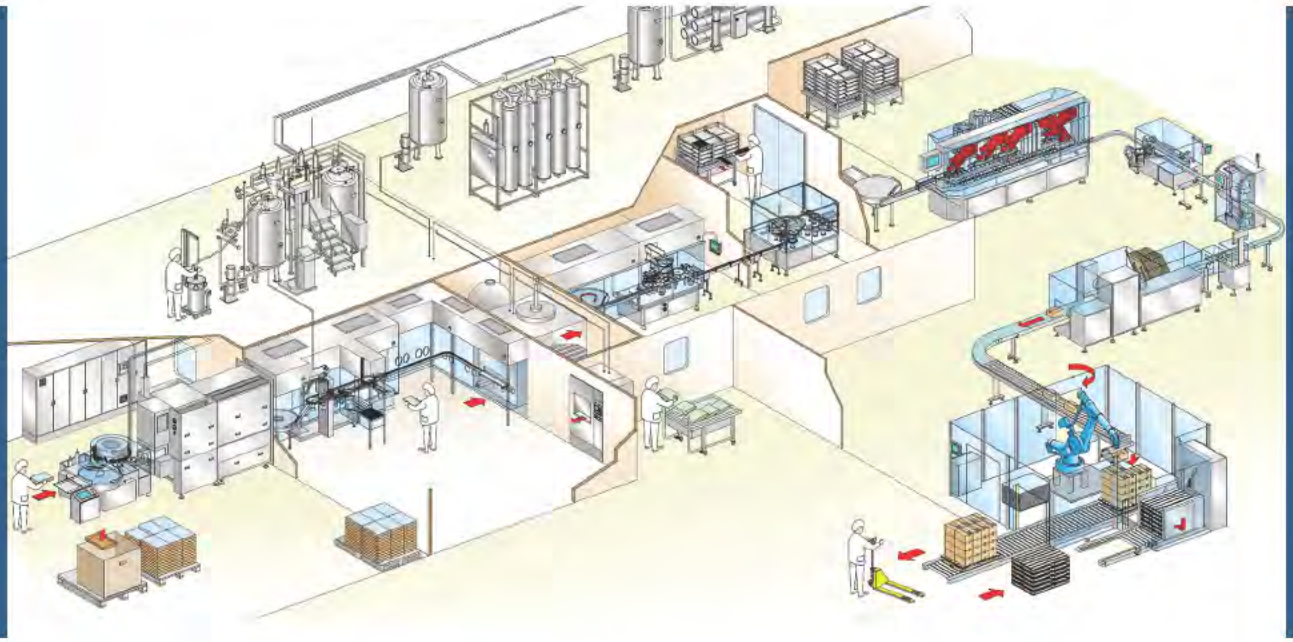


ment System (CTMS) or Customer Relationship Management (CRM) system, running in the cloud can provide business with the opportunity to move much faster when starting a new clinical trial or starting to sell a new drug product into a new market.

There is the risk that business process owners could source unqualified platforms from providers or buy into clouded applications that do not meet key regulatory requirements or that are not practically possible to appropriately validate.

Since cloud computing can be purchased over the Internet simply by using a credit card, it is important that "self-service" is defined at the level of the regulated company rather than at the level of the individual user (i.e., the regulated company is the "consumer"). The "on-demand" nature of the service needs to be balanced by use of a well thought out acquisition processes which include IT and QA groups. This will ensure that the right questions are asked at the time of acquiring the service and before contractual commitments are made (i.e., that computing platforms are qualified, that cloud service providers pass appropriate supplier assessments, that applications provide compliant functionality and can be validated).

Broad Network Access

At a time when more users are working remotely (from home or when travelling), the provisioning of broad network access is good for business flexibility and this is as true in the pharmaceutical industry as in any other.

In common with all industries, the use of "broad networks" means that the risks of unsecured wireless ("Wi-Fi") networks and cellular (mobile phone) networks need to be considered. In many cases, it may not be appropriate to allow certain data to be transmitted or applications to be accessed via insecure or less secure networks. While IT security is essential at an infrastructure level, adequate security is difficult to achieve using only technological controls and the issues of user training and procedural controls are equally important.

The use of broad network access also infers the wider use of mobile computing platforms, such as tablets, smartphones, and other emerging computing technologies. These also may pose new security risks which need to be considered and these additional platforms also will require some degree of qualification. In some cases, users may have to be told that they cannot use non-qualified or insecure platforms to access sensitive data or critical applications.

Resource Pooling

The ability to pool (share) computing resources is one way in which the cost of computing can be reduced – by increasing the effective utilization of computing resources by spreading it across a wide range of consumers.

Since this pooling of resources does require a level of shared access by all of the consumers (to a network domain, to a server or application database), it relaxes one level of security control that would be leveraged if the same resources were not shared with other consumers. While any good security model relies on security controls at multiple levels, opening up access at one level means that there is greater reliance upon the effectiveness of controls at other levels and the assessment of the effectiveness of the remaining security controls becomes even more important.

Resource pooling also provides a degree of location independence, but is important for the pharmaceutical company to know the exact boundaries of this independence. Regulated companies need to ask whether their data and applications will only be moved between servers in the one data center, or could they be moved to another data center or even another country. This needs to be defined (limited) in terms of an appropriate Service Level Agreement (SLA) or Data Transfer Agreement (DTA) and all such locations need to be appropriately assessed.

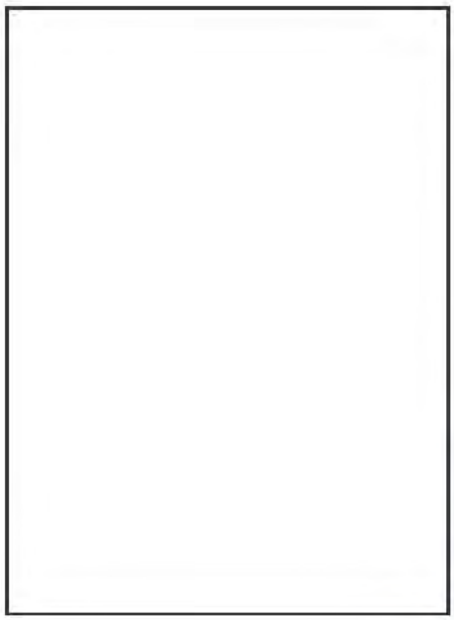
Rapid Elasticity

The ability to consume more or less resources based on moment-by-moment demand is again a cost effective way to utilize computing resources. From a business perspective, this allows more computing resources to be provisioned to an ERP system at month-end closing and means that the needs of the finance and accounting department will not adversely impact on the performance of the materials resource planning in manufacturing or batch release in QA. It also means that additional processing power can be applied to the bio-statistical analysis of clinical trial data when regulatory submission deadlines are approaching.

From a business perspective, this can only be a good thing as long as costs are controlled and it is sensible to place limits on the level of resources that can be provisioned automatically. It is also important to understand where change controls are and are not required as part of an elastic service. For instance, if capacity is provisioned from a pool of previously qualified servers or a previously qualified Network Attached Storage (NAS) array, a change control may not be required. However, at some point additional physical capacity may need to be provisioned or a previously unqualified platform may need to be qualified and a change control would need to be raised. Without this, it is possible that the controlled and qualified status of the IT infrastructure and thereby the validated status of a GxP significant application may be compromised.

Measured Service

Unlike the other Essential Characteristics, the provisioning of a measured service introduces no additional risks. In fact, the monitoring, control, and reporting which are an inherent part of a measured service are a good thing as far as Infor-



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mation Systems (IS) compliance is concerned. Therefore, regulated companies should ensure that they understand the level of monitoring, control, and reporting that is part of their SLA and that it is appropriate to achieving their IS compliance objectives.

The risks associated with cloud computing and the specific risks related to these essential characteristics obviously need to be considered at a much more detailed level than are summarized here. High level risks associated with cloud computing should be considered as part of the cloud strategy and the specific risks associated with each of the essential characteristics should be used to identify additional risk scenarios, which should be managed in accordance with an established risk management process.

What Cloud Computing Is Not

Now that the essential characteristics of cloud computing are understood, it is also important to discuss what cloud computing is not. This is because a number of suppliers in the IT industry are using the term "cloud" to refer to a number of services that do not meet the essential characteristics. These services still have many risks associated with them, but by understanding what is and what is not cloud computing, regulated companies have a much better chance of focusing limited resources on assessing and mitigating the relevant risks.

Hosting Services

It is possible for third parties to host regulated companies applications without using a cloud computing model. This is a very traditional model and in many cases, this does not provide on-demand self-service or leverage the resource pooling or rapid elasticity which is an essential part of cloud computing (the last two of which are largely provisioned a result of virtualization – as previously discussed in *Pharmaceutical Engineering*).[4,5]

Broad network access may still be an issue and a measured service should still be available. Based upon conducting supplier audits on a wide range of hosting organizations, other common risks inherent with a traditional hosted services model (and shared with cloud computing) include:

- A broad range of security issues
- Lack of a formal IT quality management system
- Appropriate GxP awareness training for staff (and associated training processes)
- Failure to formally qualify IT infrastructure in accordance with regulatory expectations

Managed Services

Varying from provider to provider, managed services may include the management and tuning of databases, the configuration of applications or general performance monitoring. These are again independent of cloud computing and may be provided for platforms and applications which are clouded or not clouded. As with general hosting, most of the risks are associated with the processes and people involved (the IT quality management system, security, and training).

Outsourcing

Although some cloud models are only provided by third parties by definition, most cloud models can be provisioned by a regulated company within their own data centers. Just because a service is outsourced, it doesn't automatically mean that it is in the cloud, and just because a service is in the cloud doesn't mean that it's provided by a third party.

There are significant risks that need to be considered with any outsourced IT service whether or not the service is clouded. The key thing is to understand the essential characteristics of cloud and to assess these in addition to common IT outsourcing risks.

Cloud Computing Models

Cloud computing can be provisioned using a number of different service and deployment models. These are defined in NIST SP 800-145 and are listed in Tables B and C.

These definitions are, again, difficult for the non-special-

Software as a Service (SaaS):	The capability provided to the consumer is to use the provider's applications running on a cloud infrastructure. The applications are accessible from various client devices through either a thin client interface, such as a web browser (e.g., web-based email), or a program interface. The consumer does not manage or control the underlying cloud infrastructure including network, servers, operating systems, storage, or even individual application capabilities with the possible exception of limited user-specific application configuration settings.
Platform as a Service (PaaS):	The capability provided to the consumer is to deploy onto the cloud infrastructure consumer-created or acquired applications created using programming languages, libraries, services, and tools supported by the provider. The consumer does not manage or control the underlying cloud infrastructure including network, servers, operating systems, or storage, but has control over the deployed applications and possibly configuration settings for application-hosting environment.
Infrastructure as a Service (IaaS):	The capability provided to the consumer is to provision processing, storage, networks, and other fundamental computing resources where the consumer is able to deploy and run arbitrary software, which can include operating systems and applications. The consumer does not manage or control the underlying cloud infrastructure but has control over operating systems, storage, and deployed applications; and possibly limited control of select networking components (e.g., host firewalls).

Table B. NIST cloud computing services models.

The Role of a Learning Management System in Regulatory Compliance

Can you afford the risk – and cost – of non-compliance?

Your industry demands compliance. Your people need training and certification.

The pharmaceutical and associated industries have been undergoing change since the introduction of the FDA's program on Good Manufacturing Practices for the 21st Century. One of the outcomes of this was ICH Q10, which sets out the requirements for Pharmaceutical Quality Systems (PQS) based on the principles of ISO 9000.

One of the foundations of the PQS is resource management, which links with the training regulations of the individual GXP (Good Laboratory, Good Manufacturing, or Good Clinical Practices) regulations that require firms to demonstrate that their staff have the appropriate combination of education, training, and experience to do their assigned jobs.

As a core element of a PQS, training records are nearly always reviewed during an inspection. Many companies' training records are paper based and may not be up-to-date, making them an easy target during an inspection. Multinational companies have the problem of having to deal with different regulations and different regulators.

FDA's 21 CFR Part 11 Regulation

The US Code of Federal Regulations Title 21 CFR Part 11 covers compliance requirements for organizations in healthcare, pharmaceutical, life sciences, biotechnology, medical device manufacturing, and other FDA-regulated industries as well as most government agencies. 21 CFR Part 11 requires companies to implement controls such as system validation, protection of electronic records, audit trails, electronic signatures, and documentation for software and systems that are involved in processing many forms of data as part of their business practices and product development.

The right Learning Management System (LMS) can play a key role in helping companies meet 21 CFR Part 11 and EU GMP-equivalent requirements. For example, the LMS can support trustworthy and reliable electronic signatures and electronic records so that no one can alter information without an electronic audit trail in place, thereby allowing companies to go to a "paperless" system of record keeping. The LMS can also support delivery and tracking of Standard Operating Procedures (SOPs) to employees as well as detailed reporting on employee training and workforce readiness.

Approaching Part 11 from a software implementation and validation standpoint, this means that the LMS software should provide organizations with the ability to go through a successful validation process or audit with the FDA by ensuring it supports the necessary functionality, quality processes, and reporting for the organization to become compliant.

Case in Point

Fresenius Medical Care is the world's largest integrated provider of products and services for individuals undergoing dialysis because of chronic kidney failure. In 2012, the company had 86,153 employees in 3,200 clinics and 40 production sites serving 258,000 patients and providing 38.6 million dialysis treatments worldwide.

Fresenius Medical Care needed a Learning Management System (LMS) that can be installed on premise, has strong compliance capabilities, supports multiple languages, is flexible and transparent in terms of customizations, and is backed by a very responsive technical support team.

Most importantly, Fresenius Medical Care needed a solution that can meet the regulatory compliance requirements that will enable the company to comply with 21 CFR Part 11 and EU GMP Annex 11 regulations, and the NetDimensions Learning software passed the validation successfully.

In April 2013, Fresenius Medical Care rolled out NetDimensions Learning to 30,000 employees in 24 countries in Europe, Middle East, Africa, and Latin America.

For more details, read NetDimensions' white paper: "The Role of the LMS in 21 CFR Part 11 Compliance". Download your copy from www.netdimensions.com today.

NetDimensions (AIM: NETD; OTCQX: NETDY) is a global provider of performance, knowledge, and learning management systems enabling companies, government agencies, and other organizations to personalize learning, share knowledge, enhance performance, foster collaboration, and manage compliance programs for employees, customers, partners, and suppliers.

NetDimensions is one of the few vendors in the industry whose Learning Management System has been validated to meet the compliance requirements for the FDA 21 CFR Part 11, 211, and 820, as well as EU GMP (including Annex 11) regulations.

NetDimensions Learning is an award-winning Learning Management System used in corporate training, compliance, and knowledge assessment solutions in highly regulated, high-consequence industries. NetDimensions Learning is qualified to address requirements from multiple global regulators, so client organizations can be confident about ensuring regulatory compliance in any global deployment.

NetDimensions Learning complies with 21 CFR Part 11 requirements via specific features for e-signatures, auditing, and reporting of electronic training records, and provides a secure environment for both on-premise and dedicated hosted deployments via NetDimensions' Secure SaaS offering.

NetDimensions' clients include Fresenius Medical Care, ING, Cathay Pacific, Behavioral Health Group, and Allied Electronics.

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Private Cloud:	The cloud infrastructure is provisioned for exclusive use by a single organization comprising multiple consumers (e.g., business units). It may be owned, managed, and operated by the organization, a third party, or some combination of them, and it may exist on or off premises.
Community Cloud:	The cloud infrastructure is provisioned for exclusive use by a specific community of consumers from organizations that have shared concerns (e.g., mission, security requirements, policy, and compliance considerations). It may be owned, managed, and operated by one or more of the organizations in the community, a third party, or some combination of them, and it may exist on or off premises.
Public Cloud:	The cloud infrastructure is provisioned for open use by the general public. It may be owned, managed, and operated by a business, academic, or government organization, or some combination of them. It exists on the premises of the cloud provider.
Hybrid Cloud:	The cloud infrastructure is a composition of two or more distinct cloud infrastructures (private, community, or public) that remain unique entities, but are bound together by standardized or proprietary technology that enables data and application portability (e.g., cloud bursting for load balancing between clouds.

Table C. NIST cloud computing deployment models.

ist to understand and real world examples of different cloud service models are perhaps more useful. These are provided in Figures 1, 2, and 3 for Infrastructure as a Service (IaaS), Platform as a Service (PaaS), and Software as a Service (SaaS) respectively.

It is important to note that with the exception of the public cloud model, all of these models can be provisioned either off-Premise or on-Premise.

Off-Premise

Services that are provisioned off-premise means that the service exists (the physical infrastructure is usually installed) on the premises of the cloud services provider. Therefore, this is usually on the premises of a third party organization, i.e., not the regulated company.

On-Premise

Services that are provisioned on-premise means that the service exists (the physical infrastructure is usually installed) on the premise of the consumer (the regulated company).

It is important that regulated companies have their own definition of what they consider to be on-premise. Even though a regulated company may have their own physically separate data center, this would usually be considered on-premise unless it was owned by the regulated company and operated by a third party. Key to considering whether such services are on-premise or off-premise is the question of who controls the service.

On-premise can be a very useful option because it can provide a balanced solution providing most of the business advantages of cloud computing, but also can mitigate many of the risks associated with some of essential characteristics and general outsourcing risks. This may not appear as cost effective as off-premise solutions because the opportunities for resource pooling are more limited. There also may be concerns about the lack of experience with cloud computing within an internal IT department. This needs to be balanced against the sometimes considerable costs of providing the necessary compliance training, support, and oversight to a third party cloud service provider who does not have experience in the pharmaceutical industry.

The ability to understand and leverage these different models is essential to assessing and mitigating the risk associated

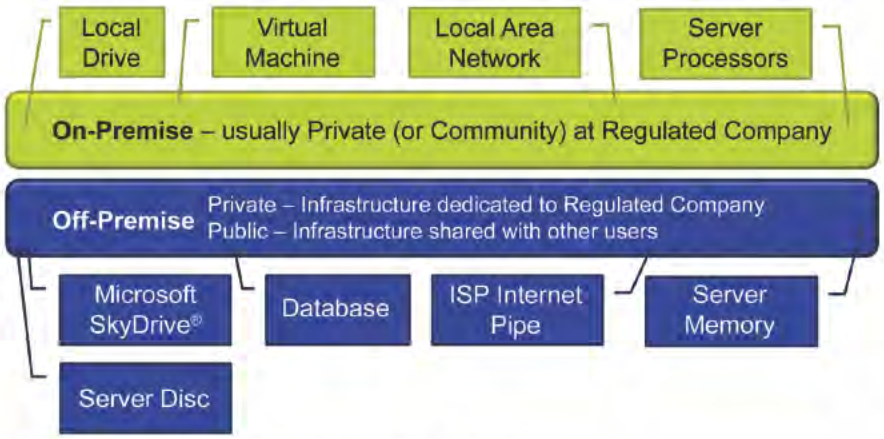

Figure 1. Examples of Infrastructure as a Service (IaaS).

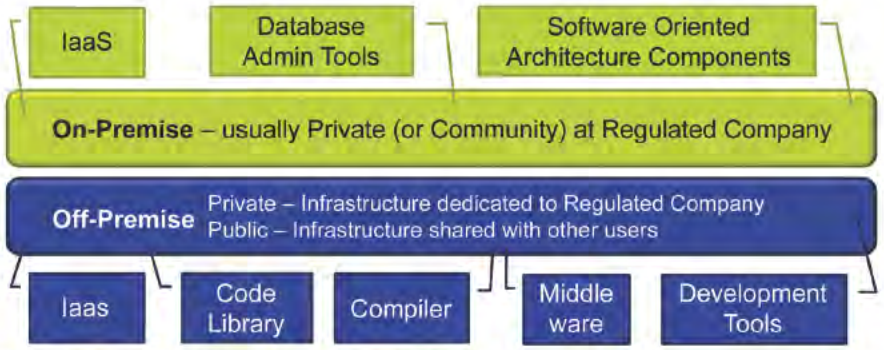

Figure 2. Examples of Platform as a Service (PaaS).

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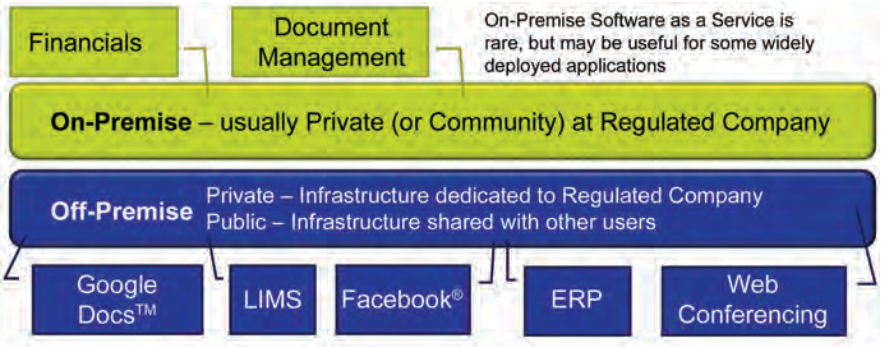

Figure 3. Examples of Software as a Service (SaaS).

with cloud computing. The decision to move to the cloud isn't an all-or-nothing, take- it-or-leave choice.

Different models may be utilized, depending upon the service required, the level of control applied by the provider (up to those who specialize in and fully meet pharmaceutical industry regulatory expectations) and the risk associated with the data or application that it is proposed to cloud.

For example, the business may like an application provisioned by a software company as a SaaS solution, but the QA department may not like the fact that the third party IaaS provider who hosts the application doesn't have appropriate controls around their IT quality management system, doesn't qualify their IT infrastructure, and does not allow the consumer (the regulated company) to review or approve critical change controls. That doesn't mean that the software solution or cloud computing needs to be dismissed out of hand. It may be possible to provision the software as a private cloud on-premise option using IaaS provisioned by the regulated companies own internal IT department, or running under a public cloud IaaS provisioned by a third party who does understand and meet the requirements of the pharmaceutical industry.

Table D provides some other "fall-back" scenarios which show how alternate cloud models could be considered and Figure 4 provides an outline process for selecting appropriate cloud models.

Initial Model and Problems	Alternative Models and Problems
Public cloud SaaS provider's application functionality does not meet regulatory requirements, e.g., inventory management rules.	• Seek an alternative SaaS solution • Ask the provider to deploy the same application as a private cloud single tenancy solution • Acquire a suitable application and deploy with a public cloud IaaS provider
Private cloud PaaS provider does not qualify their software development tools and utilities and has poor version control.	• Seek an alternative PaaS solution • Acquire equivalent software development tools and provision on your own IaaS cloud on-premise • Acquire equivalent software development tools and ask IaaS provider to deploy on public cloud IaaS
Public cloud IaaS provider does not qualify or control infrastructure.	• Ask the provider to deploy and qualify the same infrastructure on a qualified private cloud • Find an alternative IaaS provider • Provision and qualify your own IaaS cloud on-premise

Table D. Alternative, lower risk cloud models.

After this process has been undertaken a number of times, it will be understood that the decreasing level of control by the regulated company means that risks are greater for off-premise solutions, Software as a Service (SaaS), and for public clouds (as shown in Figure 5).

It also will be realized that platforms or applications with a defined relative risk are more suited to certain types of service and deployment models. Figure 5 shows a range of cloud models and relative risks. While, for instance, public cloud and off-premise models have higher risks (because of the reduced lack of control by the regulated company), these models generally have lower costs. A key part of developing any cloud strategy must therefore consider the conflict between lower costs and lower risk, both of which are strategic drivers for the pharmaceutical industry.

There are additional variations on these models such as where a cloud services provider will provision a pre-engineered, pre-qualified set of infrastructure (rack, power conditioning, air conditioning, servers, storage, virtualization, operating systems, and utilities), install it on a regulated company's site, and manage it remotely (so called "cloud anywhere" or "cloud-in-a-box"). Although these do not fit neatly within the NIST definitions, it is possible to understand the advantages and risks of such a solution when the standard models are understood.

Developing a Cloud Strategy

Based upon the above, it is recommended that pharmaceutical companies (and regulated companies in other life sciences sectors) develop a comprehensive and credible cloud strategy that isn't solely driven by the need to reduce IT costs.

Regulatory agencies are, of course, interested in cloud (e.g., the US FDA has a strategic goal to enable cloud computing by 2013[6]) and understand that there are associated risks. However, discussions with the FDA indicate that there are relatively few concerns as long as these technical and supplier risks are understood, assessed, and mitigated.

While cost reduction must, of course, be part of the strategy, it is also important to understand the overall costs associated with cloud, including the cost of IS compliance. As many pharmaceutical

companies discovered when first moving to an IT outsourcing model, costs savings were nowhere near what was initially promised by suppliers. In most cases, this is because purchasing and finance selected suppliers with little or no knowledge of the regulatory requirements of operating in the sector and massively underestimated the costs of providing on-going IS compliance training, guidance, support and oversight. In many cases, this was made worse by a failure to appropriately audit suppliers prior to placing contracts.

Experience developing cloud strategies within the pharmaceutical industry shows that the following factors all need to be considered as part of the strategy:

- The need to develop a vision for the future state of the IT landscape – is the objective to move everything to the cloud (probably not possible for most pharmaceutical companies), most things to the cloud (possible if different cloud models are leveraged, including on-premise) or only low risk data and applications to the cloud (possible, but misses cost saving opportunities)?
- Based upon the above, the decision as to whether or not on-premise clouding is required, and planning to provide appropriate training, education, and investment in necessary technology. Note that in many cases existing knowledge of virtualization can be leveraged and will already be providing resource pooling, but to successfully provision cloud services, internal processes will need to be changed to provide on-demand self-service and measured service levels by way of an internal Operational Level Agreement (OLA).

... it is recommended that pharmaceutical companies (and regulated companies in other life sciences sectors) develop a comprehensive and credible cloud strategy that isn't solely driven by the need to reduce IT costs.

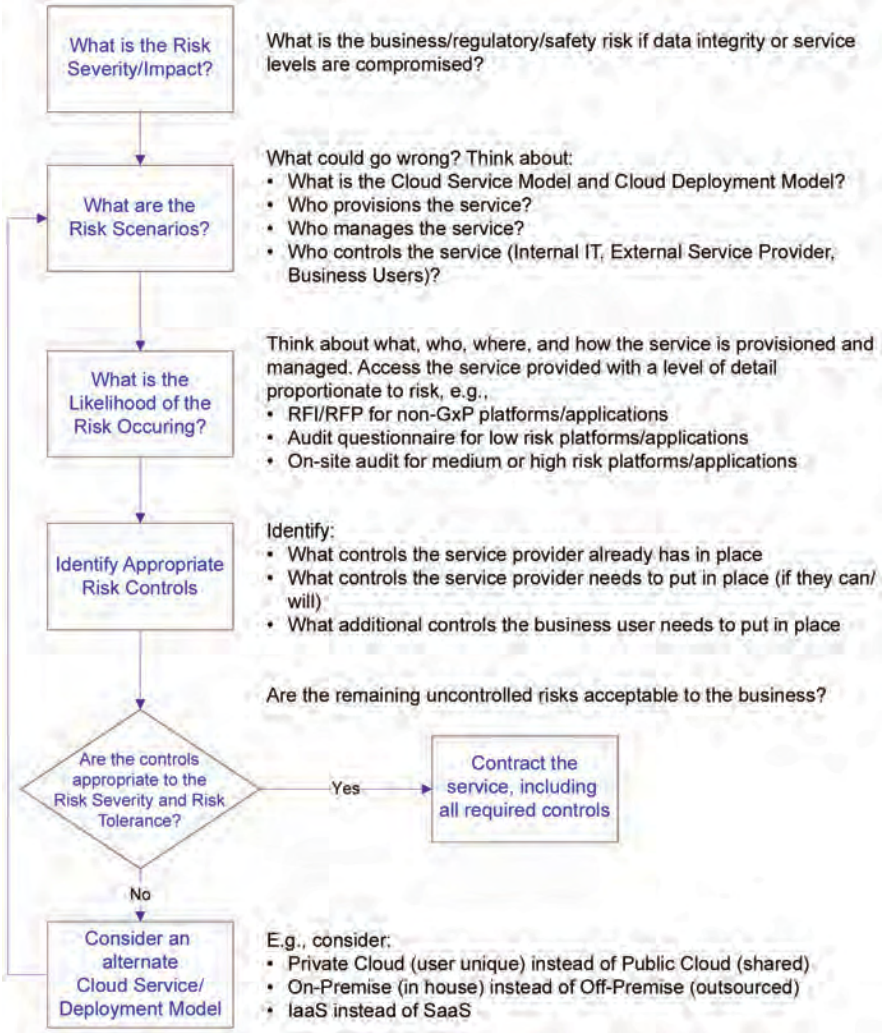

Figure 4. Process for selecting acceptable risk cloud models.

- The need to assess data and applications for relative risk, and to determine appropriate cloud models for different categories of risk.
- A process for selecting appropriate cloud models, applicable to different platform and applications risk categories.
- The need to train stakeholders with respect to what cloud computing is (and isn't) and the additional risks inherent within different cloud computing models.
- Processes for acquiring cloud services which do not add unnecessarily to the on-demand nature of cloud computing, but which also involves all business, IT, purchasing, and QA stakeholders.
- Providing appropriate trained, educated, or experienced resources to audit cloud providers, both in terms of initial pre-contract supplier audits and on-going supplier audits. Experience shows that asking the right questions prior to signing a contract is essential and any investment in auditing resources provides substantial cost saving and return on investment in terms of subsequent, unplanned cost avoidance.
- Processes for declouding (moving IT assets back out of the cloud), including legal and contractual processes, data recovery and/or data migration processes and triggering the acquisition of alternate cloud (or non-clouded) services.

Developing such a strategy should involve all stakeholder groups and should be led by someone with knowledge of both cloud services and the regulatory and business requirements of the pharmaceutical industry.

Implementing such a strategy may require considerable changes to the IT quality management system and governance processes. Given that there are multiple cloud models that need to be accommodated, it is essential that any updates to policies and procedures are non-prescriptive. Whether implementing clouded or non-clouded outsourcing, policies and procedures should also be written in such a way to recognize that while the regulated company retains accountability for regulatory compliance (using appropriately qualified IT infrastructure and validated applications), day-to-day responsibility and control may be in the hands of a third party. Therefore, it is essential to have a process in place to ensure that the processes of the regulated company and their service providers are

Figure 5. Less control by the regulated company increases risk likelihood.

aligned, e.g., change control processes, service desk, problem management, and incident management processes.

Clouding Individual Platforms and Applications

The reality is that the business drivers which make cloud computing so attractive mean that many pharmaceutical companies have gone into the cloud before developing an appropriate strategy. In some cases, this has worked well and in others there have been issues which take time and resources to resolve.

Ideally, regulated companies will have a cloud strategy in place before deciding to leverage cloud computing. This will allow them to better address the risks associated with cloud computing and to hopefully strike better deals and set up more useful partnerships with cloud service providers.

Where this is the case, it is then possible to select the appropriate cloud

Figure 6. Different risk platforms and applications with acceptable cloud models.

service model to select the most appropriate supplier and to manage any remaining risks proactively and successfully.

The current state-of-the-market is such that there are a variety of suppliers to choose from including:

- Infrastructure as a Service (Iaas) providers who specialize in the life sciences industry. Although relatively small in number, these providers deliver all of the advantages of cloud computing, appropriately qualify their IT infrastructure, operate suitable IT quality management systems, and train their staff in GxP awareness. While the headline cost of such providers is higher than that of larger non-specialists, their costs are competitive when the need for less IT compliance training, support, and oversight is included in the equation.
- Platform as a Service (PaaS) providers who provision well controlled platforms capable of supporting the development of high quality and validatable software. It is important that development tools, utilities, and libraries are able to support key process such as requirements management and traceability, configuration management, and change control and testing, and ideally PaaS should be qualified. This is available with a number of PaaS solutions and can be leveraged by regulated companies looking to develop their own applications or by suppliers of software to the industry.
- Software as a Service (SaaS) providers who provision software that delivers regulatory compliant functionality and solutions that are relatively easy for consumers (regulated companies) to validate. The majority of these suppliers are companies developing software for use primarily in the pharmaceutical industry and who understand the regulatory compliance requirements. Most of these are developing applications which require a limited range of functionality and many are currently focusing in areas such as research and development or quality processes, e.g., generic laboratory management systems, statistical and analytical applications, Corrective and Preventative Action (CAPA) processes or document management.

Essential Characteristic	NIST SP800-145 Definition	Pharmaceutical Industry Considerations
On-Demand Self-Service:	A consumer can unilaterally provision computing capabilities, such as server time and network storage, as needed automatically without requiring human interaction with each service provider.	On-demand self-service can bypass appropriate business and regulatory change controls. Changes in service provision require appropriate authorization, focusing on user specific access rights and corresponding permissions on GxP applications and data.
Broad Network Access:	Capabilities are available over the network and accessed through standard mechanisms that promote use by heterogeneous thin or thick client platforms (e.g., mobile phones, tablets, laptops, and work stations).	In all cloud models, security risks associated with third party networks and mobile computing platforms need to be assessed and mitigated through a combination of technical and procedural controls.
Resource Pooling:	The provider's computing resources are pooled to serve a multi-tenant model with different physical and virtual resources dynamically assigned and reassigned according to consumer demand. There is a sense of location dependence in that the customer generally has no control or knowledge over the exact location of the provided resources, but may be able to specify location at a higher level of abstraction (e.g., country, state, or datacenter). Examples of resources include storage, processing, memory, and network bandwidth.	The greatest cost benefits of resource pooling are achieved through the use of public cloud, but this model possesses the highest risks. In-house, private cloud resource pooling is possible but the benefits may be limited in smaller organizations. The optimum model appears to be community cloud resource pooling with other pharmaceutical companies with similar compliance requirements.
Rapid Elasticity:	Capabilities can be elastically provisioned and released, in some cases, automatically, to scale rapidly outward and inward commensurate with demand. To the consumer, the capabilities available for provisioning often appear to be unlimited and can be appropriated in any quantity at any time.	Rapid elasticity can tend to erode the level of control applied. A pragmatic balance needs to be found between change control processes and elasticity. Key changes need to be authorized, and then quickly implemented in order to support the business.
Measured Service:	Cloud systems automatically control and optimize resource use by leveraging a metering capability; at some level of abstraction appropriate to the type of service (e.g., storage, processing, bandwidth, and active user accounts). Resource usage can be monitored, controlled, and reported, providing transparency for both the provider and consumer of the utilized service.	Defining, measuring/monitoring and reporting on service levels is generally good for compliance control and allows regulated companies to better exercise their regulatory accountability.

Table E. NIST definition of cloud essential characteristics and the implications for the pharmaceutical industry.

SaaS has specific risks that need to be considered including:

- The security of the multi-tenanted software (shared by multiple users) at both the application and database level (some existing applications were not originally designed for the cloud and implement a relatively weak security model).
- The ability to make copies of records in both human and machine readable format, in accordance with the requirements of 21 CFR Part 11.[7]
- The ability of the regulated company to archive data if and when required.
- The ability to restore just the regulated company's data in the case of an error or incident.

These risks specifically need to be addressed as part of the risk assessment and supplier assessment.

Experience with SaaS to-date is that there are relatively few compliant SaaS solutions for applications that are not solely focused on the pharmaceutical industry, e.g., Enterprise Resource Planning (ERP), CRM, etc. This is because the pharmaceutical industry is a minority market for such generic applications and the providers are unwilling to invest in addressing the necessary regulatory requirements for a minority of their clients. However, even when this is the case, such applications can still leverage cloud computing by leveraging private cloud IaaS, either on-premise or off-premise.

Before committing to any cloud services contract, it is essential to audit cloud service providers. A simple assessment, such as a written assessment questionnaire, is unlikely to provide evidence that all key issues are addressed and it is important to meet with the providers to gain a very clear understanding of what they do, how they do, and to look for evidence that they do what they say. Where a cloud service provider is in turn using another third party (e.g., a SaaS provider uses another party to provision IaaS on which their application runs) then it is important to understand how they have selected and assessed such arm's length suppliers.

Cloud Monitoring and Management

Once a cloud service is provisioned, it is important that the service is monitored by the regulated company, risk-based surveillance audits are carried out, and that on-going quality and compliance oversight is put in place. Time also should be allowed to manage the service, including any internal IT costs, such as acting as a first level service desk for the service users.

The costs of this should be based on what is required to mitigate the risks associated with the specific cloud service model, the risk of the clouded data or application, and the risks associated with the specific provider.

These costs should, of course, be estimated before contracts are placed and added to the service cost quoted by the provider to provide the true cost of service.

Don't Forget De-Clouding

As mentioned above with respect to cloud strategy, it is also important to think about de-clouding when setting up the contract. This may be a planned exit at the end of a contract term or an unplanned exit due to contractual default. Although not all unique to cloud computing, key questions to ask include:

- What are the contractual penalties?
- What support will be provided by the cloud service provider once they realize they are losing the business? Can penalties, bonuses, or other forms or payment retention be put in place to incentivize a professional: end to the service?
- How can you make sure that your data is handed over and that a copy of the data is not retained by the cloud service provider (relatively easy for IaaS where you manage the applications and database, but less so with SaaS)?

Conclusion

Based upon the above discussions, it is possible to consider the essential characteristics of cloud computing in the specific context of the pharmaceutical industry. While this may need to consider some of the risks of outsourcing, as we have seen, cloud computing need not be based solely on an outsourcing model and not all of these risks may need to be considered.

Based upon the state of the market and the pace at which it is developing, it is clear that pharmaceutical companies are at a cost disadvantage if they do not leverage cloud computing.

While there are still some unacceptable risks associated with cloud computing (mainly of them associated with outsourcing) it is possible to mitigate these by:

- Choosing not to move IT assets onto a cloud architecture
- Looking at alternative cloud models, such as private cloud or community cloud instead of public cloud, on-premise rather than off-premise, and IaaS instead of PaaS
- Requiring additional controls to be established by cloud service providers (where possible)
- Putting additional IS compliance training, guidance, support, and oversight in place

For most pharmaceutical companies, there will be no single cloud solution. For most, there will be a necessary mix of non-clouded platforms and applications and different cloud models. Over the coming years, more SaaS solutions will become available and we will see more medium and high risk GxP applications being clouded as private cloud SaaS solutions.

In the interim, private cloud and IaaS provide good alternatives, which will allow the benefits of cloud to be realized without unacceptable risk. For large pharmaceutical companies, this will mean investing in and developing their own on-premise IaaS private cloud. For small-medium pharmaceutical companies, public cloud IaaS from industry specialized cloud service providers or community cloud will offer a cost effective way to leverage the advantages of cloud without the need for up-front investment in IT infrastructure.

With standard definitions, models and terminology, the risks of cloud can now be understood, assessed, and in most cases mitigated. For those pharmaceutical companies who have not looked seriously at cloud computing, now is the time to develop a sensible strategy and take advantage of one of the most significant advances in the computing industry for decades.

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About the Author

David Stokes has more than 25 years of experience in the field of computer system validation and information systems compliance. He is an active member of the GAMP® Community of Practice and has contributed to the GAMP® Guide and several GAMP® Good Practice Guides, including developing content on the testing of cloud computing, in the second edition of the ISPE GAMP® Testing Good Practice Guide. He is also an active member of the IT Infrastructure group currently reviewing the IT Infrastructure GAMP® Good Practice Guide, including looking at cloud computing, and has presented on the topic of cloud computing at several GAMP® conferences. Stokes is currently Global Lead, Life Sciences for Percipient Consulting Ltd, a specialist consultancy and systems integrator providing consulting services and IT solutions to the Life Sciences industries. He can be contacted by telephone: +44 (0)1606 871332 or by email: david.stokes@percipient.co.uk.

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Has MES Reached Maturity in the Pharmaceutical Industry?

by Desmond Savage

This article presents the findings of a study that demonstrates MES is being adopted by the pharmaceutical industry.

Compliance, process optimization, increasing profit, improving the supply chain, and aligning to corporate standards are driving investment of Information Technology (IT) in the pharmaceutical industry. According to a report in October 2010 by Gartner Group, there is a need for integrated IT manufacturing technologies, reflected in the fact that corporate IT budgets have increased for manufacturing operations from 3 percent in 2001 to 19 percent in 2007.[1] The pharmaceutical industry has adopted this strategic initiative of integrating manufacturing IT and is benefiting through improved quality and production efficiencies.

Trend of IT in Manufacturing

IT can play a role at all levels of manufacturing operations; however, it is becoming increasingly evident within Manufacturing Operations Management (MOM) level. Advancements in technology, such as Service Oriented Architecture (SOA) frameworks, has enabled IT in manufacturing to shift from being data centric to process centric; therefore, IT is becoming seamless within manufacturing operations. By not restricting technology at the MOM level, activities such as Electronic Batch Records (EBR), real-time reporting, Enterprise Resource Planning (ERP), and equipment integration all have allowed pharmaceutical companies to maximize return on IT investment, improve quality, provide a platform for continuous improvement, and ultimately increase profits.

MES in the Pharmaceutical Industry

Manufacturing Execution Systems (MES) aggregates a number of the technologies deployed at the MOM level. MES as a technology has been successfully deployed within the pharmaceutical industry since the Food and Drug Administration (FDA) decreed the final 21 Part 11 regulations on 21 March 1997. These provided criteria for acceptance by the FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. Since 1997, pharmaceutical manufacturing companies have invested in MES. Combining this on-going investment with advancements in IT, MES has become a best practice technology within the pharmaceutical industry. This is demonstrated by new pharmaceutical manufacturing facilities being fully MES enabled, that is, paperless manufacturing from day one.

The amount of IT applied to an MES project is dependent on the customer's business needs. At a minimum, an MES should strive to replace paper batch records with an EBR. Other functionality that can be applied include automated material weigh and dispense and integration to ERP systems; therefore, helping the optimization of inventory levels and production planning. MES also can be integrated at the factory level, potentially giving complete control over the entire enterprise. This level of control helps ensure "right-first-time" manufacturing and total enterprise visibility. The MES acts as a central system with effective interoperations with other manufacturing systems and departments such as operations, quality, maintenance, and inventory control. The key to a successful MES implementation is applying the right level of IT to maximize Return on Investment (ROI).

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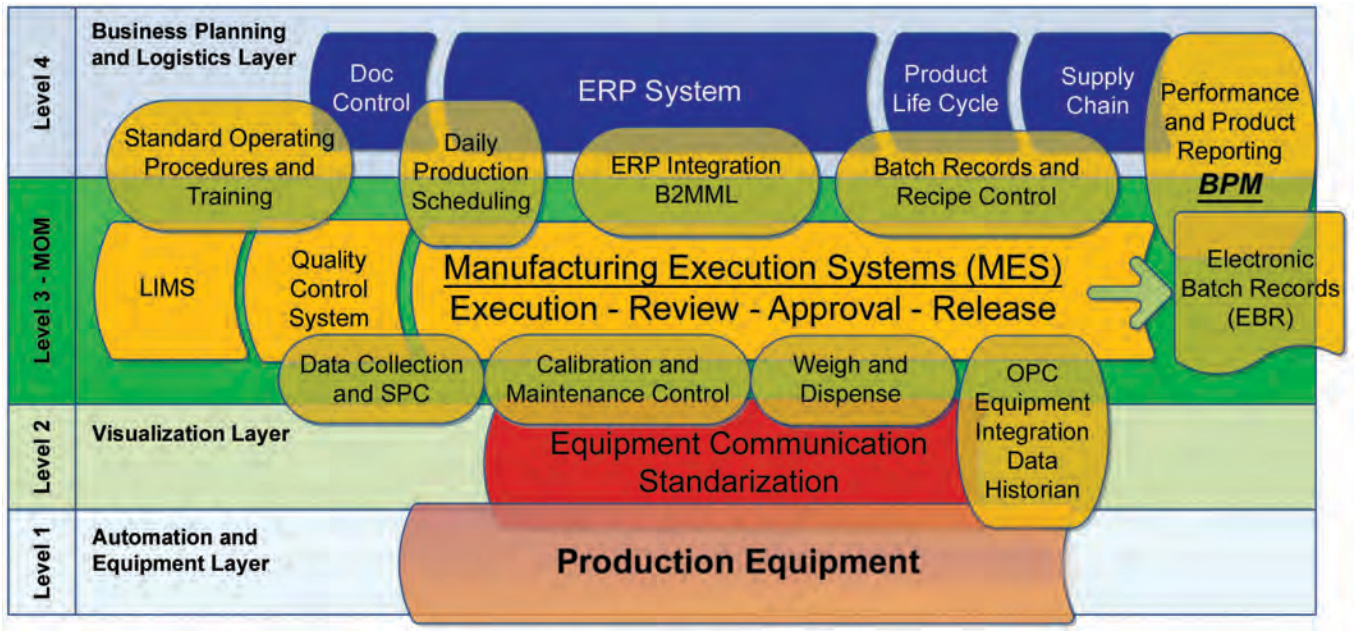

Figure 1. MES in Accordance with the ISA95 Model.

Shown in Figure 1 is a representation of MES within a typical pharmaceutical manufacturing operation.

Figure 1 is a representation of where MES would reside in a typical pharmaceutical facility in accordance with the ISA S95 standard.[2] The ISA S95 standard defines a model for manufacturing operations, including the reporting and analysis functions that are critical to effective manufacturing. The business planning and logistics (Level 4) functions are supported by ERP, Product Lifecycle Management (PLM), or Supply Chain Management (SMC) applications. The plant floor systems (Levels 2 and 3) are made up of Laboratory Information Management Systems (LIMS), OPC data integration tools, data historians, Statistical Process Control (SPC), MES, control systems, and database tools.

Has the Pharmaceutical Industry Adopted MES?

In preparation for this article, a survey was conducted by the author to establish the level of electronic MES deployment within the pharmaceutical industry. The survey was conducted between January and February 2013. More than 400 senior managers and system analysts from across the globe working in pharmaceutical companies were contacted. In total, 84 responses were documented, of which 47 percent of respondents stated that electronic MES has already been deployed in specific manufacturing facilities.

A further analysis was conducted of those facilities that had deployed MES in relation to stored batch records. Only 31 percent of companies had deployed full paperless solutions with the majority deploying a combination of paper and electronic batch records - *Figure 2*.

So what do the regulatory agencies think of MES? As far back as 2004, reports were published highlighting the compliance benefits of MES in the life science industry. In an article titled "MES Reduces FDA Compliance Costs,"[3] *Quality Magazine* discusses:

> *"The underlying premise of today's interpretation of the regulations is to ensure quality or risk management and risk mitigation by defining a management methodology for designing quality into the manufacturing process instead of attempting to build quality into products through inspection. The goal of manufacturers and the FDA is to provide and deliver safe and effective products.*
>
> *However, FDA compliance historically has been an expensive, albeit necessary, proposition. As the life science industry becomes more competitive, reducing the*

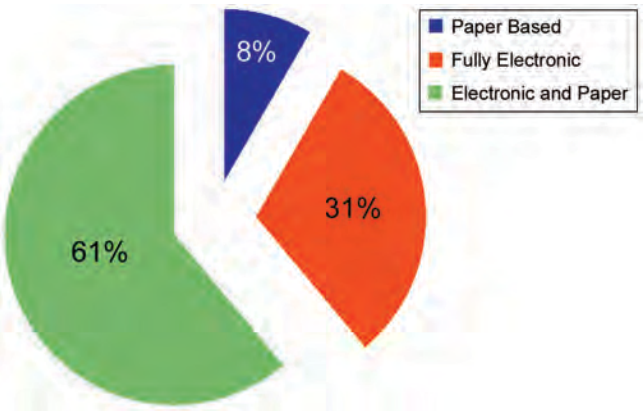

Figure 2. Batch Record Method with MES in the pharmaceutical industry.

cost of compliance is as important to success as controlling costs, quality and time-to-market. A Manufacturing Execution System (MES) helps bridge the gap between regulatory control, operational control and case management."

Since 2004, the FDA has audited pharmaceutical facilities with MES in place. It has been the experience of the author that these systems are welcomed by the FDA and there have been no citations against compliant MES implementations.

Examining the Principle Drivers for Adopting MES in the Pharmaceutical Industry

A GAMP® Guide to MES[4] states that the benefits for recipe-driven operations such as pharmaceutical production processes include:

- Improved scheduling and resource utilization
- Improved manufacturing flexibility and process changeover
- Reduced Work in Progress (WIP) and improved material tracking
- Shorter production cycles
- Enforced sequence of operations
- Reduced production record errors, electronic or hybrid
- Improved visibility, accuracy and consistency of manufacturing data, enhancing decision support, Process Analytical Technology (PAT), and investigations capabilities
- Minimized product recalls
- Increased plant reliability
- Realize paperless manufacturing
- Automated Key Performance Indicator (KPI) generation and reporting, such as an Overall Equipment Efficiency (OEE) calculation
- Support knowledge management and PAT
- Reduce Quality Unit resources required for day to day operations by providing functionality, such as Electronic Production Records (EPR) and Review By Exception (RBE)

As part of the survey conducted in preparation for this article, the respondents who had MES installed were asked to choose the primary and secondary drivers for implementing electronic MES solutions from the following five categories:

1. Quality
2. Production
3. Inventory
4. Financial
5. Corporate

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Serialization? Necessity or opportunity?

Enterprise System Partners Serialization Director, Liam O'Riordan, explains the impact of executing serialization in life science packaging facilities and why it's an opportunity rather than a regulatory necessity.

Serialization in Life Science: "A Business Perspective"

At ESP, we believe that manufacturers need to approach their design strategy from a business and not a technical perspective and see serialization as an opportunity rather than a regulatory necessity.

Serialization is the name given to the process whereby a known and unique serial number is issued to a unit of sale providing the ability to verify the authenticity of the unit's unique serial number at any point in the supply chain.

... in 2010, counterfeit medicines accounted for 8.76% of the $856billion global market.

In 2010, The Centre for Medicines in the Public Interest in the United States predicted that counterfeit drug sales would reach $75 billion globally in 2010, an increase of more than 90 per cent from 2005 based on estimates from WHO. Based on findings from the IMS Institute for Healthcare Informatics, the world pharmaceutical market was worth over $856 billion in 2010, meaning counterfeit medicines accounted for 8.76% of the global market.

A more liberalized world economy, extensive opening of borders, the internet, the cost and complexity of the manufacturing and distribution processes, all conspire to increase the risk of counterfeit medication entering the supply chain.

Serialization aids in closing many of the gaps associated with traditional pharmaceutical production and distribution that leave manufacturers susceptible to product falsification.

The principal types of serialization are:
- End to End
- Aggregation
- ePedigree

Key Business Drivers to serialization:
- Patent Safety
- Business Continuity
- Brand Protection
- Supply Chain Management

While it may seem like a straightforward exercise to issue a barcode to a label, there are complex factors that need to be addressed in the process. Often the label must be redesigned to accommodate the barcode and regulators must approve the new label. The packaging line must be revalidated as equipment is added to generate each barcode, link each barcode to product data, apply the barcode to packages and track that barcode throughout the supply chain. That data must be managed, transforming it from data to actionable information.

Significant IT upgrades are also required in order to support this data management.

Employees must be trained to use the new equipment and sometimes the product packaging itself needs to change.

ESP assist their global clients in implementing serialization by developing a multi-operational strategy. Implementation strategies should include:

- Strategic assessment of markets and products
- Review of regulatory environment in all markets
- Propose technical solutions
- Analysis and recommendations
- Program approval

Pharmaceutical manufacturers also need to consider the following factors when designing their global serialization plan:

- Stakeholder buy-in
- Global multi-functional team
- Advance planning
- Anticipate risks
- Vendor management
- Run pilot

In summary, serialization should not be seen as purely a regulatory requirement but should be approached from a business perspective where commercial benefits can be realized through increased product security.

While it may seem like a straightforward exercise to issue a barcode to a label, there are complex factors that need to be addressed in this process.

Why ESP?

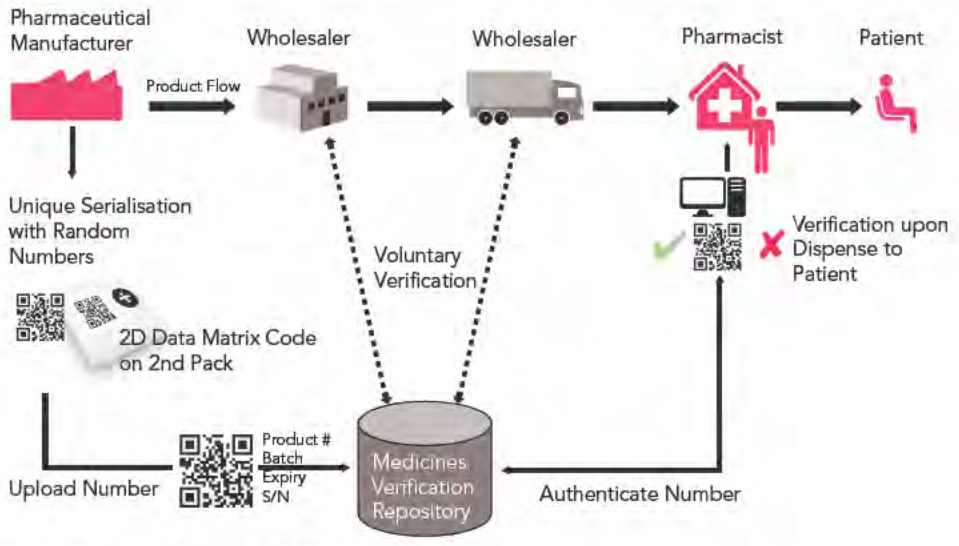
Enterprise System Partners (ESP) is a leading global consulting and program management company - supporting system implementations for the life science industry since 2003.

ESP offer specialist support and consulting services, exclusively for manufacturing operations in biotechnology, pharmaceutical and medical devices, with core focus on Manufacturing Executions Systems (MES) and Serialization.

Their specialist consultants and engineers have the expertise to deliver support for the concept, planning, vendor selection, design and implementation of systems for the entire manufacturing landscape from process automation to the enterprise layer. ESP have offices in Cork (Ireland), Boston and San Francisco allowing them to support projects with local resources worldwide.

They have led the management of global and plant level deployments through full project life cycles including:

- Strategic planning
- Program planning and budgeting
- Requirements, design, rollout and qualification
- Team assembly and management
- Vendor selection and management
- Project management and reporting
- User training and go-live support
- Managed services
- System migrations and upgrades.



Source: EFPIA European Medicines Verification System 11 Mar 2013

“50% of pharmaceutical companies have active serialization programs”

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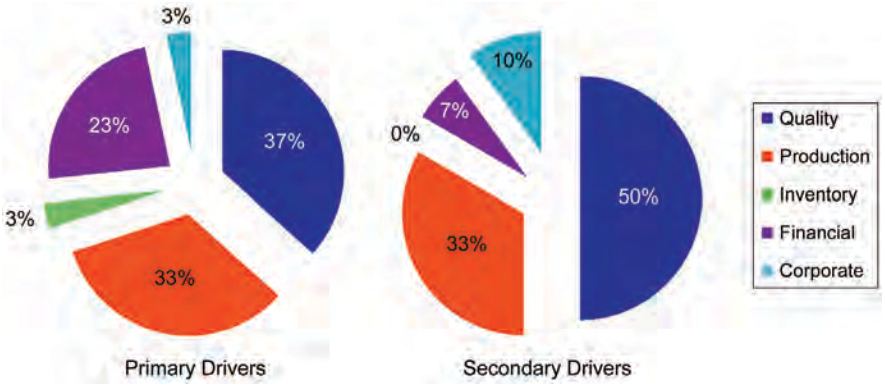

Figure 3. Primary and secondary drivers for MES in the pharmaceutical industry.

The results of the survey can be seen in Figure 3.

Primary and Secondary Drivers for MES in the Pharmaceutical Industry

From studying these results, it is evident that improving quality and production are the primary drivers for implementing electronic MES as they account for almost 80 percent of the combined drivers. The benefits to MES can be quantitative and qualitative. Quantitative benefits can be measured for financial outcomes such as calculating an ROI, whereas qualitative benefits are more subjective, but no less important. When selling an MES internally, the importance of qualitative benefits should not be ignored, as inevitably measuring MES on quantitative benefits alone is a very hard sell.

Quantitative Benefits/Tangible Cost Saving to MES

Reduced Cost of Quality: the number of deviations associated with paper batch records is an example of the cost of quality. It is the direct experience of the author that with the implementation of MES, recorded deviations can be reduced by more than 50 percent. With paper based systems, companies can maintain high levels of quality; however, there is a high cost associated with ensuring this quality level. An MES reduces the cost of quality but also ensures there is no drop in quality level.

Cost of Storing Batch Records (Quality): companies have on-going costs associated with the storing and retrieval of paper batch records. With the introduction of an MES, major cost reductions can be achieved. (However, existing records still need to be held in accordance with regulations applied by the relevant agency.)

Improved Batch Release Time (Production): review by exception can be achieved with a mature MES. EBRs typically require review and release by the operations and quality departments; however, this is significantly less than a paper review process. In some cases, pharmaceutical manufacturers have implemented review-by-exception with MES.

Production Capacity Increase: with an MES in place, companies can expect to improve the capacity of their manufacturing plant by maximizing MES lean initiatives. This enables companies to take up any future or short-term demand without hiring extra resources or overtime.

Better Financial Costing: MES can help enable companies implement multi-level Bill of Materials (BOMs) with increased visibility on the manufacturing floor. Also, MES will lead to improved routing of material and better analysis of variance. It will enable setting up new cost centres and provide all-in-all improved standard costing through the manufacturing process.

Inventory Reductions: companies with little visibility into the manufacturing floor maintain a high level of inventory. MES solutions create near real-time reports using quality-approved data, therefore allowing companies significant scope to reduce inventory levels.

Inventory Management: an MES improves warehouse efficiencies through stock movements and transactions being real time, paperless cycle counting and benefits associated with a paperless warehouse. This means there is a reduction in warehouse activities and a reduced effort for the quality department of incoming inspection labelling.

Qualitative Benefits/Intangible Cost Savings to MES

Enforced Compliance (Quality): MES provides enforced compliance in many aspects of manufacturing including enforced sequence of activities, equipment usability verification prior to use, material status checking prior to use, user group membership prior to performing system functions, and many more.

Cost of Audit Preparation (Quality): MES helps close open deviations by putting in place rigid corrective actions such as enforced in-process inspections. This compares to a paper system that will rely on procedural updates and training, which are not as effective as an enforced quality check. During audits, MES is more efficient at retrieving information, which means shorter and better audits.

Electronic Equipment Management (Production): MES enables the efficient creation and automatic maintenance of electronic logbooks. Comprehensive status moni-

toring effectively prevents the use of wrong equipment. These equipment states might include planned or unplanned maintenance, cleaning, and calibration. Business rules can be applied to manage the status of the equipment. MES can ensure that work in progress is not processed through a particular machine when flagged for being out of compliance.

Multiple Batch/Shift Production: one of the biggest benefits from MES is product changeover and new product Master Batch Record (MBR) creation or updates. The more products handled in production or packaging, the less effective paper-based systems become.

Transparent Process Data Evaluation (Corporate): MES stores data in a relational format that is available for integration and analysis with other manufacturing intelligence information systems.

Business Process Standardization (Corporate): an MES program can be used as a mechanism to define and implement common business processes as well as lean manufacturing processes.

Untapped Capital (Financial): MES accelerates the manufacturing learning curve across all facets of the organization because an MES implementation requires complete involvement and transparency of roles between different departments. This interaction between departments will unleash actionable intelligence, that is, employees adding valuable input into other functional areas. Employees can be empowered with new more value-added roles now that the control of the manufacturing process is automated.

Support the Extended Supply Chain Strategy (Inventory): MES solutions typically integrate with ERP systems. MES helps refine ERP scheduling functions to the day or even hour, whereas the ERP focuses on months or weeks. This extra level of planning helps ensure that order times are minimized and there is increased visibility into the manufacturing floor.

Corporate Business Process Management (BPM): BPM is the activity of managing your whole process, from dock to stock as well as supporting functions. As part of a demand-driven manufacturing process, increasing efficiency is critical. Real-time information from the manufacturing process is needed to prevent problems, drive quality, and enable the flexibility your customers require. MES enables this reach into the manufacturing process and is seen as a key requirement for successful BPM.

Challenges Associated with an MES Implementation

An MES project within the pharmaceutical industry is

treated as an enterprise software solution, similar to ERP projects. However, the major difference between MES and ERP projects is that MES should be led by operations whereas ERP projects are typically IT led. MES touches every aspect of the manufacturing floor and can become very complex. For this reason, companies have concentrated on ERP and automation projects as they do not have as many dependencies. MES is often the final hurdle to complete data integration across the ISA S95 model.

Implementing a complete MES solution into an existing pharmaceutical manufacturing facility could take in excess of four years. In year one, the strategy applied could be to expand the functionality of the ERP layer with improved material tracking on the production floor and warehouse. Lean initiatives can be implemented to ensure that the manufacturing and business processes are "MES ready." Into year two, focus might shift to investing into the visualization layer of automation, such as investments into Distributed Control Systems (DCS), and Data Historian technologies. The strategy might also involve investing into an automatic weight and dispense solution, either provided by an ERP or MES vendor; therefore, improving the control of raw materials on the production floor. On to year three and the company is now "MES ready." An MES solution can be deployed with the purpose of replacing a paper batch record with an EBR. Finally in year four, the focus will shift to fully integrating the MES solution into the automation and ERP layers.

MES teams typically consist of a steering committee or group with sub-groups concentrating on production, quality, validation, IT, change management, inventory, training, and maintenance requirements. Group sizes can be from six to more than 20 directly involved in the MES project. Factoring in the human resources required, time scale, software licenses, hardware costs, initial negative impact of change on production, a budget of four to six million US dollars is not unusual for an MES project deployed in a small to medium sized pharmaceutical operation, that is 200 to 500 employees.

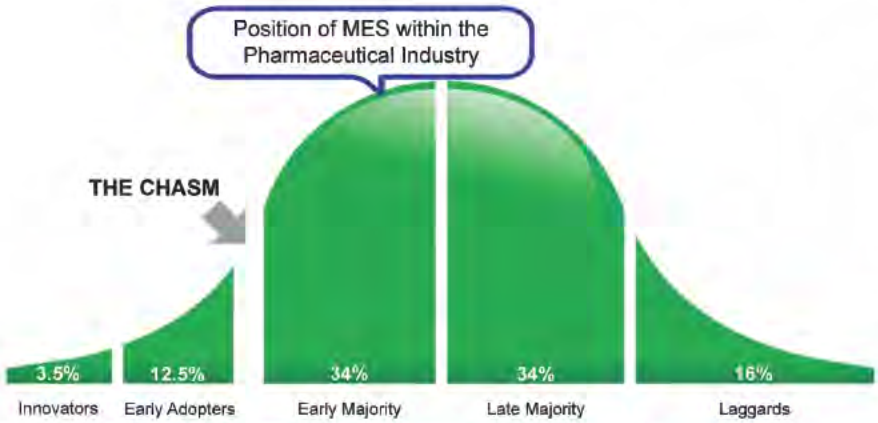

Figure 4. Crossing the Chasm of MES in the pharmaceutical industry.

MES solutions are being successfully deployed in the pharmaceutical industry; however, deciding to implement an MES solution is not a decision to be taken lightly. Careful planning and education into what MES is, is key. Organizations such as the Manufacturing Enterprise Solutions Association (MESA)[5] have been established to promote best practices and education in MES. With proper planning and education, a business case for an MES solution can be established.

The Technology Adoption Cycle and MES in the Pharmaceutical Industry

Geoffrey A. Moore in his book, "Crossing the Chasm,"[6] discusses a concept of technology adoption. Moore breaks technology adoption into five phases. Cracks exist between the phases and some technologies that fail to clear these cracks fade away. Examples of such technologies that were not fully adopted or did not reach maturity include Windows ME, the PalmPilot, and social networking site Bebo. Moore[6] goes onto discuss "the notion that part of what defines a high-tech market is the tendency of its members to reference each other when making buying decisions is absolutely key to successful high-tech marketing." The critical point identified by Moore where technologies either get adopted or fail is the chasm, the crack that exists between the "Early Adopters" and "Early Majority" phases.

So has MES in the pharmaceutical industry crossed the chasm? Based on the research conducted in conjunction with this article, yes it has. It is firmly placed in the "Early Majority" phase as demonstrated in Figure 4.

People who are deemed to be in the "Early Majority" phase are pragmatists. Moore[6] says the Early Majority "care about the company they are buying from, the quality of the product they are buying, the infrastructure of supporting products and system interfaces, and the reliability of the service they are going to get..." All these factors are very important considerations when selecting a technology in the pharmaceutical industry. There are thousands of MES products available. MES is being deployed in the pharmaceutical industry and there is an array of proven solutions available.

The S-Curve and ERP in the Pharmaceutical Industry

Another methodology used to describe technology adoption is the S-Curve. The S-Curve describes technological evolution and suggests that technologies evolve through an initial period of slow growth, followed by one of fast growth culminating in a plateau. It also breaks the take up of technologies into different phases; however, it differs from Moore's[6] model in that it accounts for shifts in technology

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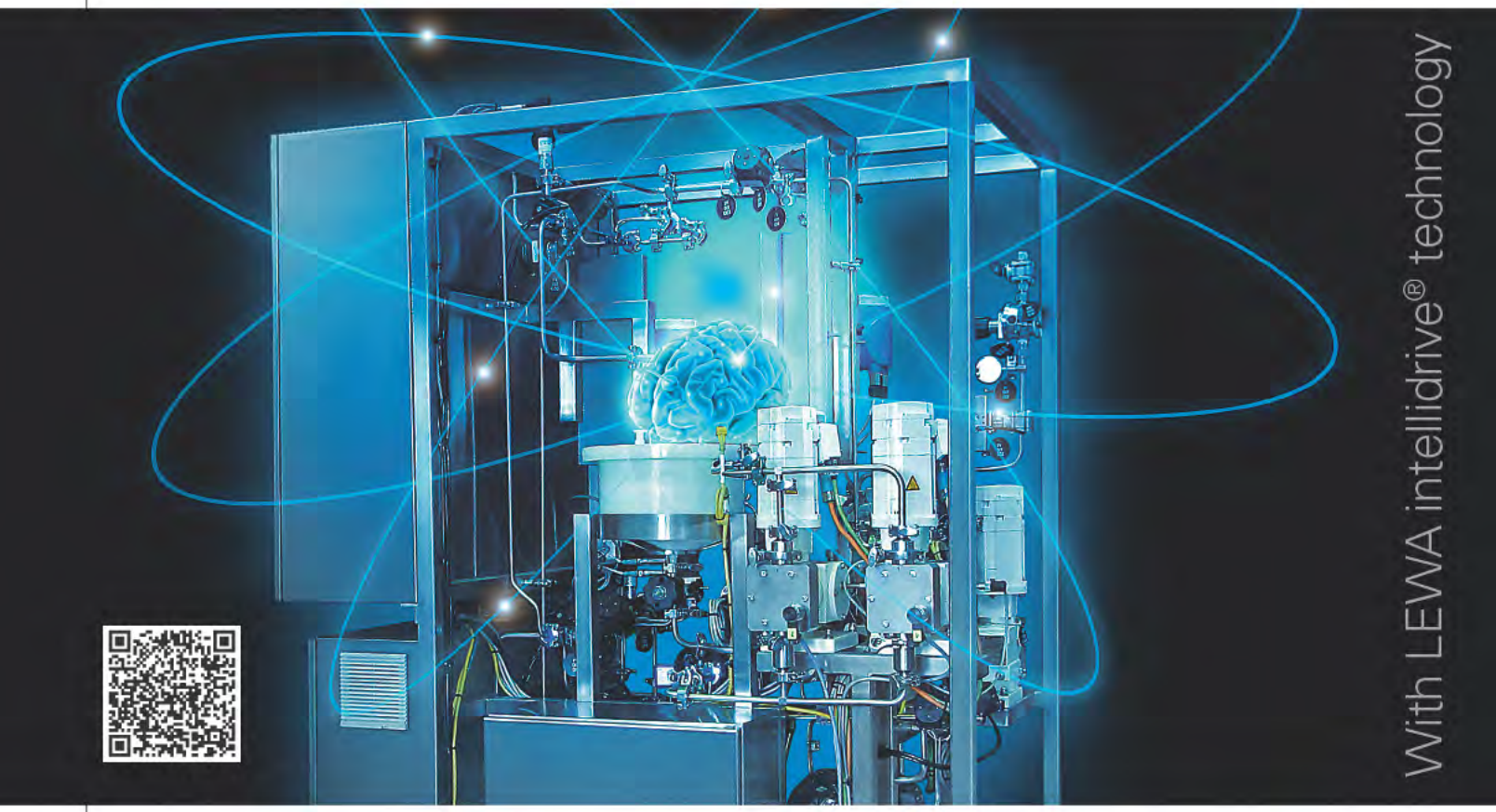

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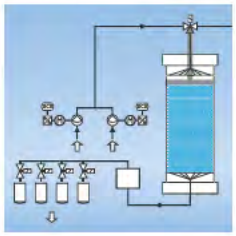

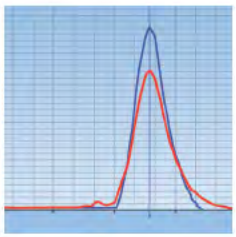

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during the adoption cycle. Traditionally, MES has been a site-specific initiative, but with increasing globalization, companies are now aligning not just their enterprise systems, such as ERP, but are focusing on manufacturing systems such as MES. Software as a Service (SaaS) and cloud computing is arguably causing a shift in the technology adoption cycle in both MES and ERP - *Figure 5.* Cloud computing is a model whereby the computer hardware and software services are typically (but not always) offered as a service in a remote data center. This compares to deploying hardware and software on local sites.

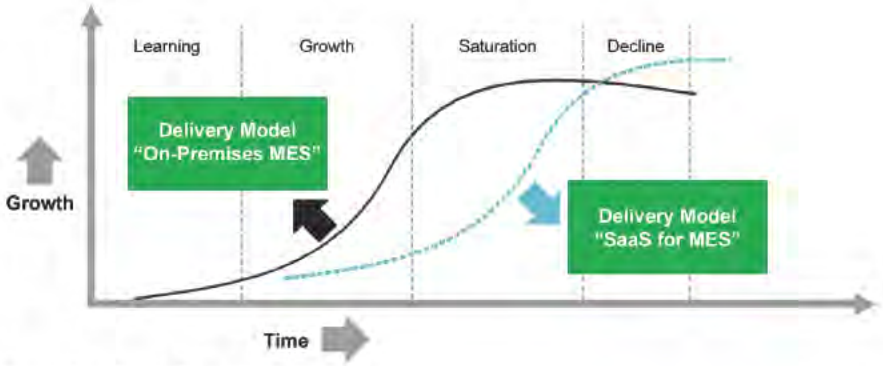

Figure 5. S-Curve Technology Adoption.

Manufacturing 2.0

With emerging technologies, such as cloud computing and increasing globalization, the dynamics of manufacturing are changing. Manufacturing plants are integral parts of the overall supply chain and need to provide real-time data. This increases the focus on reporting from manufacturing and MES plays a crucial role in insuring the accuracy and availability of data. ERP systems handle weekly or perhaps in some cases daily information. The supply chain is demanding more refined data. MES solutions typically are designed to report at an hourly rate or with less frequency, therefore meeting the requirement of the overarching supply chain.

MESA, in a recent white paper, introduces the concept of Manufacturing 2.0 (Mfg 2.0). As discussed earlier, companies are shifting manufacturing focus from data centric to process centric, and advances in the design of large software applications, through the use of frameworks such as Service Oriented Architecture (SOA) are enabling this shift - *Figure 6.* MESA discuss:[7]

"The manufacturing operations-specific requirements for SOA are called Manufacturing 2.0. Mfg 2.0 is differentiated from the so-called Manufacturing 1.0 architectures based on stand-alone client/server data base applications that attempted to represent business process modeling through point-to point interfaces and custom data transformation between applications."

By deploying Mfg 2.0 technologies, companies can meet the demands driven by the overall supply chain. Without an MES, this cannot be achieved efficiently. Companies will have to decide whether Mfg 2.0 technologies are feasible for the deployment of MES. The technology is not as mature as client/server based solutions; concerns exist in relation to data security and a total reliance of IT networks. Individual companies should weigh up benefits of these new technologies, such as economies of scale, shared services, and aligning to enterprise strategies, before deciding on a deployment approach of a technology set.

Pharmaceutical Manufacturing Without an Electronic MES

Due to the complexities at the MOM level, financial constraints, and availability of key personnel, investments in solutions such as MES are deferred. This is very understandable as manufacturing organizations need to be ready and able to clearly define their requirements for a potential solution. The downside to this strategy is a break in data flow, that is, inventory information available on the ERP system

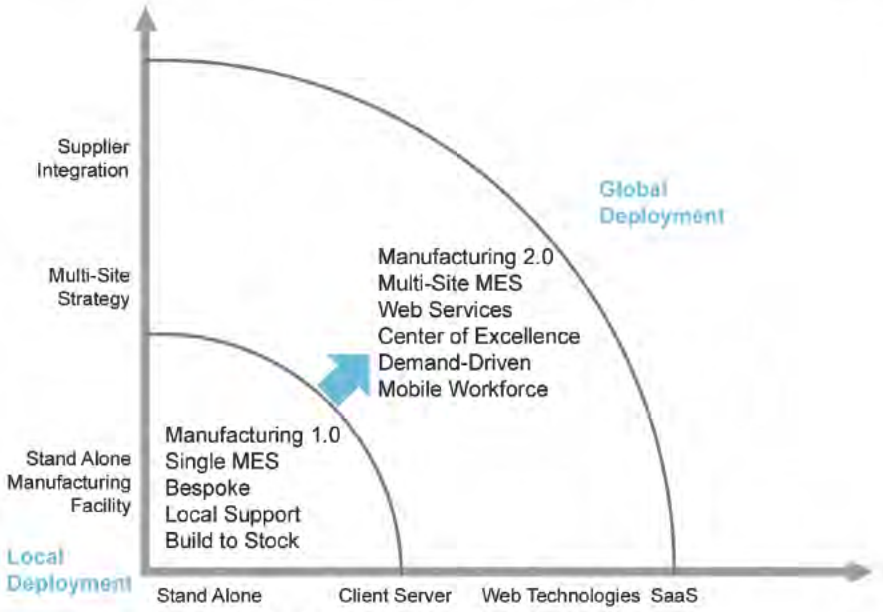

Figure 6. Manufacturing 2.0 and MES.

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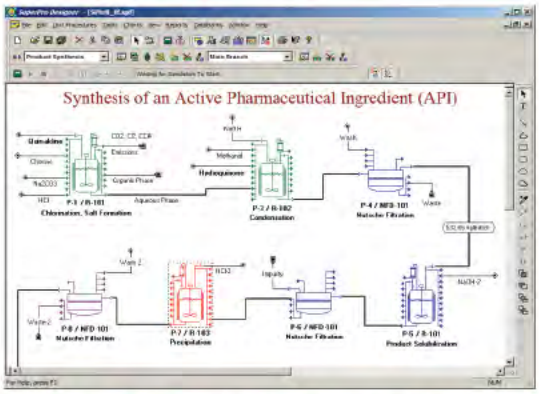

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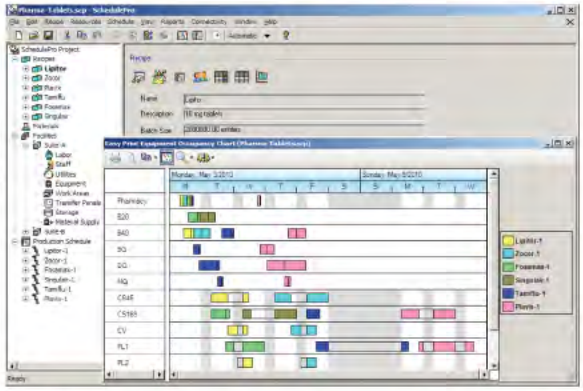

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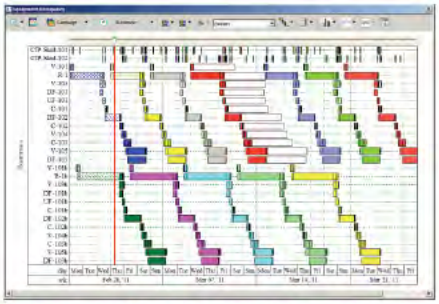

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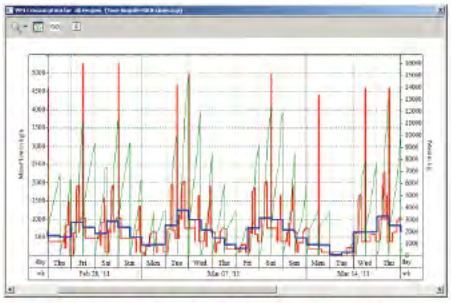
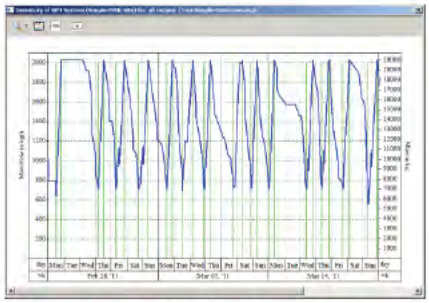


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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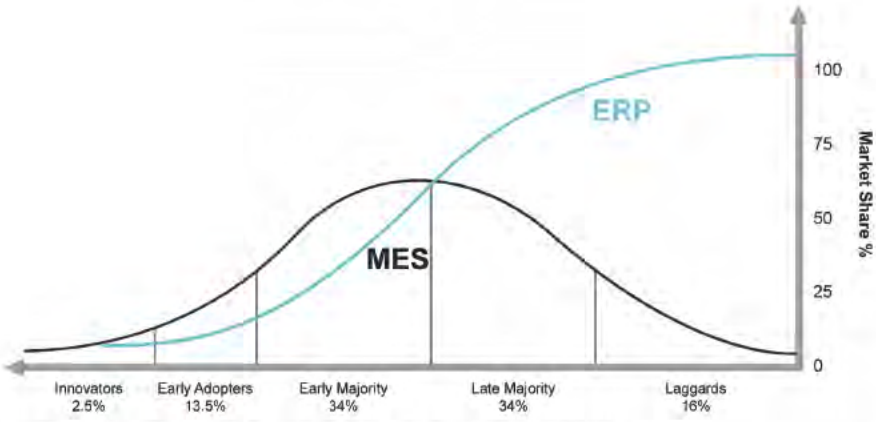

Figure 7. MES and ERP Adoption in the Pharmaceutical Industry.

and process information available from equipment sets, but no one system aggregating the data together. This impacts on the availability and quality of data, therefore negatively impacting on traceability. It is also a requirement within FDA-regulated industry to retain MOM data associated with products and processes that directly impact on the production of finished goods. With e-pedigree and serialization pending, this break in data flow requires companies to invest a lot of time in managing the data on paper.

This data is critical in the pharmaceutical industry. It is a rich, real-time, and most importantly a quality approved (that is, collected, stored, and maintained in accordance to regulatory requirements) source of data on which any decisions pertaining to manufacturing can confidently be made. The data also will help resolve traceability issues arising at the MOM level, as it plugs the gap between enterprise and manufacturing operations management.

Conclusion

Pharmaceutical companies that have adopted MES are gaining a competitive advantage with improved quality, better traceability, maximized lean initiatives, flexible manufacturing processes, improved compliance, complete business process management and accurate, real-time reporting. Companies that do not adopt this technology risk losing a share of existing and new market opportunities. This is a result of new pharmaceutical facilities starting with an MES in place, that is, paperless manufacturing from day one.

Of those companies surveyed in conjunction with the article, more than 80 percent have an ERP system in place. MES adoption is lagging behind ERP, but as Mfg 2.0 becomes more prevalent, MES will become an integral part and critical component of the overall supply chain. MES will continue to be adopted and eventually align with ERP - *Figure 7.*

Implementing MES is not a decision that can be taken lightly. Every aspect of the manufacturing process will be impacted by an MES implementation; however, companies are successfully deploying MES and reaping the reward. MES has crossed the technology chasm and is reaching maturity in the pharmaceutical industry. Don't get left behind.

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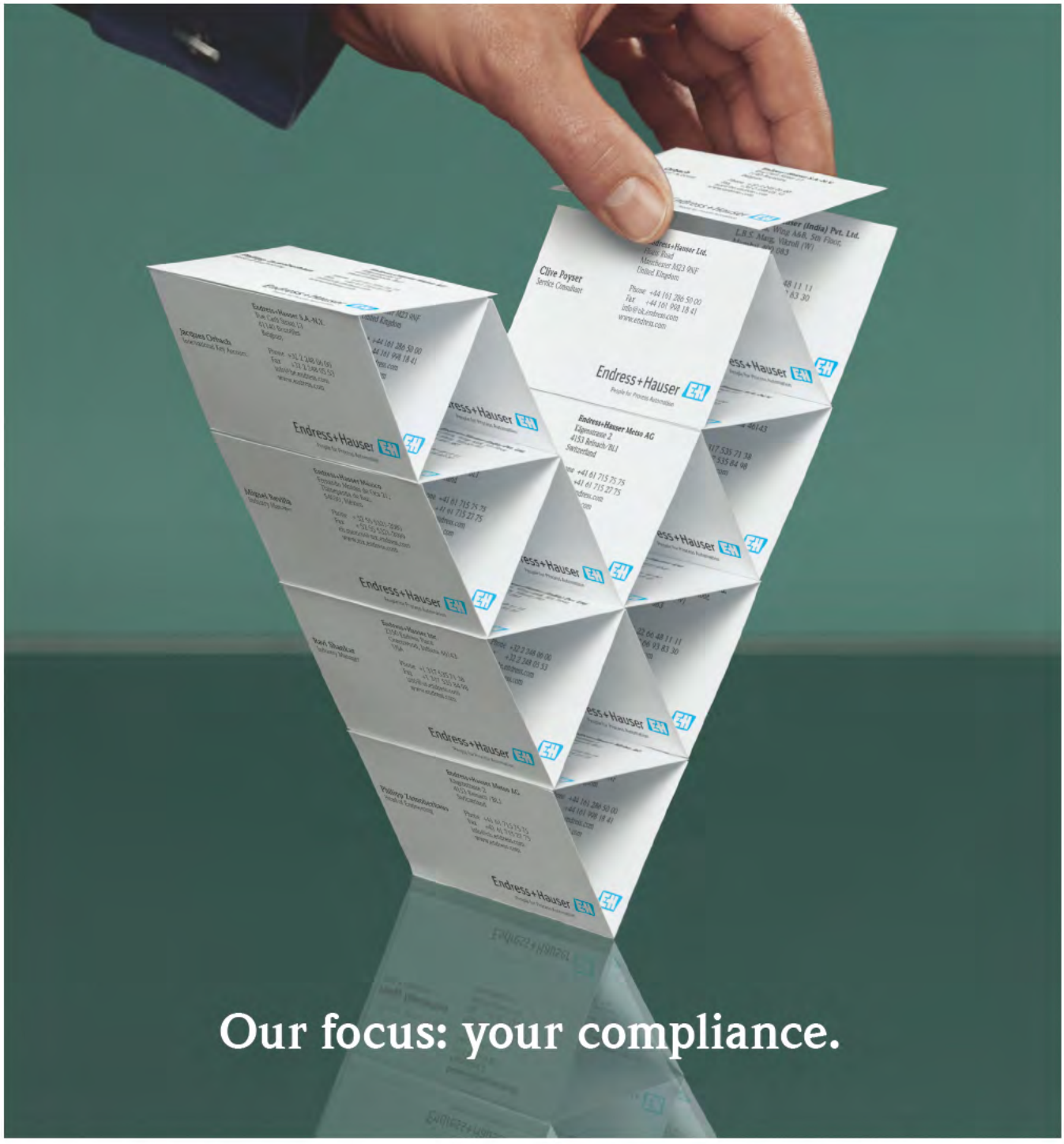
About the Author

Desmond Savage is an MES Consultant with ATS Applied Tech Systems Ltd. Ireland. He has been working in the area of MES for more than 12 years as a consultant, manufacturing engineer, and validation specialist. Since 2004, his sole focus has been on MES within the life science industry. Savage is the chairperson for MESA Ireland and in June 2011 completed the Certificate of Competency for MES/MOM Methodologies given by MESA International. He is qualified with a Masters in advanced manufacturing technology (1999) from the University of Limerick, Ireland. He can be contacted by email: Desmond.Savage@ats-global.com.

ATS Ireland, Webworks, Eglinton Street, Cork, Ireland.



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People for Process Automation

A Leaner Software System Development Process

by James E. H. Stafford, PhD

This article presents new insights into software design, including a more efficient way to implement software without undermining regulatory expectations.

Software is widely used to support the automation of product manufacturing and development and data quality-related business processes in order to increase operating efficiencies.

The need to validate regulated applications[1,2,5] can impact project costs and timescales because of the requirement for the maintenance of extensive documentation supporting activities associated with the traditional waterfall software development lifecycle (SDLC) and derived development methodologies. Strategies to reduce costs associated with the development and implementation of software in regulated environments have been advocated, e.g., risk-based verification,[3,4] leveraging supplier documentation,[3] and automation of project management processes, namely document management and test management.

However, these strategies do not address the number of document types produced during the development lifecycle, only the granularity of the document contents or rigor of the verification processes. Furthermore, the perceived complexity of software systems, their invisibility (as opposed to having a physical manifestation), and ease of modification also has resulted in the call for increased management control of the software development (SD) process.[5]

A different understanding of the software design process may provide for a rational approach to optimizing the verification and documentation requirements of SD and validation. A leaner SD process based on an alternate theory of design, called the Sensemaking – Coevolution – Implementation Framework,[6] is described. The theory focuses on the source code (or configured system) as the product of software (system) design, rather than design specification documents. This alternate theory may provide for less documentation and fewer cost and timescale overruns without compromising regulatory expectations for software quality.

Features of Traditional SDLC Processes Associated with High Costs and Poor Software System Quality

Some features of the traditional waterfall SDLC processes associated with high costs and poor software quality are inherent consequences of the adopted SDLC rather than of SD per se. Proposed attempts to manage costs and improve software quality do not solve the problem; they only treat the symptoms.

Planning

Although the waterfall concept as a prescriptive model for SD is embedded throughout software engineering literature, there is evidence of challenges in the model's application,[7] (e.g., users find it difficult to accurately articulate requirements at the start of development; developers find it difficult to provide accurate estimates of effort required to deliver software components). In practice, software developers tend to act in an amethodological manner,[8] consequently plans based on a waterfall SDLC phase approach are rapidly compromised. Attempts to enforce the waterfall approach by means of increased quality assurance activities (e.g., documentation and verification of controlled phase inputs and outputs) increase the required project resources and timelines, impacting costs.

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Separate Testing (Functional Verification) Phases

A recent study concluded[9] that some 40% of software errors were detected by end users and a major cause of software development project failure was lack of understanding of the user/business requirements.

Possible risks associated with separation of SDLC into planning phases, as exemplified by the waterfall concept, was recognized in the original description,[10] but it was believed that accurate documentation would ameliorate any impact. So, for example, any risks associated with assigning "Testing" as a separate development phase that occurred after "Coding" would be ameliorated by having accurate functional and design specifications that could be used as inputs for appropriate test specifications. Nevertheless, when project timescales or budget are under pressure, reducing the duration of testing and/or project scope can prove tempting. However, the cost in terms of failed projects and/or poor software product quality is well documented.[9]

Documentation

The overhead associated with managing and verifying documentation created to support traditional SD processes is well understood and is invariably one of the first project attributes to be scrutinized when project cost, schedule, or scope metrics are compromised. However, as observed by Royce[10] in his original description of what became known as the "waterfall" SDLC, documentation is key to the planning model of SD described. Thus, significant resources have to be employed to ensure that the input and outputs of the various planning SDLC phases are correctly documented to ensure that the correct system is designed and built.

The potential need to update upstream functional and design specifications based on test failures was also recognized as a weakness of the phased approach. Significant reworking of the design specifications could be required to correct errors detected during structural or functional verification, requiring restatements of the functional and software solution designs or even the system requirements. Inevitably, maintenance of accurate documentation becomes a project's rate limiting step and may ultimately only appear to show that development had followed a rational method.[11] In particular, documents describe the "as built" rather than the "to be built" system and show no evolution of system design.

Weakness of Proposed Solutions

Reducing the effort and cost of SDLC quality assurance activities by means of applying appropriate risk management strategies have been proposed[3,4] as a way of extracting value from SD projects by focusing resources, activities, and supporting artifacts on software functionality carrying the greatest risk to patient safety, product quality, or data integrity.

While this approach has its merits for guiding user acceptance testing, it might not be effective for documentation and verification of the development of novel software or software solutions.

The underlying assumption (often unstated) is that the planning model of SD is the only one that is valid and applicable. Yet, it remains a huge leap of faith to go from positing that the recognizably fallible waterfall planning approach to managing a SD *project* is the best way to design and develop a software *product or solution* of high quality without duly considering the changes to the capabilities of tools used to create computer programs since the original proposal.

Nevertheless, there is no general theory of design[12] that can be leveraged to validate the waterfall SDLC or closely related development models (e.g., Spiral, Rapid Application Development (RAD), Rational Unified Process (RUP™), Dynamic Systems Development Method (DSDM)), or for that matter, invalidate leaner Agile approaches (e.g., XP and Scrum methodologies).

Alternate Understanding of the Design Process Offers New Insights into Design of Software-based Solutions

Of two separate schools of thought that seek to provide an understanding of the design process, the reflection in action concept as embodied in the Sensemaking, Coevolution, and Implementation (SCI) framework is more successful in explaining how software design occurs in practice[6] and can be extended to design of software solutions by means of application configuration.

Rational Design Paradigm

The sequential process design method for SD represented by the waterfall model and its variations is an example of the application of the technical problem-solving or rational design paradigm.[13] This theory posits that an automated solution to a business problem could be found by rational sequential decomposition of the problem to an abstract set of symbols (e.g., diagrams or coding language) that can be symbolically manipulated to provide a design to solve the problem.

A theoretical basis for describing the rational design process that is applicable to any engineering domain – Function, Behavior, and Structure (FBS) framework – has been proposed[14] and refined.[15] Briefly, FBS are classes of variables that describe different aspects of the design object: what it is for, what it is expected to do or actually does, and what it is, respectively. The designer transforms the object design requirements, expressed as Function, into behavior that is expected to enable Function. The expected behavior is used to define Structure of a solution that is intended to exhibit the desired behavior. The actual behavior of the Structure is then evaluated by analysis and compared to the expected

behavior. The solution encapsulated in Structure can be reformulated until actual behavior sufficiently matches the expected to support a decision to construct or manufacture the design object. At this point, the Structure is documented in order to provide the specification for construction of the design object.

In an attempt to answer the question "What is software design?" the waterfall and an iterative SD process (RUP™) were mapped onto the original FBS framework.[16] Notwithstanding more recent critiques of the FBS model,[17,18] some interesting observations were made vis à vis elements of perceived software design processes and that of accepted engineering design, namely:

- The traditional waterfall model is a poor fit to the FBS design model. It presumes the design to be achieved in a single attempt and structural reformulation is limited to going from (software) design to code. Functional reformulations are discouraged.
- Iterative lifecycles (e.g., RUP™) are a more comprehensive fit to the framework.
- Software design is not limited to, for example, functional decomposition or UML modelling. Decisions are made while eliciting and capturing requirements that directly impact the final form (design) of the product.
- Programming is primarily a design activity because reformulating the structure solution is achieved by refactoring, which is an established programming activity.
- Testing and inspection are also design activities in as much as they are used to analyze predicted against observed behavior of the design. The results of which could lead to change in design.
- The output of software design (process) includes the source code because this artifact comprises all the information required to build/"manufacture" the product.
- The cost of "manufacturing" software is practically eliminated because of the ease, speed, and cheapness of generating the software product from the design (source code). Leading to:
- Use of the built (compiled and linked) software product to determine fitness for purpose rather than theoretical static analysis of the design representation itself.

The idea that source code is the output of software design was first published in 1992[19] by a software developer based on reflecting on how SD processes compared with those of engineering design. His insight was that an engineering design process produces a documented design that contains all the information necessary to build the product. The equivalent document for the software design process is the source code.

Reflection in Action Paradigm

The alternate view of design[20] is one of "reflection in action" where the designer does not separate thinking from doing.[21] According to this view, design is effectively emergent. Gero and Kannengiesser discussed how "reflection in action" can be fitted within the FBS framework[15] to understand how refinement of design/code and code refactoring occurs. However, a more recent theoretical framework has been proposed that posits "reflection in action" as central to the software development/design process.[6]

The SCI framework for software design is a process theory generated from existing literature and takes its name from the three core activities which form the glue of the framework: Sensemaking, Coevolution and Implementation. The definitions of these activities are as follows:

- "Sensemaking (see Reference 22 for alternative definition) is the process by which the design agent perceives the design agent's environment and the design object's environment and organizes these perceptions to create or refine the mental picture of context."
- "Coevolution is the process by which the design agent simultaneously refines its mental picture of the design object based on its mental picture of context, and vice versa."
- "Implementation is the process by which the design agent generates or updates a design object using its mental picture of design object."

These activities are each executed by the design agent(s) and apart from the initial creation of mental pictures of the context and design object, can be engaged with at will. There is no predictable sequence or phased activity as embedded in a lifecycle (or FBS). The output of the design process, the "design object," is the source code and consequently no complete specification of the software is created prior to the source code itself.

Interestingly, both theories (FBS as modified by Krutchen[16]) and SCI posit that source code is the output of the software design process. Ralph, however, proposed that there were at least three key differences between the two theories:

1. Problem setting and problem solving are separate (FBS Framework) or co-temporal and inextricably linked (SCI Framework).
2. The coding process is driven by prefigured decisions (FBS Framework) or evolves iteratively with the design process (SCI Framework).
3. Designers focus on models (FBS Framework) or code (SCI Framework).

A comparative evaluation of the two design theories, based on statistical analysis of survey responses, suggested that the SCI framework more accurately reflected how software is developed in practice than the FBS framework.

This concept can be readily extended to the design of software solutions based on configuring application packages.

Implications of Adopting the Reflection in Action Model

The implications of adopting the reflection in action model are a simpler SDLC, a reduction in the number of documentation types that must be controlled during the design process, namely reduced number of document CIs, and more focused "added value" verification activities.

Simpler Software System Development Lifecycle

An attempt to visualize the "reflection in action" design process is depicted in a Venn diagram format (Figure 1), reflecting the SCI design paradigm and the interdependencies of the key design and verification activities. Activities common to software and application design are colored green. Yellow indicates structural and integration testing. Blue text labels relate specifically to software code development and testing. Red text relates to application configuration. Note that no sequence of activities is implied other than a requirement or set of requirements is initially selected for solution design and that the design solution must be verified against its requirements before completion of the design process. The model further implies that the design deliverables cannot be finalized until the design object, namely source code or configured module, meets its functional acceptance criteria and is ready for release to the next project phase.

A proposed model incorporating the conflation of the traditional plan driven SD analysis, design and build activities into a single design (build and verify) activity is depicted in Figure 2. Four project phases are envisaged and typical phase deliverables are listed (unique deliverables are color coded as per Figure 1). The layered multiple design (build and verify) activities represent sequential or offset development "sprints" in Agile terminology or Conference Room Pilots (CRP) in COTS implementation terminology. Critical development document CI types are listed in Figure 2 under each project phase. Note that there is no mandatory requirement for functional or software design specifications.

Fewer Critical Development Document CI Types

Although originally envisaged as a model for how an individual designs, most software projects are of sufficient size to require the support of several designers, namely developers. These individuals need the capability to efficiently share their envisioned designs. Levina[23] described how multiple designers may collectively reflect in action. They achieve this by using "boundary objects" such as design models (descriptions) and prototypes. This is consistent with the use of, for example, functional decomposition diagrams, use cases, and software specifications of traditional SDLC. However, here the similarity ends. According to the reflection in action paradigm, these documents or prototypes reflect an exchange of ideas for solving the problem at a particular point in time. Their content can be transient in that a mental evaluation of the situation can cause a reframing of the problem, perhaps raising new actions and evaluations, until the design solution is reached. The implication is that attempts to formalize these exchanges is self-defeating and adds little or no value; the document authors will forever be striving to keep up with design changes implemented by the developers as they encounter new situations or realize that the design choice is not practical.

For example, functional specifications are not considered a CI during design because, if produced, they are a mecha-

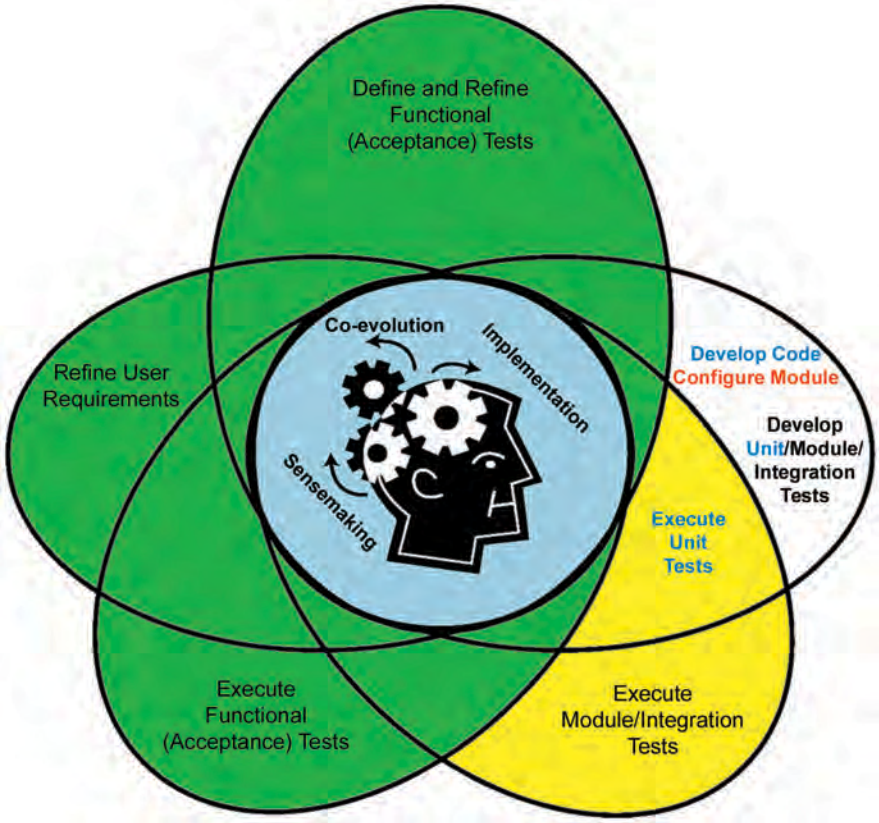

Figure 1. Revised Software Design Process "Design, Build, and Verify" based on the SCI Framework model.

nism for communication of ideas between members of the "design" team on how the requirement might be functionally fulfilled and once their purpose has been achieved, they are of no further prospective use. If retained, they provide a retrospective view of any discussion on how a design decision may or may not have been reached. The traditional software design specification is redundant for the same reason, but is superseded by the software design description, which describes the "as built" design rather than the "to be" design. The level of detail captured in this document should be a balance between providing a map for navigating the source code and providing sufficient information to facilitate the maintenance of the code once in production and possibly by new resources. The software description must be supported by appropriate comments within the code.

Where a software solution is achieved by means of configuration, a comparable deliverable summarizing the configuration settings is required. Documents generated to support design process activities between requirements (what the system must do) and the source code or configured application (software solution design) are, therefore, designated as work products and would not require formal control. On the other hand, test cases/specifications, which on execution will provide evidence to demonstrate that the design meets structural or the user's requirements, must be managed in line with source code releases or application baselines.

Traceability of requirements to software functionality would be simplified, since traceability is now between requirements, source code/software description, or application configuration and test specifications only. The proposed reduced set of core SD deliverables reflects observations on Alternate Software Development Models reported by a GAMP® SIG.[24] The proposed SCI framework theory of software design helps to explain why some of the traditional documents are not required by these alternate models and methodologies. The conclusion that alternate models can be used, provided the missing documentation is generated, is based on the premise that the generalized V-model described in the GAMP® 5 guidelines based on the waterfall SDLC model has an unequivocal theoretical basis that underpins software development. Empirical evidence would refute such a conclusion.[25]

Added Value Verification Activities

A feature of the SCI framework is the continual verification of the design solution embedded in the proposed design process. Source code, associated software description "as built" documents, and user requirements are the focus of design

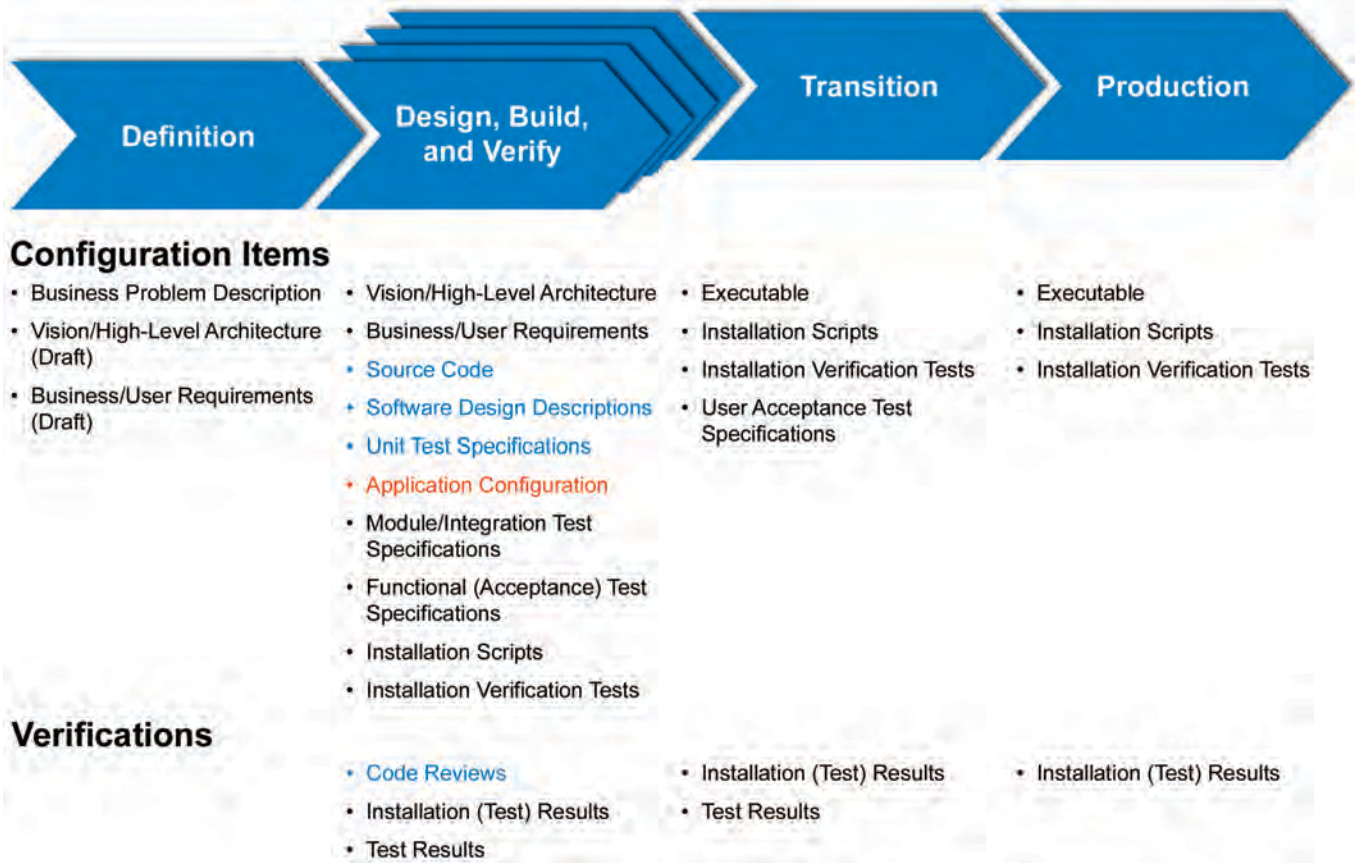

Figure 2. Design, Build, and Verify process as a phase in context of a software development project and associated documentation.


GERMANY. Almost one million children and
adolescents suffer from hay fever and will do so
for the rest of their lives, unless treated.


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– the world's first tablet-based grass pollen allergy
vaccine – out of their modernised facilities.
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control by means of code review and unit, integration, and acceptance testing. Note that test specifications are dynamic; they may change with changes in design. Therefore, there is no value in formally baselining these documents until the design is stabilized. Unit and integration test specifications will be more sensitive to changes in design/refactoring and would be baselined as late as possible, but no later than the release of code for formal verification of the "as built" design. Where a software solution is achieved by application configuration, comparable focus for design controls are user requirements, "as built" configuration, documentation, integration, and acceptance testing.

Continuous regression testing after each rebuild of the executable or master after each sprint or CRP helps to ensure that the design object remains intact and increases confidence in the integrity of the final build or configuration. The ability to automate unit and functional tests is key to the successful execution of these verification activities.

The shift in emphasis from verification of the software design specifications to the source code itself may have implications for the code review process because of the sheer volume of data (code) involved. The use of automated code review tools should be encouraged to enable a greater coverage. Risk, for example, to patient safety or data integrity can be used to determine the scope and rigor of code review, which could be manually executed for high risk functions.

Likewise for software solutions the emphasis will be on the configured application and appropriate tools required to document the electronic "as built" configuration.

No Conflict with Regulatory Expectations for Software System Quality

The proposed SD model based on a new understanding of the software design process is not in conflict with stated regulatory expectations for SD because quality, safety, and effectiveness requirements are designed and built into the software system developed under the proposed model prior to production. The condensed design, build, and verify process can be appropriately managed as a project activity and efficiently controlled to meet all quality and design requirements.

SDLC Expectations

Neither FDA[5] nor EU[2] mandate a particular SDLC, but describe typical development artifacts based on the planning SD (waterfall) paradigm. The IEC Medical Software Device Software standard[26] describes evolutionary development as an alternative to waterfall. GAMP® 5[3] describes a generic system lifecycle in which SD is an activity within the project phase in an attempt to flesh out the FDA/EU guidelines in order to address practical concerns of regulated users and their suppliers in light of changing SD practices. However, the extended GAMP® examples retain the ghost of the original waterfall planning SD paradigm with design decomposition specification artifacts as CIs.

A mapping of the proposed reflection in action-based paradigm onto the project phase of the generic GAMP® system lifecycle is depicted in Figure 3. It is important to note that the specification activities relate solely to the business/system requirements and their transformation to user/product requirements. A separate verification activity is part of transition in as much as the system is verified against the business requirements or original problem, requiring a solution as part of transitioning to production. All project activities in between are treated as design.

Quality Expectations

US regulatory software quality expectations[5] as summarized in the PIC/S guidelines[27] are the following:

- Quality, safety, and effectiveness must be designed and built into the software.
- Quality cannot be inspected or tested into the finished software.
- Each phase of the development process must be controlled to maximize the probability that the finished software meets all quality and design specifications.

These quality expectations are encapsulated by the requirement to validate software systems used for regulatory purposes, i.e., must be demonstrably fit for purpose.

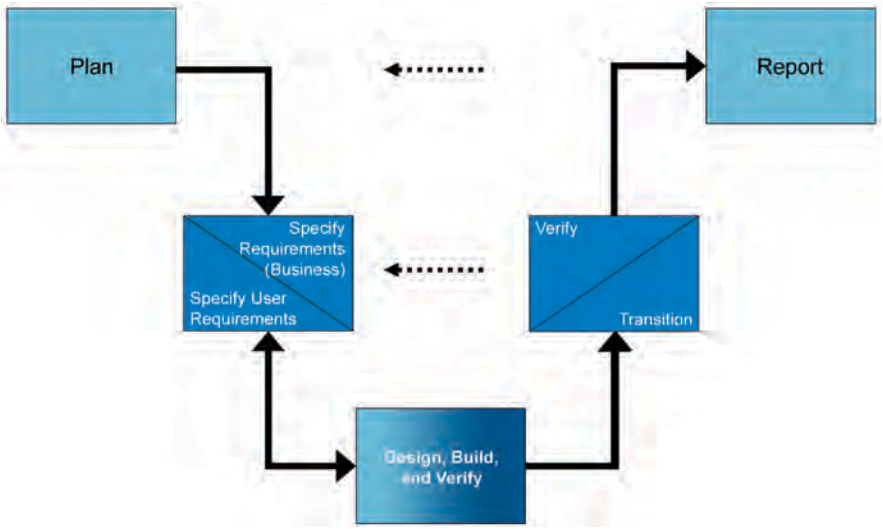

Figure 3. The proposed single "Design, Build, and Verify" process in context of the project phase within the GAMP® 5 system lifecycle.

Designed and Built In

The SCI framework for SD makes no distinction between design and building software (as in writing source code and compiling it, respectively) and posits the concept that software programming is a design activity, the output of which is the source code. The framework can be readily applied to the design and building of software solutions by application configuration. The high degree of interaction between the designers, users, and software testers ensures that the software completely meets the user's requirements and that there is functional test evidence to support this claim prior to transitioning to production. The functional integrity of the software is ensured by incrementally adding functionality supported by continuous regression testing.

Role of Testing

The idea of not being able to test quality into finished software is firmly based in the physical domain of manufacturing product. The idea has been inappropriately applied to software, as testing finished product provides information on the manufacturing process.

For engineering projects where the realized design could fail with catastrophic effect (e.g., road or rail bridge, motor car or airplane), the designs undergo extensive testing in virtual environments or as prototypes prior to documenting the design in order to support production or construction. In these examples, testing is used to improve or verify the quality of the design. In the case of software, the source code encompassing the design as proposed by the SCI framework or the configured application is "tested" by building (compiling and linking) the executable and testing a version of the product. Building (as in production of) software is cheap and quick and, therefore, a realistic and more accurate way to verify the quality of the software design compared to analyzing a virtual representation of design or desk review of design specification documents. Thus, for the most part, testing is deemed a design activity because initial (unit/integration) testing is to verify the integrity of the design, i.e., source code. Subsequent functional testing extends testing of the design in relation to answering the question "Does the design solution meet the selected user/product requirement(s)?" If the functional test fails, then a cause could be faulty implementation of the design solution or poor understanding of the requirement(s), requiring a change to the design, namely source code or application configuration.

Phase Control

The ability to maximize the probability of the finished software system meeting its quality and design specifications is built into the process by adopting a repetitive single design (build and verify) activity (sprint/CRP) with a subset of requirements as input and source code (or configured application) as the output until a solution has been established for all identified requirements or the product (requirements) backlog has been cleared. The solution is not accepted until the acceptance criteria for the design are met, source code or application configuration has been appropriately reviewed, and there is no degradation of system integrity as determined by regression testing after incorporation of each additional piece of accepted code or configured module.

A final verification occurs during the transition phase where the system is verified in its business setting, e.g., user acceptance testing. Successful user acceptance testing is critically dependent upon effective communication of requirements between software designer(s), testers, and subject matter expert(s) or user(s) during the design, build, and verify phase. This is ensured by the proposed design process.

Where a specific design review is a regulatory expectation,[28] this would occur just prior to the final software build for release to the transition phase or part of the transition phase itself. This approach was adopted by Abbot for their Agile SD model supporting medical device software development.[29]

Conclusion

A leaner SD process, based on the Sensemaking – Co-evolution – Implementation framework (an alternate theory of design applied to SD), is described that focuses on source code or configured system as the product of software design rather than software design documents. This alternate theory provides for a rational reduction in the number of controlled document specification artifacts (CIs) and associated verification activities to those that add value to the development process without undermining regulatory expectations for software quality.

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About the Author

Dr. James E. H. Stafford has 40 years of experience associated with the pharmaceutical Industry. Most recently he was principal consultant at Business & Decision (UK), specializing in the specification, implementation, and validation of computer systems subject to GxP regulations. These specialities are supported with expertise in auditing IT quality systems subject to GxP and ISO 9001 regulations and standards as a trained TickIT auditor. Prior to joining Business & Decision in 1996, Dr. Stafford spent six years as pharmaceutical consultant to a major LIMS vendor with responsibilities for pharmaceutical domain and GxP knowledge transfer, specification, and evaluation of pharmaceutical applications. In this role he was able to leverage 16 years of experience in pharmaceutical R&D at G.D. Searle (UK) and Servier (France), ultimately as Group Leader of Bioanalysis and Head of Pharmacokinetics. He has published and spoken widely on subjects as diverse as computer systems validation, data quality, Quality Systems, quality control, LIMS, veterinary biochemistry, clinical chemistry, analytical chemistry, pharmacokinetics, and robotics. He was editor of a book on Advanced LIMS Technology: Case Studies and Business Opportunities (1995) and more recently, senior author of a chapter on ERP Validation in Validating Pharmaceutical Systems – Good Computer Practice in Life Science Manufacturing (2006). Stafford received his Ph D on Magnesium Metabolism in 1971 from Reading University. He can be contacted at: compliance@quality.staffordonline.net.

An Introduction to the ISPE IP COP Survey on Patient Experience Related to Investigational Medicinal Products

by Christine Milligan, PhD, MBA, Esther Sadler-Williams, MSc, MRPharm S, and Karen Gram, MSc (Pharm)

This article presents a summary of a survey on patient experience related to Investigational Medicinal Products (IMPs) conducted by the ISPE IP COP.

The IP COP believes in the future the supply of clinical materials becoming a two-way street, with information flowing upstream from the patients and sites to drive the downstream flow of user focused products and services. This first patient survey is a small but important step.

The Patient Survey Project Team will survey no fewer than 2,000 clinical trial patients globally to gain their feedback on the suitability of clinical materials that are currently provided and to obtain the patients' suggestions for improvements. The goals of the project are:

1. ***To gain an understanding of patient experience with investigational products,*** which will support informed decisions, related to future study materials, resulting in improved patient compliance as well as more efficient and effective studies

2. ***To gain an understanding of the impact of key patient differentiators*** (demographics such as age, global location, study type, etc.) on patient experience, which will allow clinical and clinical supply teams to determine when adjustments are needed to ensure protocol compliance

3. ***To provide a data set that impacts decisions, opens new areas of inquiry,*** and generates practice implications for both Good Manufacturing Practices (cGMPs) and the GCP-GMP interface

4. ***To increase collaboration between global regulatory bodies,*** companies engaged in the GMP sector, and facilitator organizations like ISPE so that enlightened global Guidance(s) result

Introduction

The challenge for the Investigational Medicinal Product (IMP) professionals is to get *"the right product to the right patient at the right time every time"* surmounting the increasing hurdles of new product types, global trials, and financial constraints which may often require flexibility in pack design. To date, most technologies and decisions in the IMP business have focused on current Good Manufacturing and Distribution (cGMP and cGDP) processes and activities. As a result, the decision-making process may not include any focus on the downstream implications of Good Clinical Practice (GCP) related activities on the site and patient IMP experience.

During the development of ISPE's Interactive Response Technology (IRT) Good Practice Guide (GPG)[1] and the GPG on Booklet Labels,[2] the document teams acknowledged the

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importance of reaching out to sites to get their perspective. As a result, a clinical site survey was conducted with support from ISPE in 2008.[3] Feedback was received from more from 240 investigator sites from around the world on the use of IRT for the removal of expiry dates on labels, use of pooled clinical trial medication, and the use of booklet labels. The following conclusions were made regarding the use of IRT (full details can be found in the ISPE GPGs):

- There was a lack of full understanding and therefore, acceptance of interactive response technology use in IP processes.
- Training of all involved parties is of critical importance to successful use and long term acceptance of IRT.
- No real technological reason was provided as a reason for not using IRT.

Technology including multiple benefits from interactive response technology were cited – suggesting acceptance of new and emerging technology in the management of IP processes.

In addition, the importance of feedback from the end users was highlighted. Following discussions on the site survey with many of the industry stakeholders including, regulators, sponsor companies, investigator sites, and service providers it was clear to the ISPE IP COP that a task team should be set-up charged with undertaking a survey to ascertain information about the complete patient experience related to IMP materials.

IP COP Background

ISPE's Investigational Products Community of Practice (IP COP) brings together industry professionals to collaborate and interact to address issues of common concern. The IP COP is made of committed volunteers who are subject matter experts in diverse fields. It is global with a global strategic vision that supports industry professionals with interest or professional experience in all aspects of the investigational product (clinical product supply) supply chain. The IP COP consists of a global Council as well as regional Steering Committees in North America, Europe, and Japan. Joint task teams are often times formed to research and prepare guidance and respond, as needed, to proposed regulations. The task teams support the overall goals of ISPE as a first-to-market leader and neutral global facilitator of important outcomes for patients and the industry. The ISPE organization is committed to supporting its members involved across the entire product lifecycle and to connecting GCPs and GMPs at a practical level and thus enhancing ISPE's relationship with key regulatory personnel and agencies.

IP COP Patient Survey Team

In the current competitive and global clinical trial environment, the IP COP believe that the experience of the patient will and should have a bigger impact on GMP decisions on clinical materials such as the patient kit design and labeling. Hence, in 2012 the IP COP formed a global ***"Patient Survey Task Team"*** charged with undertaking a survey of up to 2,000 patients across different regions and therapeutic areas. The results will be shared with the ISPE community at the Annual Meeting in November 2013 before being published.

To accomplish the survey and to ensure that patient confidentiality is preserved, ISPE partnered with the Center for Information and Study of Clinical Research Participation (CISCRP), a US-based not-for-profit organization that has significant experience in undertaking surveys related to clinical trials and thus they have access to clinical study participants around the world. The IP COP task team prepared the technical survey questions and CISCRP is the vehicle to reach the target participants in the survey.

What Forces are Driving Changes in the Pharmaceutical Industry and the Need for This Type of Survey?

The pharmaceutical industry is experiencing major upheavals and companies are responding by trying to discover, develop, and market medicines more efficiently. The IMP business has to meet many challenges in the changing environment in clinical trials:

- New product types: IMP professionals are pivotal in managing the shift from small molecules to biologics (vaccines, insulins, and oncology products) and specialist therapies.
- Cold chain products: more than 40% of current clinical trials involve temperature-sensitive products. In addition, in some countries, even ambient products must be temperature tracked and managed throughout the entire chain of custody and upcoming GDP regulations may ultimately expect similar tracking for IMPs in the future.
- Emerging regions: clinical trials are moving away from only targeting traditional countries of North America and Europe to emerging countries and the developing world of Latin America and the Asia Pacific.
- New regulations: a growing list of locations for investigator sites means that we need to coordinate the delivery through an increasingly complex maze of import/export and country specific regulations.

- New Technologies: as an industry, we are challenged to leverage new technologies to enable us to work smarter, faster, and to high quality standards.

- Complexity: clinical trial designs are getting more complex – titrations, adaptive trials, multiple arms, concurrent stability testing (resulting in expiry update management).

- Reduced Study Timelines: with pressure on patent expiry, there is more pressure on sponsors to undertake their studies in a shorter timeframe and this also can often result in competition for patients from the same sites.

- Cost constraints: to add to the challenges above, financial pressure on organizations/sponsors across the globe has raised the stakes for greater efficiency and an overall need to manage spending. Therefore, they look for ways to do more with less.

All of this is driving the need for more "flexible clinical materials." Sponsors need to ensure that their IMP manufacturing operations are efficient and ideally enable similar IMP presentations to be used across multiple studies.

Why Run the Patient Survey Now?

For the past several years, trends in the healthcare/pharmaceutical industry have increased the importance of patient experience and patient outcomes in decision-making. The emphasis on cGCP/GMP processes is being driven by the increasingly competitive environment resulting from payer mandates, patient engagement, and patient choice. Patient experience is often a less direct consideration, and data for making informed decisions on the basis of patients' experiences or preferences is extremely limited or non-existent.

While companies may have conducted some in house surveys or solicited feedback from patient focus groups, the ***Patient Survey Task Team*** believes that this is the first survey of its kind that will publically report on the results of patients' perceptions and experience of IMP. Regulators also are keen to get firsthand feedback on patient views to ensure future guidance and regulation meet these needs as well as ensure patient safety.

In light of the trends ensuring toward patient engagement, it seems essential that greater care be taken to understand the experience of patients during clinical trials.

As IMP professionals, we must adapt to all the challenges without compromising the trial, and most importantly, patient safety. Companies have put in place many solutions, systems, and technologies to ensure this. However, these have, for the most part, focused on the regulatory requirements and the needs of the company and the clinical team.

For example, booklet labels have been a "revolutionary" change in the last decade. The previous system was the use of country specific labels, which meant potential delays in providing materials for patients if the clinical teams decided to add new countries. Booklet labels can incorporate multiple languages (including contingency countries) and hence have greatly increased the flexibility of the materials. Moreover, their use also enabled a change from a country specific distribution model to a regional hub distribution model. While there is little to argue from a sponsor perspective about the advantage of this versatile approach and although commonplace in the commercial pharmaceutical world, ironically, booklet labels also have been one of the anecdotal drivers that have led the IP COP to undertaking the patient survey; we need to understand the patient perspective around this type of labeling.

However, the need for the patient survey is greater than feedback on booklet labels. The patient and the sites are key stakeholders in the clinical trials. The use of modern technologies will make it easier for patients and all stakeholders to provide their feedback on all aspects of clinical trials. Patients will be empowered to share their experiences, as well as give feedback to sponsors and other providers on what they do and do not like.

In addition, the survey is timely, as regulations are looking more to the GCP/GMP interface at investigator sites. Indeed, regulatory bodies have directly expressed an interest to the ISPE IP COP to have subject feedback on clinical materials.

The IP COP believes that this initial survey will be a first step toward listening and responding to the patient experience, which could positively impact many aspects of the clinical trials. The survey will provide areas of focus that could enable a COP task team to develop an industry-first good practice guide on patient-friendly clinical materials.

What Questions are we Looking to Answer?

The survey is divided into four sections with 48 questions in total. Most questions are multiple choice, but there is at least one free text question in each group. To validate key themes, some questions are repeated in a slightly different way.

To be eligible to complete the survey, patient must have taken part in a clinical trial recently and have taken the medication home (not hospitalized). The survey is voluntary.

Section I. Current/Recent Experiences

In this section, we ask questions to determine the suitability of the patient kits, i.e., if the clinical trial materials currently provided are user friendly/easy to use. If not, what could be done to improve the presentation for the patient. Questions include:

- Form of medicine received
- Type of trial/type of disease being treated for
- Size of kit and how easy to transport and store at home
- What information was useful to patients when learning how to use, take, and store their medication, i.e., how is the information provided, how helpful is the information either the sponsor or the site provides?
- Would home delivery of medication be useful?

Questions are also included to determine the patient experience of using booklet labels. It is very important to understand how the patient makes use (or not) of the information on the labels. Questions include:

- Do patients read the labels?
- If so, what information is useful?
- Is the dosing information clear?

Funding for the Patient Survey

The survey on Patient Experience with Clinical Trial Materials has been made possible by the generous support of 11 underwriting companies. Their investment in the mission and work of ISPE has allowed the Patient Initiative task force to design and carry out this comprehensive project to the ultimate benefit of patients around the world. ISPE wishes to thank the underwriters shown on page 57 for their assistance in making this project possible.

Future Studies. ISPE believes that it is uniquely positioned to serve as a bridge between companies with common interests and other important stakeholders such as health authorities and patients. As a neutral, nonprofit global organization made up of highly skilled technical and scientific professionals, ISPE can engage in research that is credible and ultimately beneficial to all those concerned. We look forward to conducting one or more follow up studies to the Patient Survey, and we will be considering other concepts in the months to come. When appropriate projects are identified, we will invite the support of additional underwriters to fund the work. For more information about becoming an underwriter for an ISPE research project, contact Karleen Kos, Vice President of Member and Industry Services (kkos@ispe.org).

- Do patients refer to the expiry date?
- Do patients refer to the dosing instructions?

From this section, we will learn the importance of the ease of use (and other packaging and supplies attributes) to the patient's overall satisfactory experience in their most recent clinical trial.

Section II. Attitudes and Perceptions

In the second section, we will determine the patient's preferences. Questions include:

- Which characteristics of a patient kit and its associated labelling are most important?
- Which form of medication presentation is preferred?

We also explore if pictograms, which in theory could be an international indicator of conditions for storing the medicines, are understood and useful to the patients.

A very important question for the industry is "how can we improve compliance?" In this section, we ask a series of questions to determine if the presentation of the trial medication assists compliance:

- Does the format of patient kit assist with taking your medication on time?
- If yes – what factors are helpful?
- If no – what changes could help?
- How easy is it to return unused medication to your site?
- Have you ever missed a dose of your medication?

Section III: Improvements for the Future

In this section, we let the patient imagine they are the IMP professional and ask them to state if the packaging and labelling of their trial medication could have been improved and if so how.

Many companies in our industry are looking into the use of modern technologies to provide information to patients. In the second part of this section, we gauge interest in the usefulness to the patients of information provided electronically and if they would be interested to get electronic reminders to take their medication.

Section IV: Background About You

The final short section contains the questions on demographics and technology use. The responders are asked to provide their country of residence, gender, age, and number of trials they have taken part in and indicate which electronic devices they have access to. Demographic information will be a key variable in the analysis.

How has the Survey Been Organized?

With ISPE's support, the Patient Survey team identified and contracted with 11 pharmaceutical, contract research organizations and supplier companies that would be prepared to underwrite the survey work. The team also worked with CISCRP to design the questions to be included in the survey. Of paramount importance was to ensure that the question terminology was consistent and would be easily understood by the patient, as well as assessing appropriate demographic factors to assist in a meaningful analysis. Additionally, a process of implementing the survey instrument and gathering results that preserved patient anonymity needed to be adopted.

Identification of Patients to Survey

Predominantly using CISCRP's patient database, an appropriate patient population will be targeted. The goal is to balance the 2,000 planned participants across global geographies, age groups, and disease states. CISCRP will administer the distribution and return of the survey and will not disclose patient identities.

Beta Testing

The survey instrument has been beta tested. The six beta testers included two current and former trial participants as well as feedback from clinical-trial naïve respondents, ranged in age from 31 to 69 years old (average age 47 years), two males and four females. All testers reported that the survey flowed well, was easily understood, and well-written. All of the testers felt that the survey was not too long.

The beta testing was run with a paper version of the survey. The testers noted that the "paper" survey felt somewhat old-fashioned and a bit cumbersome, and expressed a preference for completing an online survey instead. The final survey will be electronic with the results being fed back only to CISCRP.

Focus Groups with Patients

Using the findings from the Patient Survey, CISCRP with ISPE will develop a focus group discussion guide to complement the survey instrument. Two focus groups will be run, one in North America and the other in Europe. The focus groups will include up to 15 participants each, comprises of patients who have received or completed the use of a clinical supply kit within the last six months. The results will be reported along with the survey report-outs.

Conclusion

This landmark undertaking, that has both industry and reg-

ulator support, will conclude in the fall of 2013. The survey will complete late summer and undergo thorough analysis after which the focus group work will begin. The complete results will be presented during the Executive Series at the ISPE Annual Meeting in Washington in November 2013. It is anticipated that although the results also may indicate areas for fuller exploration, overall the results will lead to an improved, compliant, and safer patient experience with the associated positive impact on the industry studies that adopt "patient centric" approaches to their IMP processes.

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Ken Getz (CISCRP)

Annick Anderson (CISCRP)

Zachary Hallinan (CISCRP)

About the Authors

Christine Milligan is currently Global Director, strategic development solutions, Catalent Pharma Solutions. She has more than 30 years experience in early drug development; 13 years in developing drugs in CNS, pain, and cardiovascular areas; four years in program management of CTX/IND submissions, and latterly more than 10 years in managing clinical materials. Dr. Milligan has a PhD and MBA from University of Glasgow; honorary lectureships at University of Glasgow UK and University of Edinburgh UK in drug development. She has numerous papers and presentations to the scientific community. Dr. Milligan served as 2010 Chair and council member for the international ISPE Investigational Products COP. She can be contacted by email at: christine.milligan@catalent.com.

Catalent Pharma Solutions, Inchwood, Bathgate, West Lothian EH48 2EH, United Kingdom.

Esther Sadler-Williams is currently Senior Director, Strategic Alliance Development and Innovation for Catalent Pharma Solutions. Catalent acquired Aptuit CTS in February 2012, a company which had previously acquired Almedica where Sadler-Williams was Director of Client Development having been a founder member of the then 10-year-old European facility. As a pharmacist, Sadler-Williams has had more than 30 years experience in various pharmaceutical fields including five years with Sanofi Winthrop where she was Head of Research Services during which time she managed groups of CRA's medical writers and information/adverse event surveillance specialists. Previous roles include Principal Pharmacist with the Regional Drug Information Service at St. Mary's Hospital in Manchester, and Pharmacy Manager with Boots the Chemist.

Karen Gram has been employed since 1973 in Ferrosan A/S, and transferred to Novo Nordisk A/S in 1987. She has been in product development – oral preparations – for 20 years; heading Clinical Packaging department for five years, and introduced usage of IVRS to Novo Nordisk back in 1993 to manage a big phase 3 program. Gram has worked in the Clinical Supplies area during her entire professional career and is now working as a principal specialist, coaching and training colleagues in Clinical Supplies. She was a member of the first ISPE IP COP Steering Committee for five years, and returned to the Steering Committee in 2008, leading the Booklet Label Task Team.

Be sure to join us for Dr. Milligan's preliminary report on the survey during the ISPE Annual Meeting, Executive Series and Investigational Products Track, 3-6 November, Washington, DC, www.ISPE.org/2013annualmeeting.

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Good Manufacturing Practices for *Halal* Pharmaceuticals

by Kenny Peng, MASc, RAC, PEng and Roziah Hanim Abdul Karim, BS

This article presents an overview and analysis of a new national standard on *halal* pharmaceutical products, MS 2424:2012, published by Malaysia, a member of PIC/S.

In 2012, Malaysia – a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) – became the first country in the world to develop a national standard on *halal* pharmaceutical products: Malaysian Standards MS 2424:2012.[1] With an estimated 23 percent of the world's population today being Muslims,[2] this represented another significant step toward addressing the increasing demand from muslim consumers.

Halal (حلال) is a term designating an object or action as permissible according to Islamic law; on the contrary, prohibited objects or actions are termed *haraam* (حرام).[3] Most commonly used to refer to permissible foods, for example, *halal* foods must be free from pork or pork by-products, blood and blood by-products, alcohol, and animals that are not slaughtered according to Islamic principles (the method of slaughter, termed *Dhabihah*).[4]

Although modern Muslim scholars debate whether medicines should be considered in the same class as food, most acknowledge that the principles governing the use of haraam ingredients in these products still apply. Exceptions may arise when:

1. The medicine containing *haraam* ingredients is necessary for the preservation of life of the person who takes it.
2. A knowledgeable and trustworthy Muslim physician recommends such types of medicine containing haraam ingredients as necessary for critical treatment.

In November 2012, the authors published an article on the overall requirements of *halal* pharmaceuticals[5] intended for regulatory affairs professionals. This article discusses in further detail the technical considerations when implementing Good Manufacturing Practices (GMPs) with *halal* pharmaceutical products.

Scope of *Halal* Pharmaceuticals

MS 2424:2012 is a national standard published by the Department of Standards Malaysia, Ministry of Science, Technology and Innovation (MOSTI), Malaysia. According to MS 2424:2012, *halal* pharmaceuticals are required to adhere to the following aspects of *Shariah* law. *Shariah* (also *Sharia*) law is the religious law of Islam. The *Shariah* law is primarily derived from the Quran, the religious text of Islam, and from the *Sunnah* of Prophet Muhammad, which is a collection of his specific words, habits, practices, and silent approvals.

1. They must not contain any parts or products of animals that are non-*halal* or are not slaughtered accordingly.
2. They must not contain *najs*. *Najs* (e.g., use of raw materials from swine-derived sources) according to *Shariah* law are:
   - Dogs, pigs, their descendents and derivatives
   - Products contaminated or in direct contact with items that are non-*halal*
   - Any liquid and objects discharged from the orifices of human beings or animals, such as urine, blood, vomit, pus, placenta, excrement, and sperm and ova of pigs and dogs except milk, sperm, and ova of human and other animals.
   - *Maitah* or carrion or *halal* animals that are not slaughtered according to *Shariah* law
   - *Khamar* (fermented alcohol) and food or drink which contain or is mixed with *khamar*

3. They must be safe for human use: non-poisonous, non-intoxicating, or non-hazardous to health according to prescribed dosage.
4. They cannot be prepared, processed, or manufactured using equipment contaminated with *najs* (e.g., use of equipment that has been used to process products contaminated with swine-derived materials).
5. They must not contain any human parts or derivatives that are not *halal*.
6. During preparation, processing, handling, packaging, storage, and distribution, they must be kept physically separated from any other non-*halal* products and *najs*.

Except for the third point, all other points are exclusively applicable to *halal* pharmaceutical products.

Good Manufacturing Practices (GMPs) for *Halal* Pharmaceuticals

The primary objective of GMPs for *halal* pharmaceuticals is to avoid cross-contamination of non-*halal* or *najs* premises, utilities, equipment, materials, and ingredients.

Premise, Utilities, and Equipment

There is explicit requirement for dedicated facility and equipment, as well as storage and transport hardware. Potential routes of cross-contamination during production are no different than all aseptic and non-aseptic facilities, such as direct contact, air, personnel contact, etc. Therefore, for example, a filling machine that has been used to fill products containing *najs* should not be used to fill *halal* products. At the moment, there is a lack of data on acceptable residues.

The design and location of the facilities shall consider the risk of contamination with non-*halal* materials or products. For example, the premises shall be separated and well insulated from pig farming, eateries serving pork products, and avoid the possibility of cross-contamination through air, water, sewage, personnel, and equipment. Therefore, although not explicitly stated, the utilities and HVAC shall be isolated from non-*halal* production areas as well.

Ritual Cleansing

If the premises or equipment become contaminated with *najs*, they shall be washed and cleansed according to ritual cleaning methods supervised and verified by the competent authority (see section on *Competent Authority*).

In brief, ritual cleansing requires seven washes, one of which must be water mixed with soil. The soil and water shall both be free from *najs* and contaminants, as well as *musta'mal* (i.e., soil or water that has already been used for another purpose). While some Muslim scholars debate the use of substances equivalent to soil, the exclusive use of soil as an irreplaceable ingredient is widely accepted in the *halal* manufacturing industry.

MS2424:2012 refers to food-grade soil for the purpose of *halal* cleansing, which are commercially available. For pharmaceuticals application, the soil shall be sterilized prior to use to avoid any possible microbial contamination.

The ritual cleaning is not meant to result in any chemical or biological reaction to the equipment. Therefore, following ritual cleaning, the premises or equipment shall be cleaned for production use, subject to validation. Use of commercially-available food-grade soil minimizes the risk of contamination from residual soil; however, for aseptic processes or other critical processes, the introduction of soil increases the difficulty of validation. Therefore, dedicated equipment is strongly recommended. Repeated conversion of the line to *najs* and back to *halal* products is not acceptable.

Ancillary Areas

Prayer rooms shall be available. Prayer room facilities are subject to additional requirements outside the scope of MS 2424:2012; however, examples of which include nearby ritual washing facilities, free from religiously impure objects and materials, adequate space for men and women, etc.

Where applicable, animal testing facilities shall be well isolated from other areas with a separate animal entrance and HVAC. As MS 2424:2012 addresses manufacturing and handling only, there is currently no further guidelines on the animal facilities.

Materials

All materials must be clearly defined and be *halal*. This includes all starting materials, packaging materials, and any in-process lubricants or agents that may come in contact with the product. As with any GMP, adequate documentation and procedures must be in place.

All types of plants, plant products, and their derivatives are *halal except those prohibited by competent authority*.

All land animals are *halal* except for dogs and pigs, animals with long, pointed teeth intended to kill (such as tigers, bears, cats and elephants), predatory birds (such as eagles and owls), pests and poisonous animals (such as rats, cockroaches, centipedes and snakes), animals forbidden to be killed or eaten in Islam (such as bees, woodpeckers), creatures that are considered repulsive (such as lice, flies), and farmed halal animals intentionally and continuously fed with *najs*.

All aquatic animals are *halal* except for most vertebrate amphibians (such as crocodiles, turtles, and frogs), as well as animals that live in or are fed with *najs*.

In rare cases, some products may be declared *haraam* by local authorities, but not by others. The manufacturer is advised to consult with local competent bodies.

As with food products, any animal source shall be of those slaughtered according to *Dhabihah*.

Materials of Genetically Modified (GM) Origin

Whether GM materials can be considered *halal* remains under debate around the world.[6] In December 2010, an international workshop for Islamic scholars, "Agri-biotechnology: *Shariah* Compliance," held in Penang, Malaysia, declared GM foods to be *halal* as long as the sources from which they originate from are *halal*. Muslim organizations, such as the Islamic Foundation for Ecology and Environmental Sciences of the UK, however, insisted that GM material is non-*halal*.

Materials Containing Alcohol

Alcohol for consumption is *haraam*. Nonetheless, the use of alcohol is often necessary in medicines and in some manufacturing processes. Further, in some processes, alcohol is naturally present. Some scholars have argued for a defined limit, rather than zero-tolerance. However, this view remains controversial, and for international compliance, zero-tolerance is still generally expected.

The *Fatwa* Committee of the National Council for Islamic Religious Affairs Malaysia on the issue of alcohol in foods, beverages, perfumes, and medicines held a special discussion in 2011, and issued the following guidelines on 15 July 2011:

1. Alcohol derived from wine making or the fermentation process is *haraam* and *najs*.
2. Processed products not made with the intention to produce alcohol and contain alcohol below the level of one percent v/v can be consumed.
3. Products made with the intent to produce alcohol and produced using the process of fermentation and containing any amount of alcohol or distilled alcohol are *haraam*.
4. Products containing natural alcohol, such as ripe fruits, nuts or grains, or its extract, or containing alcohol produced during the manufacturing process are not *najs* and can be consumed.
5. Products containing a flavoring or coloring containing alcohol for the purpose of stabilization can be used if the alcohol was not produced through the fermentation process. The quantity of alcohol in the final product may not be intoxicating and its level shall not exceed 0.5 percent.
6. Non-fermented alcohol (industrial alcohol) used as a solvent, processing aid, or cleaning agent is not *najs*.

Quality Control

The purchase, handling, and sourcing of chemicals, reagents, apparatus, equipment, and other items required for sampling and testing shall be made from *halal* source.

Documentation

It is important to note that all records of manufacturing and quality assurance, such as incoming inspection records, batch records, non-conformance reports, vigilance reports, and CAPA, will need to be adopted for *halal* traceability purposes.

> *For pharmaceuticals, the HAS shall further ensure that the pharmaceuticals are designed and developed in a way that comply with the requirements of halal, as well as adequate, written procedures for all halal-related operations...*

Halal Assurance System (HAS)

MS 2424:2012 requires a *Halal* Assurance System (HAS) to be implemented. The HAS is a well-established requirement in the *halal* food industry. Similar to modern quality system concepts, the HAS sets forth requirements for management policy, procedures, documentation system, training programs, internal audits, corrective action system, etc., but adds requirements for administration system, socialization program (referring to the conveyance of *halal* awareness and compliance throughout the organization and stakeholders), and internal and external communication system (referring to communication among stakeholders and religious authorities). General HAS guidelines are published by such institutions as the Indonesian Assessment Institute for Foods, Drugs, and Cosmetics under the Indonesian Council of Ulama (Lembaga Pengkajian Pangan Obat-obatan dan Kosmetika Majelis Ulama Indonesia, or LPPOM MUI).[7]

For pharmaceuticals, the HAS shall further ensure that the pharmaceuticals are designed and developed in a way that comply with the requirements of *halal*, as well as adequate, written procedures for all *halal*-related operations mentioned in this article (for example, production, quality control, and ritual cleansing).

MS 2424:2012 further requires the establishment of a *Halal Committee* within the organization, which must consist of purchasing personnel and a minimum 2/3 Muslim quorum.

Competent Authority

Besides controls and inspections required by relevant pharmaceutical regulatory bodies (in the case of Malaysia, the

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National Pharmaceutical Control Bureau), *halal* products are subject to certification from Islamic competent authorities.

Countries with large Muslim populations commonly have institutionalized (sometimes nationalized) bodies designated for certification, such as the LPPOM MUI of Indonesia and JAKIM of Malaysia. In other countries, *halal* certification is granted by diverse bodies with varying degrees of mutual recognition. For example, in the UK, *halal* certification may be granted by the Halal Monitoring Committee, Halal Food Authority, and Institute of Islamic Jurisprudence, to name a few; in the US, the list includes the Islamic Food and Nutrition Council of America and Islamic Services America; in Canada, the Halal Monitoring Authority and Halal Certification Agency.

Differences Between *Kosher* and *Halal*

Kosher in Hebrew means "fit or proper for use" according to Jewish law. Similar to *halal* food, *kosher* food are subject to religious rules of slaughtering, cleaning, and acceptable source materials. While *kosher* requirements are out of the scope of MS 2424:2012, and there is currently no equivalent of MS 2424:2012 for *kosher* pharmaceuticals in the world, there are similarities from a technical perspective, although the procedural differences might be the most significant.

This article shall not endeavor to analyze the details of *kosher* requirements. The reader may refer to published sources such as Wikipedia's *Comparison of Islamic and Jewish Dietary Laws*;[8] however, some examples of major similarities include:

- Common prohibition of many animals and their derivatives, such as swine, amphibians
- Common permission of many animals, such as bovines
- Requirement for isolated premises, religious cleansing

Examples of major differences include:

- Alcohol is permitted in *kosher*
- Due to the fermentation and purification processes involved, permitted sources of gelatin and enzymes differ
- *Kosher* requires further isolation between dairy and meat products
- Religious procedures during slaughtering and cleansing

As with *halal* principles, debates exist with finer details of *kosher* principles amongst Jewish scholars. Users are always recommended to seek the advisory of competent authorities.

Conclusion

Muslims comprise a sizable portion – by some estimates, one-quarter – of the world's population today. In this article, we discussed the general technical considerations when implementing GMP with *halal* pharmaceutical products based on the world-first national standard MS 2424:2012 from Malaysia.

At the present, the manufacturing of halal pharmaceuticals is largely limited to domestic manufacturers of generic pharmaceuticals in Muslim-majority countries. The need for participation from brand-name pharmaceutical manufacturers and of major multinationals has been acknowledged by some of the original authors of MS 2424:2012 and we look forward to progress in this area.

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About the Authors

Kenny Peng, MASc, RAC, PEng, is Director of Asia for PharmEng Technology, an international consultancy based in Toronto, Canada. Born in Taiwan and educated in Canada as an engineer, he has spent his career on international projects in North America and across East and Southeast Asia, and across diverse disciplines spanning GMP engineering, validation, compliance, as well as manufacturing and commercial regulatory affairs. He can be contacted at: kenny.p@pharmeng.com.

PharmEng Technology, 3760-14th Ave., Suite 201, Markham, Ontario L3R 3T7, Canada.

Roziah Hanim Abdul Karim, BS, is Senior Manager, QA, for CCM Pharmaceuticals Division, the second-largest pharmaceutical manufacturer in Malaysia, and a member of the Technical Committee on Halal Food and Islamic Consumer Goods. She is a contributing member to the Malaysian Standard MS 2424:2012. She can be contacted at: roziah-hanim@ccmberhad.com.

Regulations and Guidelines of Computer Systems in Drug Manufacturing – 25 Years Later

by Orlando López

This article presents a regulatory review of the current requirements applicable to computer systems in the manufacturing environment.

Since 1963, the United States Food and Drug Administration (FDA) has considered validation a requirement protected by the current Good Manufacturing Practice (cGMP). The equipment, facilities, processes, and procedures used in production and control shall be properly designed and tested to ensure that the drug products have proper identity, strength, quality, and purity. As equipment, this requirement is applicable to computer systems[1] performing functions covered by the cGMP regulations and/or managing electronic records known to be required by existing regulation.

Pharmaceutical Engineering[2] presented the FDA point of view of the regulations applicable to process control computers. By 2001, the attention of the Agency to computer systems was significant. Even after publishing in 1988 the expectations of the regulator on computer systems, prominent findings during FDA inspections, such as inadequate written procedures, inadequate control of automatic, mechanical, and electronic equipment and inadequate laboratory controls[2] were recorded.

In 2001,[3] the author of this article provided an overview of the expectations of the US FDA applicable to computer systems in the regulated environment.

Since 2001, what has happened with the cGMP regulations impacting computer systems performing functions in the manufacturing environment? In addition to the regulatory changes discussed in this article, there are two improvements on computer systems performing functions in the manufacturing environment.

> Regulatory requirements for data do not change whether data are captured on paper, electronically, or using a hybrid approach.

The first improvement is systems and functional levels risk assessments to determine the GMP criticality of the system and the impact of the computer system on patient safety, product quality, or data integrity.[4] A risk assessment approach assumes that the rigor of validation of a computer system is commensurable with the risk.

The second improvement is the global manufacturing environment in the healthcare industry. Manufacturing sites that have been operating independently are faced with corporate policies that require these sites will now use particular software as specified by the corporate IT department or link existing systems with corporate systems gaining efficiencies. This approach creates networked computer systems stretched worldwide altering the approach of inspections by the regulated authorities. The regulated user obligation is to ensure and demonstrate that the system meets all the code requirements relating to the system.

Understanding the global regulatory requirements provides the expertise of the areas impacting computer systems performing worldwide regulated functions.

This article is an update of the one published in 2001. It presents an overview of the current regulatory requirements and regulatory guidelines applicable to computer systems

in drug manufacturing. This article provides the regulatory framework implemented by key regulatory authorities. The regulations and guidelines discussed in this article assist the regulated user to develop a computer system validation program consistent with recognized applicable principles of system development methodology and quality assurance that are current good practices in this global environment. A comparison of many of the following regulations and guidelines can be found online.[6]

Survey of Regulations and Guidelines (2001 – 2013)

21 CFR Part 211.68[7]

Since 1970, the FDA's attention to the computer systems performing operations covered by the drugs cGMP regulation has increased because almost all FDA regulated products are being manufactured under the control of computer systems directly impacting drug quality.

The Food Drug and Cosmetic (FD&C) Act Section 704(a), for prescription drug products, would allow inspectional access to computer systems. By 1978, the FDA addressed in Section 211.68 the total quality management of computer systems in the cGMP for Finished Pharmaceutical. Section 211.68 requires applicable cGMP controls to e-records (e-recs), application software, system software, and computer infrastructure.

The accurate implementation of this critical requirement provides the high degree of assurance the reliability, consistency, and accuracy of computer systems performing function defined by the drugs cGMP regulation. In addition to the critical requirement referenced above, 211.68(a) requires that if a computer system is used on a regulated function "it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance." This requirement is generally taken as to establish[8] a written validation and the associated maintenance procedures.

Since then, the industry practices have moved to a risk-based approach, which includes the complexity and reliability of such systems. One area to stress during the risk assessment to computer systems are the inputs and outputs (I/Os).

The updated 2008 cGMP, effective since December 4, 2008,[9] defines the applicable regulations to the computer systems as follows:

- Computer systems can be used to perform operations covered by the drugs cGMP regulation. These computer systems require a written validation process.
- Computers systems documentation and validation documentation shall be maintained.
- There must be procedural controls for managing changes to infrastructure and application software, including documentation.
- Computer systems' electronic records must be controlled including records retention, backup, and security.
- Based on the complexity and reliability of computer systems, there must be procedural controls and technologies to ensure the accuracy and security of computer systems' I/Os electronic records and data.
- Computer systems must have adequate controls to prevent unauthorized access or changes to data, inadvertent erasures, or loss.
- There must be written procedural controls describing the maintenance of the computer system, including an ongoing performance evaluation and periodic reviews.
- Specifically for Sections 211.101(c), 211.103, 211.182, and 211.188(b)(11), verification by a second individual may not be necessary when automated equipment is used as described under Section 211.68.

In addition to 211.68, Table A lists additional key sections in Part 211 pertinent to computer systems performing functions covered by the cGMP. Equivalent sections can be found in other FDA predicate regulations.

The maturity of the practices, technology improvements, and the guidelines published by the FDA and industry groups, provide the main source of regulatory innovation and the gradual progression of the Section 211.68.

Section 211.68 has a lot of possibilities to grow. For example, the author of this article considers that in the future we may see elements of the current Subpart B in 21 CFR Part 11[10] (Part 11) in Section 211.68. At that time, Subpart B may be removed from Part 11.

EU Annex 11: Computerized Systems

Eudralex Volume 4, Annex 11 (EU Annex 11[11]), which pertain to computer systems, provide guidance for the interpretation of the GMP for all European Union (EU) members. EU Annex 11 is found in Volume 4 of "The rules governing medicinal products in the European Union." Volume 4 covers the interpretation of the principles and guidelines of GMP regulated activities.

The first edition dates back to the 1992. In January 2011, the European Medicines Agency (EMEA[12]) announced the new revision of this EU Annex 11. This revision came into operation in June 2011. EU Annex 11 is strictly applicable to the EU GMP/GDP on electronic systems used in regulated manufacturing processes, although US manufacturers who wish EU market approval need to take it into account as an applicable requirement. The main principle of the EU Annex 11 states that: "The application should be validated; IT infrastructure should be qualified."

US Drugs CGMP	Description
211.22	Responsibilities of QC Unit
211.25	Personnel Qualifications
211.42	Design and Construction
211.63	Equipment design, size, and location
211.67	Cleaning and Maintenance
211.100	Written Procedures, Deviations
211.100(a)	Process control (e.g., computer systems) properly designed
211.101(c) 211.103 211.182 211.188(b)(11)	Double Check on Computers
211.105(b)	Infrastructure Hardware Identification
211.180	General (Records and Reports)
211.180(a)	Records Retention
211.180(c)	Storage and Record Access
211.180(d)	Records Medium
211.182	Use of Log(s)
211.188(a)	Reproduction Accuracy
211.188(b)	Documentation and Operational Checks
211.189(e)	Records Review
211.192	QC Record Review

Table A. Other cGMP drugs regulations applicable to computer systems.

This document then continues on with two additional principles and 17 specific recommendations for computer operations. Paragraph 4 of the annex specifically refers to the need to ensure that the software has been under an appropriate quality management system which incorporates a system development lifecycle.

Annex 11 has a much broader scope than Part 11. Speaking strictly about e-recs and electronic signatures (e-sigs), Part 11 goes beyond Annex 11. Annex 11 complements Part 11 very well, providing some specificity in areas that are left vague in Part 11. An analysis of Annex 11's Main Directive, Principle and four main clauses: Risk Management, Requirements Management, E-records Management, and Validation can be found at: http://pharmtech.findpharma.com/Lopez.[13]

At the time of writing this review, the European Compliance Academy had published answered questions concerning the first four items of the Annex 11.[14] These answered questions were provided by inspectors and industry experts during the Conference on Computer Validation from 8 - 9 June 2011 in Mannheim.

During the Pharmaceutical Inspection Co-operation Scheme (PIC/S) events in Kiev, Ukraine, 30 September - 5 October 2012, members reviewed the revision of several PIC/S GMP Guides and Annexes based on the revisions of the EU GMP Guides and Annexes. The updated EU Annex 11 on Computerized Systems was adopted and based on the revisions, the PIC/S also adopted the revision of its associated guide, PIC/S PI 011-3.[15]

Clinical Trials

Computer systems are used in clinical investigations to create, modify, maintain, archive, retrieve, and/or transmit clinical data. Computer systems range from isolated pieces of equipment that are used at a clinical site to collect/archive clinical data to complex integrated systems that consist of a variety of hardware, firmware, and software components that are located at multiple sites such as web-based systems managed by an independent software vendor to which the sponsor and clinical sites have controlled access.

CPG 7348.810 – Sponsors, CROs, and Monitors and EMEA Procedure

CPG 7348.810 provides instructions to the field and Center personnel for conducting inspections of sponsors, Contract Research Organizations (CROs), and monitors, and recommending associated administrative/enforcement actions.[16] One area of advice to the field inspectors in this CPG is basic principles on e-recs.

- The regulatory requirements for the clinical data do not change whether clinical data are captured on paper, electronically, or using a hybrid approach.
- Only certain electronic records will be subject to Part 11 and the Agency intends to exercise enforcement discretion with regard to specific Part 11 requirements.

When assessing compliance with Part 11, any discrepancies should be documented under the appropriate predicate rule requirement. In the context of Part 11, this CPG provides guidance on key issues such as: Scope of electronic records/electronic signatures; procedures; data collection; and security.

The EU GCP inspectors agreed in November 2007 to use PIC/S PI 011-3 as the reference for inspection of computer systems in clinical.

Some computer systems inspection essentials on clinical applications were published by EMEA (EMEA/INS/GCP/197221/2005) for the EMEA and EU/EEA Inspectorates on the "Procedure for the Conducting GCP Inspections Requested by the EMEA: Sponsor Site and/or CROs." This

procedure compiles the main aspects, including computer systems inspection approach, that are to be verified at sponsor site or at a CRO performing sponsor's trial related duties during a GCP inspection requested by the EMEA.

Specifically on operating procedures, the inspector must:

- Review the validation of computer systems used in safety and adverse events reporting
- Review the validation of computer systems used and audit trails in the data handling and clinical trial report
- Audit data management, archiving, computer validation activities, and audit trails on sponsor audit and quality assurance system

On specific clinical trial inspections and computer systems, the procedure requires inspections in the data handling and clinical trials report (CTR):

- Data tracking from CRF to the database
- Validation of the computer systems used
- Data management
- If applicable, e-signs

Even the procedure is applicable for the EU, it can give an indication of what an inspection on computers applicable to clinical trials may be in other inspectorate.

Electronic Source Data in Clinical Investigations

According to the draft US FDA November 2012 guidance document,[17] the initial documentation of data in a clinical study is considered "source" documentation or "source" data. The originator or recorder may document the data either on paper or electronically.

This draft provides directions on the reliability, quality, integrity, and traceability of electronic source data and source records captured, used, and archived electronically in FDA-regulated clinical investigations.

This guidance refers to two other e-recs related guidelines: Computerized Systems Used in Clinical Investigations and Part 11.

FDA Inspections of Clinical Investigations

The Information Sheets Guidance for IRB's, Clinical Investigators, and Sponsor's – FDA Inspections of Clinical Investigators, published on June 2010,[18] provides guidance on refer-

ence materials around Part 11 to the field investigators. The three references provided are:

- Part 11
- Part 11, Electronic Records; Electronic Signatures – Scope and Application (Part 11 Guidance)[19]
- Computerized Systems Used in Clinical Trials

All of these references are discussed elsewhere.

Computerized Systems Used in Clinical Investigations

Based on the FDA, Part 11 Guidance, the Computerized Systems Used in Clinical Trials guidance document[20] explains the implementation of Part 11 applicable to clinical trials computer systems.

Specifically, the document applies to computer systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained, or submitted to the FDA, in electronic format.

Computer Systems Used in Medical Device Clinical Investigations

The intent of FDA's regulatory requirements and guidance to Medical Device Clinical Investigations computer systems[21] is to ensure that electronic records used in clinical investigations are accurate, complete, and current. FDA Regulatory Requirements:

- 21 CFR 812.140(a) requires that participating Clinical Investigators maintain "accurate, complete, and current records relating to the Investigator's participation in an investigation."
- 21 CFR 812.140(b) requires Sponsors to maintain "accurate, complete, and current records relating to an investigation."

Like many other guidance documents, the key elements are security, retention of records, audit trails, and SOPs to manage computer systems use in clinical trials. These requirements are important because data is used to support a product's safety and effectiveness. These are critical elements to consider during the assessment of the project risks.

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

This is a December 2009 US FDA Guideline[22] applicable to review and evaluation of existing, modified, or newly created Patient-Reported Outcome (PRO) instruments used to support claims in approved medical product labeling.

Part 11 is applicable for ePRO systems. Because ePRO data (including data gathered by personal digital assistants or telephone-based interactive voice recording systems) are part of the case history, electronic PRO data should be consistent with the data standards described in this guidance. Sponsors should plan to establish appropriate system and security controls, as well as cyber-security and system maintenance plans that address how to ensure data integrity during network attacks and software updates.

Sponsors also should avoid the following:

- Direct PRO data transmission from the PRO data collection device to the sponsor, clinical investigator, or other third party without an electronic audit trail that documents all changes to the data after it leaves the PRO data collection device.
- Source document control by the sponsor exclusively.
- Clinical investigator inability to maintain and confirm electronic PRO data accuracy. The data maintained by the clinical investigator should include an audit trail to capture any changes made to the electronic PRO data at any point in time after it leaves the patient's electronic device.
- The existence of only one database without backup (i.e., risk of data corruption or loss during the trial with no way to reconstitute or verify the data).
- Ability of any entity other than the investigator (and/or site staff designated by the investigator) to modify the source data.
- Loss of adverse event data.
- Premature or unplanned access to unblinded data.
- Inability of an FDA investigator to inspect, verify, and copy the data at the clinical site during an inspection.
- An insecure system where records are easily altered.
- Direct PRO data transmission of important safety information to sponsors, clinical research organizations, and/or third parties, without ensuring the timely transmission of the data to the clinical investigator responsible for the patients.

Blood Establishments

Blood Establishment Computer System Validation in the User's Facility

This draft guidance document[23] was originally written in 1993, revised as a draft again in 2007, and finalized in April 2013.

Since blood and blood components are defined as drugs in the FD&C Act, the CGMP in 21 CFR, Parts 210 and 211, are applicable. This guidance document is intended to be used in conjunction with the applicable federal standards in 21 CFR, Parts 600 through 680, and Parts 210 and 211, as they pertain to biological products for human use.

In addition, blood bank software products are medical devices. Therefore, the medical devices 21 CFR 820 regulatory requirements for software (that is itself a medical device) are applicable.

As in many US FDA computer systems validation guidance documents, the component highlighted in this blood establishment guidance document is computer systems validation program. The program, when executed correctly, establishes and demonstrates:

- Proper performance
- Proper implementation of the functions to be performed
- The way in which it will interact with both manual and automated operations
- Data integrity

Irrespective of the source of the software model (acquirer,[24] supplier,[25] or developer[26]) the development of the computer system should follow accepted standards for System Life Cycle (SLC) including, but not limited to, proper design, software validation and verification procedures, change control, and detailed documentation.

Regulated users must ensure that the computer systems are either assessed for compliance to the applicable regulatory requirements or that compliance is built into the system during its development and implementation.

The 1993 draft version of this guidance document makes reference to the implementation of audit trails as part of the functionality of blood bank software. "An audit trail documents changes made to the data. Audit trail records are part of the system's documentation and should only be accessible or reviewed by authorized persons (e.g., identified establishment personnel, FDA Investigators). Audit trails can be used to record access to the system. Each time an authorized or unauthorized user tries or gains access to the system there should be a log entry. At a minimum, an audit trail should include:

- The name of the person making the change
- Date
- Time
- Field name
- Previous data
- Current data

A similar note can be found in the 2007 draft version.

PIC/S PE-005-3 establishes guidelines to the GMP-inspectors to use during inspections of blood establishments' computer systems. These guidelines can be found from section 9.8 to section 9.13.

- The hardware and software of the computers should be checked regularly to ensure reliability. The software (program) should be validated before use.
- Computer hardware and software should be protected against use by unauthorized persons. The users of computers should be trained and should be authorized only to

handle data required for the task(s) they perform.
- There should be documented procedures for backup protection against loss of records in the event of planned and unplanned function failures.
- A procedure should define the routine action taken in the event of breakdown. Checks of these actions should be performed at least once a year.
- Changes to computerized systems (hardware, software, or communication) should be validated, applicable documentation revised (if appropriate), and personnel trained before the change is introduced into routine use. Only authorized persons should make changes to software.
- Records of the changes to computerized systems (hardware, software, or communications) should be retained for at least ten years.

Note that records retention schedules for blood establishments mentioned in the PIC/S PE-005-3 may vary in the FDA applicable regulations. Refer to 21 CFR Part 606.

Blood Establishment Computer Crossmatch

This guidance was published in April of 2011. "Computer crossmatch" is a process used to ensure that the blood released for transfusion is compatible with the intended recipient. The US FDA considers computer crossmatch an acceptable method of compatibility analysis when it is properly designed, validated, implemented, monitored, and maintained.[27]

The use of a computer reduces the risk of human error through the use of software controlled decision-making. However, the use of the computer crossmatch requires a high degree of testing and validation to ensure accuracy.[21] CFR Part 211.68, as discussed above, is applicable to these systems.

Tissues

Current Good Tissue Practices

Published in December 2011, this FDA guidance document titled Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) provide guidance on compliance with 21 CFR Part 1271, Current Good Tissue Practice.[28]

Current good tissue practice is the requirement in subparts C and D of 21 CFR Part 1271. It governs the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including, but not limited to, all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution.

Part 1271.160(d) refers to computers performing operations under the core CGTP requirements. CGTP provides guidance on computer system validation, verification, and documentation.

- Software must be validated for its intended use.
- Custom software or commercially available software that has been customized or programmed for you must be validated.[29]
- Off-the-shelf software that has not been modified must be verified.[30]
- Validation/verification activities must be approved and documented before implementation.

Some of the topics specific to computers and software throughout the guidance document are:

- Section VII (Procedures) Part B allows for electronic (rather than physical) access to SOPs.
- Section XVII (Storage) Part A gives an example of using a validated system to quarantine HCT/Ps.
- Section XIX (Records) Part C provides guidance on backing up electronic records and discusses when you can and can't destroy original paper records.
- Section XVI (Label Controls) Part A allows for electronic (rather than hard copy) retention of electronic labels.

WHO

As part of GMP guidelines on validation, the World Health Organization (WHO) published in 2006 Technical Report 937, Annex 4 in Appendix 5 covering the computer systems validation.[31]

In addition to the maxims provided by similar guidelines on computer systems validation, this particular guideline provides in Section 3.3 "general Good Manufacturing Practice (GMP) requirements" applicable to computer systems in a post-validation program:

- Verification and revalidation – after a suitable period of running a new system it should be independently reviewed and compared with the system specification and functional specification.
- Change control – alterations should only be made in accordance with a defined procedure which should include provision for checking, approving, and implementing the change.
- Checks – data should be checked periodically to confirm that they have been accurately and reliably transferred.

Electronic Records/Signatures

Approved in 1997, Part 11 regulation allows the use of electronic records and electronic signatures for any record that is required to be kept, maintained, and submitted electronically by other FDA regulations. Part 11 and equivalent regulations allow signing electronic records using electronic signatures. Benefits for regulated user firms are increased overall efficiency and reduced costs for handling and storing

paper records. Records which are electronically maintained following the provisions of Part 11 are recognized as equivalent to traditional records. In addition, electronic signatures used as per the provisions of this regulation will be equivalent to full handwritten signatures and initials, unless specifically exempted by regulations issued after the effective date of the regulations.

In August 2003, the FDA published its final interpretation of Part 11 in the Part 11 Guidance.[32] Section III stated that the FDA intends to interpret the scope of Part 11 narrowly and to exercise enforcement discretion with regard to Part 11 requirements to:

- Validation of computerized systems
- Use of computer-generated, time-stamped audit trails
- Use of legacy systems
- Generation of copies of records
- Protection of records (i.e., record retention and availability)

Section III B. 2 in the Part 11 Guidance, provides the scope of Part 11. Part 11 is applicable to the following electronic records and electronic signatures:

- Records that are required to be maintained under the predicate rules and that are maintained in electronic format in place of paper format
- Records that are required to be maintained under the predicate rules, that are maintained in electronic format in addition to paper format, and are relied on to perform regulated activities
- Records that are submitted to FDA, under predicate rules, and that are in electronic format
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, or other general signings that are required by the predicate rules

Asked to comment on the status of the 2003 guidance, Erica Jefferson, an FDA press officer, told *GxP Lifeline:* "There are currently no plans to update the guidance. We are still performing inspections per the 2003 guidance."[33]

Since the approval of Part 11, it was clear that Part 11 is not essential to establish the controls for electronic records for the reason that the correlation with specific regulatory requirements in the predicate rules. For example, the elements contained in 21 CFR 11 Subpart B, Electronic Records, bring together all applicable requirements to computer systems in Part 211.[34]

As in Part 211, a similar analysis to other predicate rules provides the same results. The analysis demonstrates that FDA regulatory expectations on regulated e-recs are embedded in each predicate rule and that Part 11 Subpart B is not necessary.

With the on-going evaluation of Part 11, including the Part 11 Guidance, the consideration of the software as a record within the context of the cGMP regulations is under scrutiny. In the context of cGMPs, the software should not be considered as an electronic record. The regulated industry and the FDA had to work for many years on developing approaches to deal with software in the cGMPs regulatory environment. These approaches are based on validation of computer systems, configuration management, and adequate procedures and plans for maintaining the validated state. The focus of the software should be placed on accuracy of the system related to the intended use, security, access, design reviews, documentation and, specifically for medical device software, accuracy of reproduction. These approaches are consistent with the applicable predicate regulation.

To the World Health Organization,[35] software is considered a record. To the majority of regulated bodies around the world, all regulatory principles which apply to equipment apply to both hardware and software.

On July 2010, the US FDA officially announced that it would focus on Part 11 in a series of inspections.[36]

With this measure, the FDA intends to find out how the Part 11 requirements are currently implemented by the industry. These inspections are based on the Part 11 Guidance.

OMCL Network of the Council of Europe[37]

Under the auspice of the European Directorate for the Quality of Medicines and Healthcare, the Validation of Computerized Systems, Core Document and three Annexes were published, defining the basic principles for the validation of computer systems used within the Official Medicines Control Laboratories (OMCL) with impact on quality of results.[38-41]

These four documents cover in-house and commercial software for calculation, database computer systems, Laboratory Information Management Systems (LIMS), Electronic Laboratory Notebooks (ELN), and computers as part of test equipment.

Like many other guidance, it establishes that "validation is to guarantee the confidence in scientific results obtained with each computerized system. A validated system ensures accurate results and reduces the risk of failure of the system."

IPEC Good Manufacturing Practices Audit Guideline for Pharmaceutical Excipients

The International Pharmaceutical Excipients Council (IPEC) published in 2008 an Audit Guideline[42] designed as a tool to assist in evaluating the manufacturing practices and quality systems of excipient manufacturers. It is also a reference to assist excipient manufacturers in meeting appropriate Good Manufacturing Practice (GMP) requirements to assure consistent product quality.

Section 6.3.2.3 in the Audit Guideline refers to computers. The questions in the audit guideline related to computers are:

- If computerized systems are used in a manner that can impact excipient quality, have they been demonstrated to consistently function as expected?
- What process is used to control changes to systems and programs that can have an effect on the quality of the product to assure that changes receive the proper review and approval with regard to potential effects before being instituted and that only authorized personnel can make such changes? Are personnel trained subsequent to changes?
- How is access to computerized systems limited in order to protect records from tampering, and prevent data alteration?
- If passwords are used as a security measure, are there provisions for periodic changing of passwords? Are there designees for all critical system operations and emergencies?
- What is the procedure for reviewing and updating security access when a person leaves the department or company? Is their access to the system or their access codes to the system revoked in a timely fashion?
- What backup systems are in place, such as copies of programs and files, duplicate tapes, or microfilm, and has retrievability of information from master tapes and backup tapes been verified? Are there procedures in place for disaster recovery, in the event of a power outage, loss of server and computerized systems, etc.?

EMEA's Answers to FAQ on Computerized Systems

Based on the framework of the updated EU Annex 11, the EMEA published answers to questions on computerized systems under "Q&A: Good Manufacturing Practices (GMP)."[43] The main topics are:

- Requirements for spreadsheets
- Data security of databases
- Risk management in the system lifecycle
- Use requirements as part of the retrospective validation of legacy systems
- Revalidation of computerized systems
- Storage time of electronic data and documents
- Validation efforts for small devices
- Alternative controls in case a system is not capable to generate printouts

The guidance around one of the critical issues in computer systems in the regulated industry, risk management, states:

"Risk management should be applied throughout the whole lifecycle. A first risk assessment should be performed to determine the GMP criticality of the system. Does the system have an impact on patient safety, product quality or data integrity. User requirement specifications usually are developed with consideration of potential risks and form the basis for the first formal risk assessment.

Complex systems should be evaluated in further more detailed risk assessment to determine critical functions. This will help that validation activities covers all critical functions. Risk management includes the implementation of appropriate controls and the verification of them."

API

Guidance Computer Validation API (CEFIC)

Based on ICH Q7, the European Chemical Industry Council or Conseil Européen des Fédérations de l'Industrie Chimique (CEFIC) Task Force Computer Validation published a CSV best practice document in December 2002.[44] The guidelines addressed the specific issues applicable to computer systems in the Active Pharmaceutical Ingredient (API) production control and data handling situations.

Underlining the validation of computer systems, it stressed in the compliance of critical key points to be considered:

- Proven fit for purpose
- Access control/user management
- Data integrity including prevention of deletion, poor transcriptions, and omission
- Authorized/unauthorized changes to data and documents
- Critical alarms handling (process)
- Audit trails
- Disaster recovery/back-up and retrieval
- System maintenance and change control
- Training

The validation of computer systems "must be integrated using the SLC approach, and clearly identified in the user requirements phase for any new computerized systems."

Other Regulatory Bodies

Australia

Applicable computer systems regulations and guidelines in the Therapeutic Goods Administration (TGA) are:

- Medical Products – Chapter 4 section 4.9 in the TGA Code of GMP and its Annex 11
- API's – Q7A Good Manufacturing Practice Guidance for API, Part II section 5.4
- Medical devices -- IEC 62304: Medical device software – Software life cycle processes

Of a great relevance is Section 4.9 in the TGA GMPs. It provides the expectations of TGA's inspectors on electronic records.

> *"Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention."*

Brazil

There are two important elements describing the components applicable to computer systems performing regulated functions applicable to medicinal product in Brazil. The regulations on computer systems performing good manufacturing practice of medicinal products in Brazil are contained in Title VII Resolution of the Executive Board No. 17, Computerized Information Systems.[45]

These regulations, from April 2010, are very comprehensive and similar to the recent EU Annex 11. At the same time, in April 2010 Anvisa[46] published the "GUIA DE VALIDAÇÃO DE SISTEMAS COMPUTADORIZADOS" or Computerized Systems Guideline.

This guide was developed to assist in the management and validation of computerized systems which have an impact on GxP. The accuracy and integrity of data records are essential to the life cycle of the product, from the area of research, through pre-clinical and clinical studies, quality control and production to distribution and storage area.

As all current computer systems validation methodologies, this guideline provides a risk-based approach to validate computer systems. Part 11 and the Part 11 Guidance are referenced.

Canada

The Canadian GMPs (GUI-0001) applies to pharmaceutical, radiopharmaceutical, biological, and veterinary drugs. Regarding computer systems, these are subject to documented validation. The main guidelines are the PIC/S Annex 11 for Computerized Systems, PE 009-6 April 2007. PE 009-6 is similar to the 1992 EU Annex 11.

As evidence of compliance to the appropriate regulatory quality system requirement, Health Canada requires medical

device manufacturers to be certified in a quality system. ISO 13485 is the Health Canada standard providing a comprehensive management system for the design and manufacture of medical devices. The provisions in Section 7.5.2 in ISO 13485, Validation of processes for production and service, are associated with software validation; regulated organizations shall establish documented procedures for the validation of the application of computer software (and changes to such software and/or its application) for production and service provision that affect the ability of the product to conform to specified requirements. Such software applications shall be validated prior to initial use.

The specifics related to Section 7.5.2 in ISO 13485 are contained in ISO 62304 and ISO 12007. According to ISO 12207 Systems and software engineering, software life cycle processes are an international standard for software lifecycle processes. It aims to be the standard that defines all the tasks required for developing and maintaining software. ISO 62304 Medical Device Software – Software Life Cycle Processes is an international standard which specifies life cycle requirements for the development of medical software and software within medical devices.

China

The most recent Chinese GMP for Drugs requirements defined by the State Food and Drug Administration, P.R. China (SFDA) went into effect on March 1, 2011. As in many GMPs, computer systems are considered equipment.

Article 95 states automated or electronic equipment used in production, packaging, and storage should be regularly calibrated and checked according to procedures, in order to ensure their proper functioning. Calibration and checks should be recorded accordingly. Based on the above, Chapter 5 in the Chinese GMP, Equipment contains the requirements for computer systems.[47]

In addition, there are two articles specifically applicable to computer systems. Article 109: Where computerized storage systems are used, operation procedures should be in place to prevent mix-ups and errors of materials and products in cases of system malfunction or outage, etc. Where fully computerized storage systems are used for identification, the information of materials and products may not be necessarily labeled in a written form.[47]

Article 241: Operation procedures should be established to define the request, assessment, review, approval, and implementation of changes in starting materials, packaging materials, specifications, testing methods, operation procedures, premises, facilities, equipment, instruments, manufacturing process, and computer software. The quality management department should assign a designated person to take charge of the change control.[47] China plans in 2013 to comply with the EU GMP guidelines.

Japan

Japanese's GMP requirements are defined by the Pharmaceuticals and Medical Devices Agency (PMDA). Similar to PIC/S PI 011-3, the Japanese requirements on computer systems in the area of GMP are established in the "Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-Drugs."[48]

Conclusion

The FDA and other worldwide bodies increased attention to computer systems in 1988, when the use of computers became part of drug manufacturing and controlled processes impacting drug quality. The records created and maintained by such computer systems are used to demonstrate the quality of products.

This article presented a regulatory review of the current requirements applicable to computer systems in the manufacturing environment. Notice the great amount and the quality of the regulatory requirements and regulatory guidelines provided by the worldwide regulatory bodies.

One of the significant differences between computer systems validation regulations and regulatory guidelines of 2001 and 2013 is that today's regulatory practices and guidelines require a risk-based approach throughout the lifecycle of computer systems taking into account patient safety, product quality, and data integrity. The regulatory framework in many of the current computer related regulations and guidelines are:

- Computer systems performing regulated function must be suitable for its intended purpose, maintained appropriately and technically applicable for use, to give assurance that product is manufactured to required specifications.
- Comprehensive procedures relating to the computer system in use should be available.
- The validation of a computer system is based on the applicable SLC.
- All changes to computer systems and electronic records must only be made in a controlled manner in accordance with a defined procedure.
- Regular back-ups of all relevant electronic records (e.g., batch records electronically stored) should be done.
- Electronic records are readily available throughout the period of retention.
- The accuracy of the electronic records should be checked.
- Physical and/or logical controls must be in place to restrict access to computer systems and electronic records to authorized persons.

These are important activities that together help to support a final conclusion that software is validated. The regulations

and guidelines assist the regulated user to develop a computer system validation program consistent with current recognized principles of the applicable system development methodology and quality assurance that are current good practices. It is very important that the regulated user keep track of updates to the applicable regulations and guidelines.

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About the Author

Orlando López is a Software Quality Assurance Specialist. He has more than 20 years of experience within pharmaceutical and medical devices manufacturers. He is the author of two books: "21 CFR Part 11 – "A Complete Guide to International Compliance," published by Sue Horwood Publishing Limited and "Computer Infrastructure Qualification for FDA Regulatory Industries" published by Davis Healthcare International Publishing (www.suehorwoodpubltd.com). He can be contacted by email: olopez6102@msn.com.

Global Regulatory News

International

CFDA Commissioner Zhang Yong Meets the Delegation of Swedish Ministry of Health and Social Affairs[1]

On 16 April 2013, Zhang Yong, Commissioner of China Food and Drug Administration (CFDA), met with the delegation led by Goran Hagglund, the Swedish Minister for Health and Social Affairs, and Lars Freden, the Swedish Ambassador to China. Both sides exchanged ideas on strengthening cooperation in the field of food and drug supervision. Directors of CFDA's relevant departments attended the meeting.

US FDA's Collaboration with Chinese Partners Gets Stronger Each Year[2]

The US Food and Drug Administration's (FDA) collaboration with China, which began in 2007 with the first high level talks, has been strengthened to better address challenges to consumer and patient safety in years to come. Much of this strengthening and maturing has happened through day to day collaboration between US FDA's China Office and the China Food and Drug Administration. Officials from both agencies met in April to clarify the deep collaboration between FDA and CFDA across more than a dozen topic areas.

EU Issues Questions and Answers on Agreement between Israel and the EU on Conformity Assessment and Acceptance of Industrial Products[3]

The EU issued a two-page document in question and answer format outlining the agreement between Israel and the EU on conformity assessment and acceptance of industrial products. The document can be found at: http://ec.europa.eu/health/files/international/2013_qa_israel-eu.pdf.

PIC/S

Turkey Applies for PIC/S Membership[4]

On 3 May 2013, Turkey's Medicines and Medical Devices Agency applied for PIC/S membership. The Rapporteurs were expected to be appointed at the PIC/S Committee Meeting on 28-29 May 2013 in Geneva.

Mexico Applies for PIC/S Pre-accession Membership[5]

On 7 May 2013, Mexico's Federal Commission for the Protection from Sanitary Risks – Ministry of Health applied for PIC/S pre-accession membership. The Rapporteurs for this pre-accession were expected to be appointed at the PIC/S Committee Meeting on 28-29 May 2013 in Geneva.

Asia/Pacific Rim

China

China Obtains ISO/TC150/SC7 Voting Rights[6]

On 26 March 2013, the secretariat of the Tissue Engineered Medical Products Subcommittee of the National Technical Committee on Implants for Surgery and Orthopedic Devices of Standardization Administration of China received the notification of the International Organization for Standardization (ISO), declaring that China has registered as a P-member of the ISO/TC150/SC7 (International Organization for Standardization/Technical Committee 150 for Implants for Surgery/Sub Committee 7 for Tissue Engineered Medical Products) and obtained the ISO/TC150/SC7 voting rights.

Japan

Japanese MHLW Joins Japan's First Public-Private Partnership to Facilitate the R&D of New Health Technologies for the Developing World[7]

The Ministry of Health, Labour and Welfare (MHLW) of Japan supports the research and development of new health technologies for the developing world, through financing the United Nations Development Programme and collaborating with the Global Health Innovative Technology Fund, a non-profit organization based in Japan that announced its establishment on April 8.

Road Map for the PMDA International Vision[8]

While the Pharmaceutical and Medical Devices Agency (PMDA) presently conducts its international activities based on the "PMDA International Strategic Plan" and the "PMDA International Vision," the agency has decided to establish a "PMDA International Vision Roadmap" for more specific action plans to achieve the goals indicated in the Strategic Plan and the Vision prior to the development of the

Third Mid-term Plan in order to meet future challenges in the constantly evolving international environment.

Europe

European Union

EMA Publishes its Work Program for 2013[9]

The European Medicines Agency (EMA) work program for 2013 focuses on new legislation and increased efficiency and transparency.

European Commission Introduces Quality Risk Management into Revised Guideline on Good Distribution[10]

The European Commission (EC) published a revised Guideline on Good Distribution Practice (GDP) on 7 March 2013. The effective date for its implementation is 8 September 2013. The new guideline revises one that had been in place for 19 years and introduces a number of new requirements. It is the first time that the EMA has introduced Quality Risk Management to GDP. There also is greater emphasis on computer validation and expanded focus on quality systems.

EMA Releases Guideline on Similar Biological Medicinal Products[11]

This Guideline describes and addresses the application of the biosimilar approach, the choice of the reference product, and the principles of establishing biosimilarity.

Details on EMA Reorganization[12]

The first details of the planned reorganization of the EMA have been announced. Rooted firmly in the Agency's overall public- and animal-health mission, the changes reflect a renewed focus on three key elements:

- how to better support the scientific work of the EMA committees
- how to better share the data the Agency holds
- how to better meet the needs of its stakeholders and partners

EMA Issues Six Key Recommendations to Tackle the Issue of Medication Errors[13]

The EMA has issued six key recommendations to tackle the issue of medication errors causing harm in the EU. These recommendations are described in the medication-errors workshop report, which can be found at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf.

Six key recommendations resulted from the discussions. These are to progress:

- the harmonization and further development of terminologies and definitions of medication errors at EU and international levels
- the establishment of collaborative relationships between national patient safety authorities, national regulators, the EMA and the European Commission
- the development of new methods to identify medication errors from a patient-safety and pharmacovigilance perspective through data pooling and analysis
- the systematic assessment and prevention of the risk of medication errors during the life-cycle of a medicine, including prior to granting marketing authorization through the EU risk-management planning process
- active engagement and capacity building with patient and consumer groups and healthcare professionals to improve safe medication practices
- support to research into safe medication practices

Estonia

Overview of Changes to the Estonian Medicinal Products Act[14]

On 27 March 2013, the plenary session of the Riigikogu adopted an amendment to the Medicinal Products Act initiated by the Government of the Republic. In this connection, the Penal Act, Act on Narcotic Drugs and Psychotropic Substances and Precursors Thereof, and State Fees Act will also be changed. The consolidated text of the amended Medicinal Products Act was published in the State Gazette on 17 April and the Medicinal Products Act entered into force 10 days after publication.

The expected impact of the amendment is, based on the transposition of Directive 2011/62/EC, prevention of falsified medicinal products. For this purpose, additional requirements and obligations have been introduced mainly for holders of activity licenses for manufacture and wholesale trade in medicinal products, holders of activity licenses for pharmacy services, and the State Agency of Medicines.

Great Britain

Medicines and Healthcare Products Regulatory Agency Launches its 2013-2018 Corporate Plan[15]

The corporate plan sets the strategic direction for the next five years; frames how MHRA works with its stakeholders; and creates a structure for work, flowing into annual business plans.

North America

Canada

Summary of the Canadian Quality System Framework[16]

The Quality System Framework (QSF) outlines a quality system approach for compliance and enforcement activities shared by Health Products and Food Branch and Regions and Programs Bureau of Health Canada. This quality system, under the mandate of the Health Products and Food Branch Inspectorate, was developed and implemented to ensure strong functional linkages, fairness, consistency and a high standard for quality in all Inspectorate program activities. For a

complete copy of the QSF contact the Quality and International Assessment Division at: http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/insp-quality_qualite-eng.php.

United States

US FDA Publishes Budget Request for Fiscal Year 2014[17]

The US FDA is requesting a budget of $4.7 billion to protect and promote the public health as part of the President's fiscal year (FY) 2014 budget. Industry user fees would fund 94 percent of the proposed budget increase, including new fees to support the landmark Food Safety Modernization Act (FSMA) and strengthen the FDA's ability to oversee imported food. The remainder of the budget increases would support programs which are necessary to preserve the safety of medical products and meet the agency's growing duties. Recognizing the need for fiscal constraint, the budget includes spending cuts in several areas, including a $15 million decrease in budget authority for human drug, biologics, and medical device programs.

US Senate Committee Releases Draft Proposal on Pharmaceutical Compounding[18]

Following the recent illnesses and deaths from contaminated compounded drug products, a bipartisan group of Health, Education, Labor, and Pensions (HELP) Committee Senators have released draft legislation. Their proposal would help improve the safety of compounded human and animal drugs by making clear the oversight responsibilities of state and federal authorities.

US FDA Commissioner Gives Speech on "Using a Public Health Approach to Regulatory Processes"[19]

US FDA Commissioner Dr. Margaret Hamburg addressed the Gates Foundation Product Development Partnership (PDP) Forum on the importance of using a public health approach to regulatory processes. The speech can be found at: http://www.fda.gov/NewsEvents/Speeches/ucm350743.htm.

US Official Testifies on Pharmacy Compounding[20]

Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, US FDA, testified before Congress on the topic of drug compounding. In light of the recent fatal outbreak of fungal meningitis associated with this practice, she provided an historical overview of pharmacy compounding, what FDA has learned in the past year, and the use of a risk-based approach to identifying pharmacies that are most at risk.

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Innovative Mixing Technology

by Gabriela Mikhaiel

This article discusses fundamental challenges in powder mixing and an innovative mixing technology aimed to improve blending processes.

The mixing of powders is a common and critical element of many solids processing industries. Many challenges have to be overcome not only in terms of safety and hygiene, which are of paramount importance, but also to achieve the best possible homogeneity knowing that a perfect blend of two or more components is very difficult to achieve.

The aim of each mix or blend is to obtain a uniform distribution of all components. The lower the variation of the composition of a sample in comparison to the same amount of powder of the mixture, the better the quality of the mixing.

Statistically, however, perfect homogeneity is unlikely to be achieved. At best, one achieves a random mixture, i.e., a mixture, in which the probability of finding a particle of any component is the same at all locations and equal to the proportion of that component in the mixture as a whole (stochastic homogeneity) - *Figure 1*. This type of mixture generally achieves the best results, provided the different powders have the same physical properties, according to Rhodes.[1]

However, different product properties can lead to segregation. With significant loss in quality when mixing solid materials, the pharmaceutical industry is particularly concerned with the problem of particle segregation. Williams says that one of the most common causes of segregation consists in the motion behavior of particles with different particle size and density, namely segregation by percolation of fine particles.[2]

The Selection of a Mixer

Segregation must be balanced by the mixing principle with respect to an ideal distribution. An ideal blending system achieves statistically the best possible distribution. When selecting a blending system, it is therefore important to choose the type of mixer that is able to compensate for the different properties of the mixed particulate solids.

Mixing Mechanisms by Lacey[3]

1. **Diffusive mixing** – this type of mixing includes blenders, which move the particles by rotation, e.g., drum, double-cone, and V-blenders.
2. **Shear mixing** – the mixing occurs in slip zones between the powder. This category includes rotor mixers.
3. **Convective mixing** – the mixing process takes place by the circulation patterns within the powder, e.g., through rotating paddle systems. One of the most common convective mixers is the ribbon blender.

Although there are more or less suitable mixers for individual product characteristics, most conventional systems tend to have limitations and disadvantages, such as product loss, powder abrasion, and weak containment and are inflexible with respect to the batch sizes. With these issues, industry is seeking solutions that move away from traditional batch process engineering to improve operating and economic efficiency. The future lies in semi-continuous and continuous blending systems.

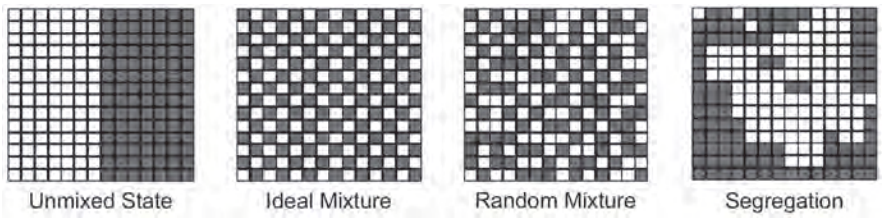

Figure 1. Mixing progressions.

New Developments in Blending Processes

With the aim of improving and/or removing the current blending issues, DEC developed an in-line mixing system to blend active substances without modifying their physical properties and without the risk of contamination for operators and environment. Based on Powder Transfer System (PTS) technology, the system transfers, mixes, and discharges products fully automatically by means of vacuum and pressure under inert conditions. It is especially suited to meet the needs of the pharmaceutical industry and offers the possibility to mix hygroscopic, oxygen sensitive, or explosive powders.

Flexible Scope of Application

With the same unit, different batch sizes can be run, from laboratory scale to large scale production. The mixing system blends powders with large differences in blend ratios (1/10,000) and different properties, ensuring homogeneity and high containment.

This technology is easy to integrate into production lines. Powders can be transferred automatically from drums, sacks, or from process equipment (e.g., a dryer, etc.).

Operating Principle

The system comprises a main mixing vessel with an integrated central deflector, allowing a homogeneous powder distribution. A PTS consisting of a cylindrical chamber with two tangential inlets is installed on top of the tank.

The blender is further equipped with pneumatic valves that are connected to a pneumatic or an electro-pneumatic control cabinet. The PTS chamber is filled and emptied in a cyclic manner by alternating vacuum and pressure. The powders are introduced automatically into the PTS chamber by the opening of one inlet valve, the vacuum valve, which is connected to the vacuum pump and one of the two 3-way-valves. The chamber is emptied by the opening of the outlet valve and the pressure valve for compressed air or nitrogen to dispense the powder over the deflector into the main vessel. Once the powders are all introduced in the main receptacle, the mixing process starts by circulating and conveying the powder again upwards through two mixing pipes into the PTS body where the two jets of product meet, enhancing the efficiency of the mixing process to be emptied back again into the mixing tank.

A flat filtration membrane in the upper part of the PTS prevents fine particles from entering the vacuum system. In order to guarantee its suction capacity through the cycles, this membrane is cleaned with each emptying cycle in a counter current fashion by compressed air or inert gas.

The materials are transferred in dense phase mode and as the speed at which the powders are circulated is limited, particles are not damaged or subject to attrition.

After mixing, the system can be automatically discharged and the mixed powder is conveyed through the bottom towards the next process step by another vacuum source.

Blending Effectiveness

Mixing trials, conducted by the University of Applied Sciences Institutes of Life Technologies and Systems Engineering in Switzerland, reporting the validation of the mixing performances and efficiency for a mixture of two cohesive powders, lactose monohydrate as excipient, and salicylic acid as tracer have proven to obtain promising results. The tests were carried out with a 100 l system with a theoretical mixing capacity varying between 5 l and 90 l, controlled by computer software regulating filling, mixing, emptying and cleaning steps. They studied the effect of the fill levels (25%, 50%, and 90%) and tracer concentrations of 0.01% to 10% (w/w) achieved without pre-blending on the blend homogeneity (relative standard deviation, RSD) and the mixing

Figure 2. PTS Batchmixer, fully contained, self-filling powder blender.

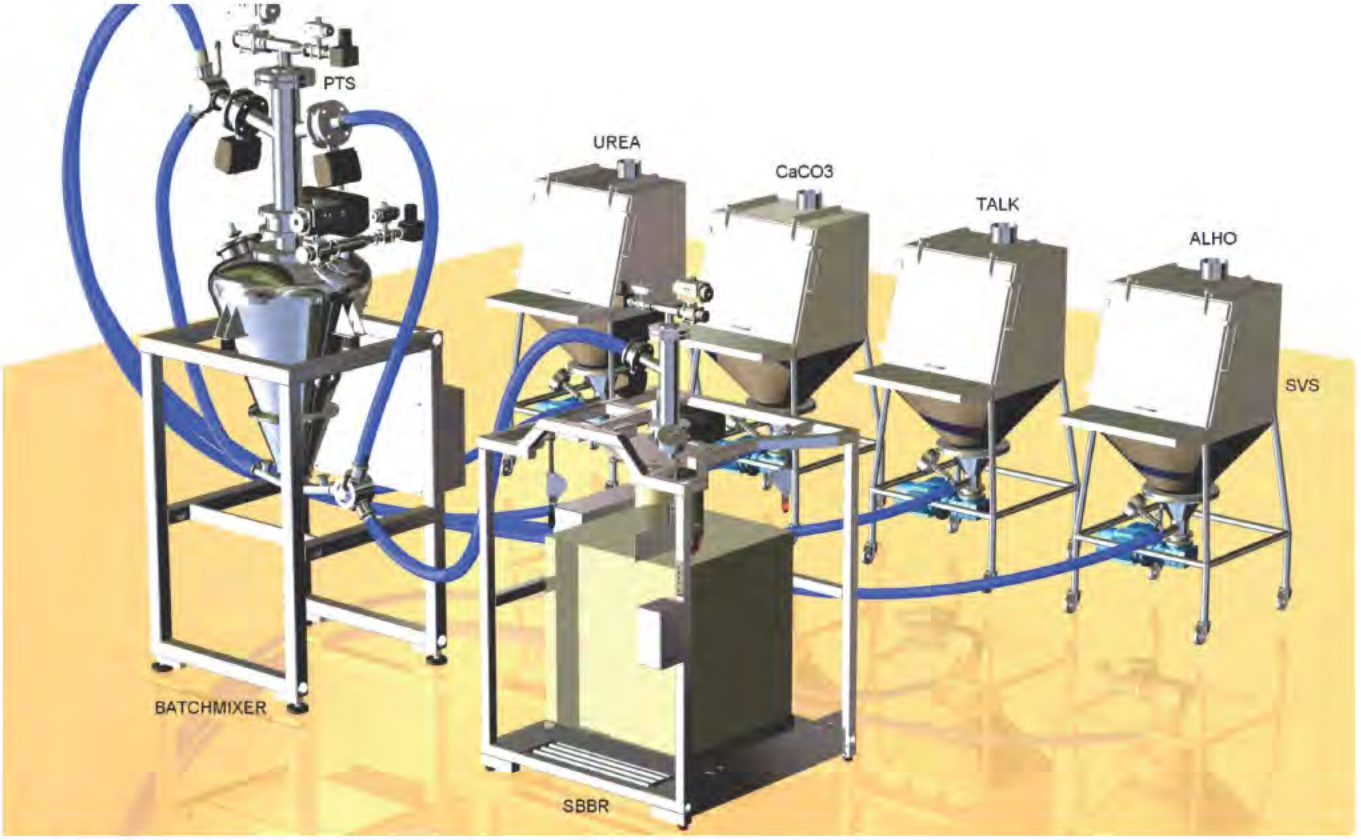

Figure 3. Multiple ingredients powder blending.

time. They also investigated the effect of the sampling size (30 g vs 1 g) on the stochastic homogeneity of salicylic acid blends with an automatic sampling device.

The crucial operation of the sampling, which results should be representative for the whole mixture, was done by two in-line sampling devices taking samples during the mixing process; the MPTS sampling device for 30 g samples and the MicroPTS system for 1 g samples. Both systems work with vacuum and pressure in dense phase mode.

The system has achieved very good results. It obtained highly diluted blends up to 0.01% w/w without premixing stages within 6 min. and without segregation after the mixing process of about an hour. Concerning the repeatability, the target concentrations are reached with RSD values between 1.5% and 7% as far as the 30 g in-line sampler is concerned, depending on the concentrations studied. The 1 g in-line sampler allows the investigation of the homogeneity of high-dilution blends within the limits of +/- 10% of the target value, without any disturbance of the actual mixing state. See reference for complete test results and discussion.[4]

Conclusion

The mixing system discussed is available in different sizes from 5 to 3000 l and is a closed self-filling blending system ensuring satisfactory product homogeneity, a high level of containment, and significantly reduced mixing times in comparison to traditional systems. It has no moving or rotating mechanical parts, therefore requires little maintenance and is easy to clean (CIP/SIP).

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About the Author

Gabriela Mikhaiel is the Business Marketing Manager for products and services of Dec Group, global supplier of powder processing and containment technologies. She graduated in business administration. She can be reached by email: g.mikhaiel@dec-group.ch.

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jphillips@ispe.org

ISPE Headquarters
Dan Murphy
Tel: +1-813-739-2274
dmurphy@ispe.org

ISPE Headquarters
Gene Steinberg
Tel: +1-813-960-2105 x 231
gsteinberg@ispe.org

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Quality by Design in the Biopharmaceutical Industry

by Christopher Potter, PhD, PQLI Technical Project Manager*

This article summarizes presentations from The ISPE State of QbD in the Biopharmaceutical Industry Conference held 10 - 11 April 2013 in San Francisco, California, USA. The conference was attended by more than 70 participants from a wide range of disciplines from large and start-up biotech companies with a number of small molecule experts also present. There were two plenary presentations and a biopharmaceutical case study which identified the benefits of application of QbD and challenges that remain to enable full implementation of the ICH vision as expressed in ICH guidelines Q8, Q9, Q10, and Q11[1,2,3,4] and in FDA's cGMPs for the 21st Century.[5] Participants interacted to produce answers to questions developed by industry leaders in four workshops on topics identified as challenges to full introduction of QbD:

1. Scalability of Design Space
2. Developing and Implementing an Effective Control Strategy
3. Communicating an Effective Story
4. Demonstrating and Maintaining a State of Control Throughout the Lifecycle

The conference developed more detail on these challenges to full implementation of the ICH vision and provided ISPE with suggestions for potential resolution. The main themes from the meeting were:

- Application and presentation of the outcome of risk management exercises are extremely important.
- Some changes or clarity relating to regulatory principles are desirable, for example, relating to justification of how design space proposals are verified in commercial manufacturing, if and how much information relating to a company's pharmaceutical quality system (PQS) should be placed in an application, and how expanded comparability protocols (eCPs) could be more extensively used.
- Further discussion and clarity is desirable regarding translating the continuum of criticality assessment for critical quality attributes (CQAs) and critical process parameters (CPPs) into rational commitments in submissions.
- Further learning would be helpful regarding how and where to present information in the quality sections of the common technical document (CTD) given that the current structure of CTD – Q is not ideal for presenting enhanced, science- and risk-based information.
- Management of knowledge by industry throughout the product lifecycle could be improved.

Summary of Presentations

Roger Nosal, Vice President and Head, Pfizer Global Chemistry, Manufacture and Controls, presented Pfizer's experience with "QbD filings" globally and spoke as leader of a PhRMA team working with FDA on improving implementation of regulation of "QbD filings" in the US. He presented data and experiences to support his key messages that:

- The technical value of QbD has been demonstrated.
- QbD improves quality assurance.
- Establishing clear regulatory commitments may reconcile divergent regulatory perspectives.
- QbD can improve confidence in quality and promote global regulatory harmonization.

His presentation also supported the following conclusions given at the end of this section.

Steven Kozlowski, Director, Office of Biotechnology Products, CDER, presented "FDA Perspective: Quality of Biopharmaceuticals." Kozlowski re-stated FDA's commitment to deliver The Desired State of "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight" by implementation of guidances, cGMPs for 21st Century[5] and Process Analytical Technology.[6] He recognized that analytical characterization of biopharmaceutical products had improved and would continue to improve, however, there were still uncertainties arising from the process. He referred to the risk ranking of quality attributes in the A-Mab case study[7] and how this continuum could be divided into attributes kept within pre-defined ranges, an extended set of attributes evaluated in comparative characterization of process changes, and those not routinely evaluated. He summarized the status of the Office of Biotechnology pilot program for "QbD filings," concluding that FDA is moving away from designating filings as "QbD" or "non-QbD" – many filings contain some QbD elements. A key point was made that the agency needs trust in a company's PQS.

Lynne Krummen, Vice President, Technical Regulatory, Biologics, Genentech/Roche, summarized lessons learned

QbD in the Biopharmaceutical Industry

Continued.

and current perspectives on benefits of QbD implementation from Genentech/Roche's experience with two submissions in the FDA QbD Biotech pilot program. One submission was an original BLA filed globally with a proposed design space. EMA and FDA conducted a collaborative review and PMDA acted as observers. The other was an eCP for multi-product, multi-site drug substance transfers filed only in the US. For the BLA, accomplishments were reduced control strategy testing and wider than current CQA acceptance criteria. The design space proposal was not accepted since the regulators were not confident that the small-scale data provided could be used to justify the design space at scale and adequately described all CPPs. There were also questions regarding how change could be managed within the proposed design space. For the eCP there was agreement on the scope and criteria and the eCP was approved in the US with subsequent changes meeting eCP criteria approved as Changes Being Effected in 30 days.

Ranjit Deshmukh, Senior Director, Corporate Manufacturing Science and Technology, MedImmune, described an "A-Vax" QbD vaccine case study developed by a consortium of five companies[8] and MedImmune's experience in the FDA OBP pilot study with a monoclonal antibody. Given that vaccines are more complex even than monoclonal antibodies, the case study shows how QbD approaches could be applied to some (not all) steps and how a systematic risk tool could be applied to develop an appropriate list of CQAs.

Alain Bernard, Vice President, Biopharma Process Sciences, UCB, gave further exemplification of how development following QbD principles gave technical benefits when developing a monoclonal antibody.

Conclusions from the presentations were that there are different perceptions of residual risk between sponsors and regulators, as well as across different regulatory bodies. These differences influence:

- Issues with approvability of Design Space, and misalignment in sufficiency criteria
- Submissions with more information generate more questions and the success the applicant has with justifying wide acceptance criteria is based on the quality of the justification.
- Review by regulators of justifications in submissions. These can be difficult for regulators to follow – "data dump" is insufficient, however, no single "right" approach exists.
- Insufficient confidence on the part of regulators that "change" post approval can be managed effectively within a company's Pharmaceutical Quality System (PQS).

Summary of Workshops

The main themes from the workshops were:

1. Risk management is the main key – how it is performed, documented by the company (for review by inspectors), summarized in submissions for assessors, and used by companies in the post-approval change management processes within their PQS.

2. Some changes in regulatory processes are desired to facilitate approval of practical design space proposals, particularly in regard to justification of design space at commercial scale. It is not scientifically justified or technically practical to expect full scale experiments to verify parts or all of a design space prior to a submission. The commercial target within a design space (at time of submission) is by default verified in the commercial facility. Typically a design space is developed in the laboratory. It should not be necessary to verify the whole design space as part of initial at-scale verification. Verification can be achieved through multiple options, such as: risk assessments based on scale independent and dependent information, prior knowledge, scale up experience, etc., under an effective PQS. Design space is a lifecycle activity that is a natural subset of a good change management process also taking

QbD at ISPE 2013 Annual Meeting

The ISPE 2013 Annual Meeting, to be held 3 - 6 November 2013 in Washington, DC, is expected to feature an education session on Industry and Regulator (FDA) Perspectives on Current Issues and Implementation Status of:

- Quality by Design (including both NCE and biotech)
- Pharmaceutical Quality System
- Pharmaceutical Quality Metrics

The first part of the session will involve presentations discussing the industry and regulator perspective on the implementation of QbD as related to small molecules followed by presentations addressing industry and regulator perspectives as related to biotech products. During the second part of the session, industry and regulator leaders will discuss the status and current issues related to implementation of PQS and Pharmaceutical Quality Metrics.

QbD in the Biopharmaceutical Industry

Continued.

place under an effective PQS – these processes include risk assessments discussed above, coupled to verification at-scale, if deemed necessary, at the time of change implementation.

ISPE, through its PQLI program, will continue to facilitate implementation of the enhanced, science- and risk-based approach (QbD) to development and manufacturing…

3. The importance of developing an effective control strategy, clear presentation in a dossier, and implementation in manufacturing are confirmed.

4. Criticality of QAs and PPs (and material attributes) is a continuum. A common understanding with regulators is required regarding how to separate those critical parameters and attributes which are commitments in submissions, and which require a regulatory post-approval change process, from those in other categories.

5. The CTD format does not easily support a "QbD submission." Short of re-addressing ICH M4Q, creative solutions were suggested for providing a road map or table of contents (ToC) which points to various sections within a dossier where relevant "QbD information," e.g., QTPP and CQAs, and prior knowledge are given. More than one roadmap/ToC could be given, for example, a separate roadmap(s) could be given for presentation of a summary of the proposed control strategy showing where the elements are described.

6. Some summary of the PQS may be desirable in a submission as supplementary information or assured by inspection, particularly the change management system. This information could be used to provide reviewers with assurance that, for example:
   a. Design space will be verified at commercial manufacturing scale.
   b. While movement within the design space is not considered a change requiring regulatory communication, any movement within design space is appropriately assessed and managed within a company's PQS.
   c. Any movement outside design space is identified and initiates a regulatory post-approval change process.
   d. New knowledge of risks impacting an approved design space leads to appropriate decisions in line with an approved dossier and that these decisions mitigate/reduce risks.
   e. Other movements of process or control strategy elements are effectively managed within an approved dossier.

   This summary should give the reviewer assurance that post-approval change will be managed within a company's PQS and serve as a good roadmap for an inspector. It must not, however, be too detailed or become a regulatory commitment, which would be a hindrance to continual improvement of the PQS, an important element of Q10.

   The desirability of including a PQS summary in a submission, what it would contain, and where it would be located require further consideration with regulators.

7. More use of eCPs in initial applications is proposed to support pre-agreed post-approval change for both large and small molecules. Some flexibility should be encouraged to allow comparability protocols to be developed based on pre-agreed principles in addition to pre-agreed protocols with acceptance criteria.

8. As indicated in ICH Q10, companies need to develop robust knowledge management mechanisms as enablers to support PQS elements, for example, the change management system.

These technical discussions closely align with themes developed by Nosal's limited duration PhRMA team on QbD implementation.

Proposals and Next Steps

ISPE, through its Product Quality Lifecycle Implementation (PQLI) program, will continue to facilitate implementation of the enhanced, science- and risk-based approach (QbD) to development and manufacturing using the following mechanisms:

- Resolution of some of the identified themes will be further explored at the ISPE Annual Meeting to be held in Washington, DC 3 - 6 November 2013.

QbD in the Biopharmaceutical Industry

Continued.

- A white paper has been produced containing the above themes, challenges, and proposals to facilitate implementation of QbD. This paper is being reviewed by ISPE leadership to identify how challenges could be moved forward for example by:
  - direct interactions between industry representatives and regulators
  - international meetings co-sponsored by regulators
  - organizing training programs for regulators and industry

Please follow communication regarding forthcoming conferences and papers on the ISPE web site (www.ispe.org/pqli-resources) and in ISPE publications such as *Pharmaceutical Engineering*.

Conclusion

This successful conference identified for ISPE challenges that require resolution to facilitate full implementation of the ICH vision. ISPE, through its PQLI program, is developing conferences, papers, and interactions with regulators to address and overcome these challenges.

Further comments, reaction, and alternative proposals from Members are welcome and can be emailed to PQLI@ISPE.org.

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Planning Committee

This paper was developed in cooperation with the following members of the Planning Team:

Joseph Famulare, Vice President, Global Quality Compliance and External Collaboration, Genentech Inc. – *Honorary Chair*

Joanne Barrick, Advisor, Global Validation Support, Eli Lilly and Co.

Bob Baum, Regulatory Affairs Executive, ISPE

John Berridge, Pharma Quality and Regulatory, ISPE

Bruce Davis, Principal, Global Consulting

Ranjit Deshmukh, Senior Director, Corporate Manufacturing Science and Technology, MedImmune

Beth Junker, Director, BioProcess Development, Merck and Co.

Lynne Krummen, Vice President, Technical Regulatory, Biologics, Genentech/Roche

John Lepore, Senior Director, Chemical Process Development, Merck and Co.

Line Lundsberg, Senior Consultant, NNE Pharmaplan

Roger Nosal, Vice President and Head, Pfizer Global Chemistry, Manufacture and Controls, Pfizer Inc.

Stephen Tyler, Director, Quality Assurance, AbbVie Inc.

Tim Watson, Research Fellow, Pfizer Inc.

Wendy Zwolenski-Lambert, Global Validation Lead, Novartis Pharma AG.

** On behalf of the Planning Committee*

The GAMP® Community Celebrates 21 Years

by Chris Clark and Sion Wyn

This article gives an overview of the history and achievements of the GAMP® COP, showing how the COP has been a truly international and collaborative effort.

In 2012, the GAMP® Community of Practice (COP) celebrated 21 years of activity in helping the pharmaceutical and associated life science industry to achieve compliant and validated computerized systems.

This article gives an overview of the history and achievements of the GAMP® COP, which together with a special Online Exclusive commemorative article including personal comments from some of the individuals involved, shows how the COP has been a truly international and collaborative effort.

Why Was GAMP Necessary?

The organization that we all know today as GAMP was initiated in 1991 by David Selby (Glaxo), the founding chair, and Clive Tayler (Wellcome), and a core of other experts in the United Kingdom, who realized the pharmaceutical industry needed to consider and meet evolving regulatory agency expectations for computerized system compliance and validation. This was primarily in response to a number of pivotal FDA inspections in the late 1980s and early 1990s.

During this period, the FDA and other regulators were taking an increasing interest in the role of computerized systems in regulated pharmaceutical and associated life science industry processes, and had realized that the reliability and integrity of such systems played an important role in product quality and patient safety. In response to this increased scrutiny, it was clear that an industry response was required.

Three key figures in the development of GAMP (from left to right): Tony Margetts, Guy Wingate, and David Selby.

The first product of the organization was a Draft Supplier Guide, produced by a sub-team led by Tony Margetts (ICI Pharmaceuticals), released to the membership on 1 March 1994 and officially published a year later. As the expectations and industry good practice continued to evolve, so did the Guide, with GAMP® 2 being launched in Amsterdam in late 1996, and a two volume GAMP® 3 being released in 1998. By this time GAMP was a truly international effort with increasing involvement and contributors from all around the world.

These initial versions of the GAMP guides were primarily focused on GMP systems until the scope was broadened to all GxP systems in late 2001 with the release of GAMP® 4. This version quickly established itself as the definitive source of industry good practice for computerized system compliance and validation. Between 2001 and 2008, a number of Good Practice Guides (GPGs) applied, expanded, and clarified the principles of GAMP good practice to a wide variety of computerized systems. The topics covered by these Good Practice Guides included calibration, process control systems, laboratory systems, infrastructure, global information systems, and manufacturing execution systems (MES).

The GAMP Community

The GAMP COP works toward GxP regulated computerized systems that are compliant, fit for intended use, and that safeguard patient safety and product quality.

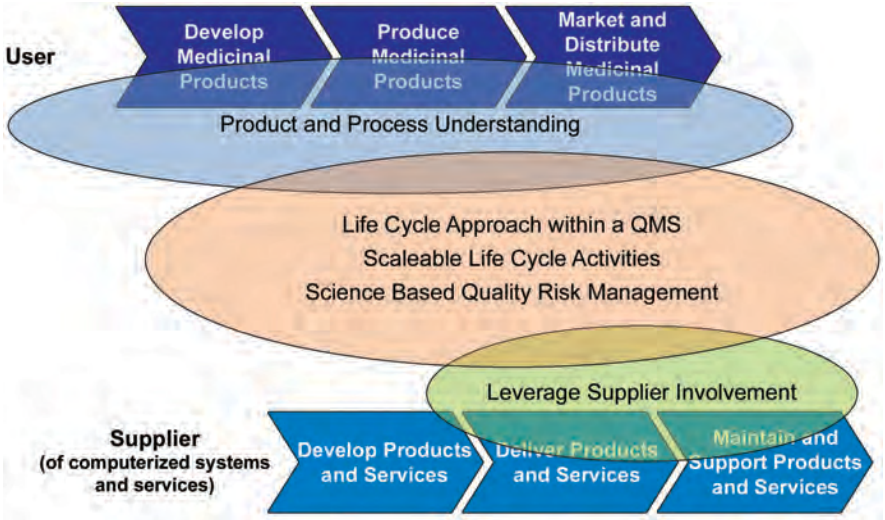
The objectives of the GAMP COP are to:

- Develop effective, efficient, and pragmatic approaches to compliance for regulated computerized systems
- Apply the latest quality risk management approaches to regulated computerized systems
- Promote innovation and technical advance, while safeguarding patient safety and product quality
- Increase understanding of the regulations governing computerized systems worldwide
- Work with regulators to influence regulations and inspection practice in this area

The GAMP COP works with other ISPE COPs in support of ISPE's strategic objectives. The GAMP COP works to form

...GAMP® Community Celebrates 21 Years

Continued.



Key concepts of GAMP 5.

relationships, coordinated through ISPE, with like-minded industry associations to create or support globally harmonized standards or guidance.

The GAMP COP helps regulated companies and suppliers to identify and share best practices in order to improve the quality and reliability of computerized systems used in the pharmaceutical, biopharmaceutical, medical device, and other related life science industries.

GAMP Guidance

GAMP guidance aims to achieve computerized systems that are fit for intended use and meet current regulatory requirements, by building upon existing industry good practice in an efficient and effective manner.

GAMP guidance also aims to apply the latest quality risk management approaches to promote innovative and technical advancement, while safeguarding patient safety and product quality.

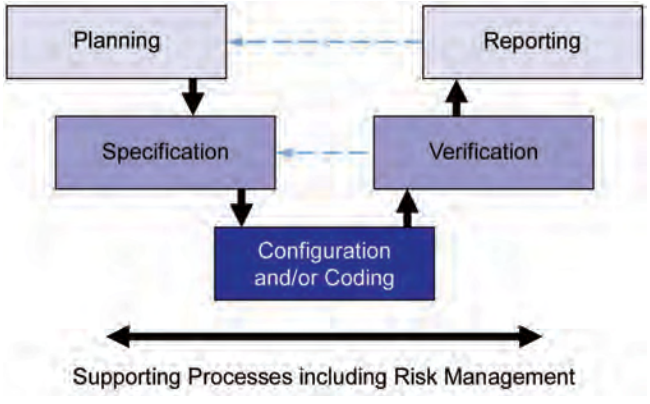
These documents are guidelines and not standards. It is the responsibility of regulated companies to establish policies and procedures to meet applicable regulatory requirements. As GAMP is only guidance, it is inappropriate for suppliers or products to claim that they are GAMP certified, approved, or compliant.

GAMP® 5

GAMP 5 is the current iteration of the GAMP guidance and was published in 2008. It was created in response to the changing regulatory and industry environment which placed greater emphasis upon science risk-based management approaches, product and process understanding, and the application of Quality by Design concepts.

GAMP 5 provides a cost effective framework of good practice to ensure that GxP regulated computerized systems are fit for intended use and compliant with applicable regulations. The framework aims to safeguard patient safety, product quality, and data integrity, while also delivering business benefit.

The Guide also provides suppliers to the life science in-



A general approach for achieving compliance and fitness for intended use.

GAMP documentation structure.

Concludes on page 98.

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A Special Thank You to ISPE Guidance Document Team Members

In this issue of *Pharmaceutical Engineering*, ISPE would like to express our considerable appreciation and sincere thanks to the individuals who have freely given their valuable time and expertise to help produce the ISPE family of Guidance Documents.

During the 15 years in which ISPE has been publishing guidance, dedicated volunteers have contributed their worldwide experience and knowledge to produce guidance which benefits the entire global pharmaceutical community. Volunteer reviewers from both industry and regulatory agencies also have provided real-world commentary on drafts, helping to enhance guidance content. Their contributions continue to be fundamental in maintaining and enhancing the relevance and quality of all ISPE Guidance Documents.

We hope that the entire ISPE membership will join us in recognizing the enormous efforts made by these volunteers so that they can receive the recognition they truly deserve for their indispensable contributions.

The ISPE Guidance Document Development Teams represent participation from numerous pharmaceutical specialties and all regions of the global pharmaceutical community. The list of volunteers, from 2011 to the present, can be found on the ISPE Website at www.ISPE.org/guidance-documents.

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ISPE update

...GAMP® Celebrates 21 Years

Continued from page 95.

dustries with guidance on the development and maintenance of systems by following good practice. This Guide is intended for use by regulated companies, suppliers, and regulators and is built on the concepts embodied in the previous versions of the GAMP guides.

GAMP 5 describes a life cycle approach to management of computerized systems, based on defining and performing activities in a systematic way from conception, understanding the requirements, through development, release, and operational use, to system retirement.

The GAMP 5 life cycle includes a general specification, design, and verification process aligned with *ASTM E2500-07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*.

Associated with and supporting the main GAMP 5 Guide is a series of GAMP Good Practice Guides (GPGs). These GPGs are documents providing practical guidance on the implementation of GAMP for different applications. All are intended to be used in conjunction with the main GAMP Guide.

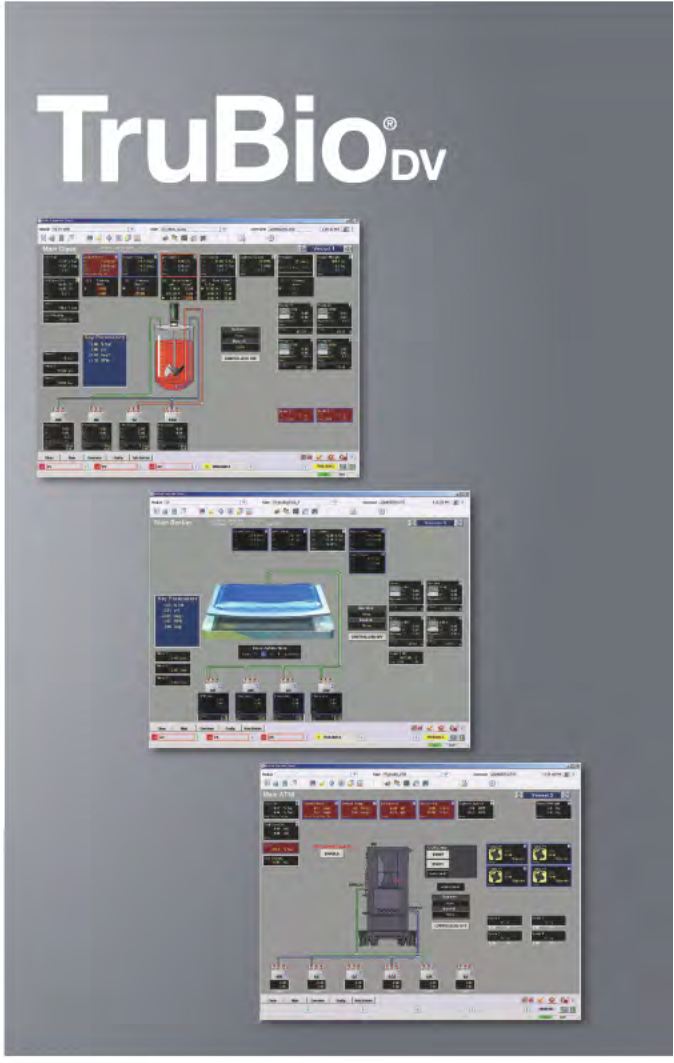
About the Authors

Chris Clark is Chair of the GAMP COP Editorial Review Board responsible for the oversight of the publication of GAMP 5 and other GAMP Guides on behalf of ISPE. He has been involved in the GAMP initiative since 1994, is a member of the GAMP Council and a former Chair of the GAMP European Steering Committee. As Head of Computerised Systems QA for the Napp Pharmaceutical Group he has responsibility for ensuring the application of GAMP principles throughout the organization.

Sion Wyn is the editor of GAMP 5 and several other GAMP Guides on behalf of ISPE. He has been involved in the GAMP initiative since the early days, and is a member of the GAMP Council. He is also the lead ISPE GAMP trainer and course developer. At Confirmity, he provides consultancy, audit, and training services. He can be contacted by email: sion.wyn@conform-it.com.

Conformity Ltd., Bod Euron, Station Road, Sir Conwy, Llanrwst, United Kingdom LL26 0DB.

In a special Online Exclusive GAMP 21st Anniversary commemorative article, founding chairman David Selby and other GAMPers give a personal view of the history, the present, and the future of the GAMP COP. Visit www.pharmaceuticalengineering.org.



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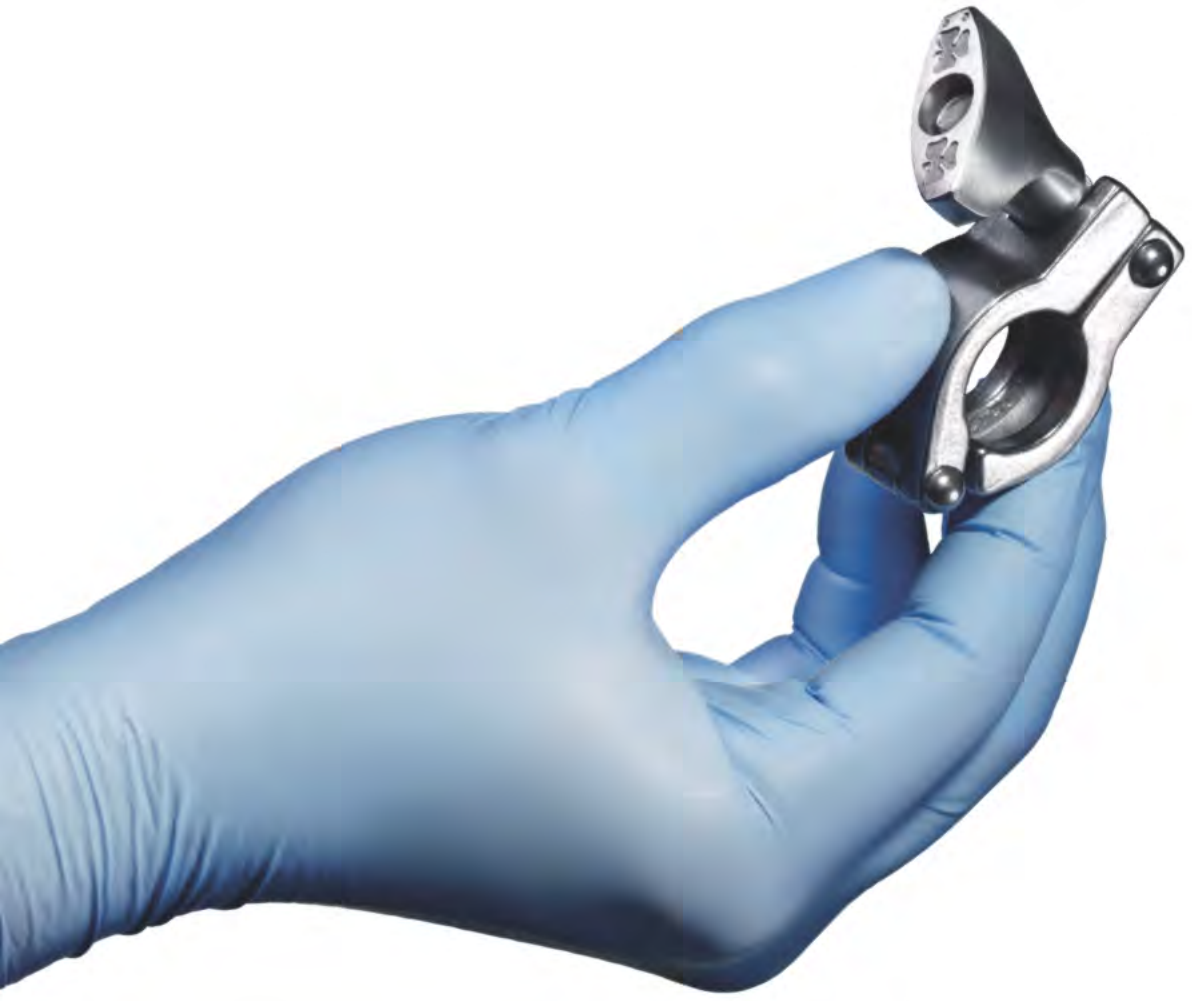

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