Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Quality Risk Management (QRM) Tool Selection: Getting to Right First Time

by Kristin S. Murray and Stephen Reich

This article presents how the quality and utility of Quality Risk Management (QRM) may be highly influenced by the selection of risk management tools. Tangible job aids and methods that have been proven to facilitate right-first-time tool selection are presented.

Introduction

Quality Risk Management (QRM), according to the International Conference on Harmonization (ICH) Q9 Guideline, is having an increasingly influential and visible impact on the facilities, processes, and systems that assure the quality of pharmaceutical products across their lifecycles.[1] As risk-based approaches continue to materialize and evolve, it has become clear that the quality and utility of those approaches and their resultant deliverables is highly influenced by the selection of the QRM tools that power the execution of those approaches. Even though QRM tool selection presents a critical and challenging exercise for risk management teams, industry guidance on the topic is surprisingly limited. This article presents practical guidance and tangible job aids that will allow QRM practitioners to optimize the tool selection process and produce effective risk-based deliverables right first time.

There are many risk management tools available that may be utilized to support QRM per ICH Q9. This article references the most commonly utilized tools in the pharmaceutical industry:

- Failure Modes and Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Fishbone Diagrams (also referred to as Ishikawa Diagrams)
- Hazards Analysis and Critical Control Points (HACCP)
- Hazard and Operability Studies (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RR&F)

Successful QRM requires pragmatism and flexibility in the selection of QRM tools. The ICH Q9 document suggests the need for a flexible approach that emphasizes understanding of the risk problem statement as a prerequisite to tool selection:

> *When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable.* – ICH Q9 Section 4.3.

Specifically, this assertion implies that QRM tool selection is a function of the risk assessment problem statement. Since quality risks and their associated data may take many forms, it follows that practitioners must have knowledge and expertise across an array of QRM tools in order to best face a diversity of risk management challenges. The ICH Q9 Expert Working Group (EWG) that crafted the Q9 document adds:

> *It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used* – ICH Q9 EWG Briefing Pack.[2]

This insight reminds practitioners that our capability to manage quality risks may suffer if we apply a "one size fits all" approach in our use of QRM tools. While standardizing around a single tool or a limited subset of tools may seem attractive from the perspectives of consistency, reduced training efforts, simplifying work instructions, and reducing overall complexity of the risk management process, these benefits may come at the expense of risk management outputs that may only marginally meet stakeholder expectations. Meaningful, effective, and efficient QRM is best realized when risk management tools are carefully chosen to fit the problem statement and the intent of the risk assessment.

Consequences Associated with QRM Tool Selection

QRM tools are designed to translate data into knowledge in an objective and transparent fashion that enhances the overall quality of decisions and risk controls. Each QRM tool has its own distinct characteristics that influence the ways risks are identified, data is input, information is processed, and outputs are presented. With a well-crafted risk question and knowledge of the quantity and types of supporting data available, QRM tools may be strategically selected for compatibility with study data and for capability to deliver and communicate a cohesive risk control plan. The consequences of tool selection decisions are not trivial; the tool selection decision may have significant impact on the usefulness, ease of execution, quality, and potentially even the validity of the risk assessment.

A well chosen QRM tool facilitates the execution of risk assessments, emphasizes the strengths of existing risk controls, effectively processes and communicates data within easily understandable means, and may even help reveal risks that were previously unknown. Well chosen tools will naturally prompt user inputs and pose questions in a manner that is immediately sensible to the risk assessment team and will promote simple analyses and straightforward answers. Identifying compatibility between tools, the risk problem statement, and the supporting data is essential. Quantitative tools are often more compatible with quantitative data, while more qualitative tools are often selected to process qualitative inputs. Simple tools should be utilized when process knowledge is limited or the risk topic is straightforward, while more complex tools will provide greater insight and value when process knowledge is more advanced or the problem statement is more complex. The compatibility between tools and inputs helps ensure success on several fronts:

- The use of the QRM tool will be intuitive and logical, without substantial modification of the tool required in order to perform the assessment.
- Results and decisions will be presented in a transparent manner that accentuates the available supporting data.
- The tool's process flow or mechanism of action provides a structure for risk analyses that helps ensure risk assessments are comprehensive and will lead to levels of control that are commensurate with the level of risk.
- Results will be documented and communicated in a fashion and format that is more likely to meet the expectations of the intended audience.

On the converse, poorly chosen QRM tools may make risk assessments frustrating exercises and may reduce the overall effectiveness of risk management efforts. Incompatibilities between the tool, the risk problem statement, and the supporting data may lead to several unintended consequences, including:

- Known risks and unknown (but probable and potentially catastrophic) risks may go unaddressed.
- Significant risks may be underrated, while insignificant risks are overrated; this is especially common when identified risks do not properly fit into the structure or context of predefined rating schemes and "worst-case" or "best case" risk ratings are assigned by default.
- Strengths in risk control may be underemphasized or overlooked, while weaknesses in risk control may be overemphasized.
- Risk assessments may become overly complex and lengthy.
- Misuse of QRM tools may be cited as nonconformance. The validity or usefulness of the risk assessment may be called into question by stakeholders in cases where QRM tools need to be substantially modified or reinterpreted in order to force-fit the problem statement or data type.

Examples from typical industry scenarios demonstrate some of the positive and negative consequences associated with QRM tool selection. Failure Modes and Effects Analysis (FMEA) is a popular and well-accepted QRM tool in the pharmaceutical industry. The power of FMEA lies in its ability to prioritize risks relative to each other based on knowledge of risk attributes, such as the probability of occurrence, severity of impact, and the capability to detect failure modes. However, such a highly analytical approach to risk prioritization is only feasible and meaningful if data exists to support the rating of risk attributes. For certain failure modes where occurrence rates may not be well known (for example, due to human performance factors), where severity is unknown (for example, where there are gaps in product characterization), or where detection is not always feasible (for example, as a result of limitations arising from instrument or analytical method sensitivities), uncertainties in risk rating may skew the overall study results and lead to misfocused risk control efforts. Industry examples include assessments where the absence of data for certain failure modes has led to arbitrary "worst case" ratings. In another case, the failure modes and effects that were being examined were so difficult to detect that every single failure mode in the study was rated with the exact same capability of detection, thus, effectively eliminating the FMEA benefit of considering risk detection within the risk prioritization methodology. Such studies leave stakeholders wondering whether risks are being accurately prioritized and whether other qualitative tools or techniques that emphasize prevention (as opposed to measuring detection capability) might have yielded more appropriate risk controls.

Another illustrative example of the potential consequences associated with QRM tool selection comes from pharmaceutical manufacturing process hazards analyses. Such studies are commonplace in support of the development and optimization of control strategies for process hazards, such as contaminants

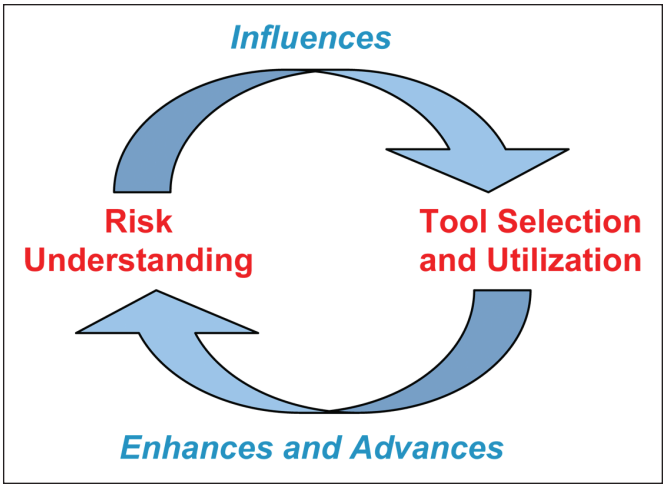


Figure 1. Interrelationship between Risk Understanding and QRM Tool Selection.

and undesirable manufacturing process byproducts. Over the lifetime of a product or process, different tools may be considered in order to leverage available process knowledge into a hazard control plan that is appropriate for the lifecycle stage. For example, process hazard control during early-stage development may be preferably assessed via a simple tool such as Preliminary Hazard Analysis (PHA) as opposed to a rigorous tool such as Hazard Analysis and Critical Control Points (HACCP). During early-stage development, the use of HACCP would likely prove very challenging or even impossible since critical limits for hazard control parameters may not be known or may be rapidly changing. As process understanding evolves through progression into later lifecycle phases, migration of the PHA's elegant outputs into to a HACCP approach may become increasingly feasible and desirable. With greater process knowledge in hand, more sophisticated and rigorous tools such as HACCP would begin to provide benefits such as the formulation of highly detailed and robust hazard control plans. Such control plans provide the level of specificity and scientific justification that are commensurate with regulator expectations for late-stage development and commercial lifecycle phases. This example highlights the importance of matching the rigor of the risk assessment and its associated tool with both the risk problem statement as well as the phase in the product lifecycle in order to deliver optimal risk management.

Selecting QRM Tools Right First Time

Successful QRM tool selection begins with an awareness of the interrelationship between risk understanding and the choice of QRM tools. Knowledge pertaining to potential risks both influences, and is influenced by, the selection of QRM tools as illustrated in Figure 1.

This interrelationship may seem paradoxical; QRM tools are typically used to facilitate and organize risk identification, yet it is premature to select a QRM tool before knowing the nature of the risks to be assessed. This paradox is typically overcome by risk management facilitators who focus the team on the following aspects of risk management prior to tool selection:

- defining a preliminary risk problem statement
- defining the scope and boundaries of the risk assessment
- identifying available data to support the assessment
- undergoing a preliminary risk identification exercise

By taking the time to evaluate each of these aspects prior to tool selection, the risk assessment team will be better able to identify the best risk management tool for the risk problem statement at hand.

Preliminary risk identification may be quickly performed using simple and elegant methods. Depending on the complexity and criticality of the risks, this preliminary understanding may be achieved through informal means, such as unstructured team discussions or through more structured brainstorming exercises, such as Ishikawa (fishbone) or affinity diagramming. No matter which mechanism is used, the preliminary understanding of risks will lead to a well-defined problem statement, an identification of the available data pertaining to the anticipated risks, and a common understanding of the types of risks that will be evaluated during the risk assessment process. These are essential prerequisites for the process of QRM tool selection.

Once the risk management team has a common understanding of the risk problem statement as well as the scope and supporting data, they will be ready to formally initiate the QRM tool selection process. To select the most appropriate risk management tool, it is helpful for the risk assessment team to consider the 10 key prerequisite questions listed in Table A.

The answers to these 10 key questions will help the team navigate subsequent decision trees and analysis matrices and ultimately choose the right QRM tool for the problem statement.

1.	What is the problem statement or intent of the risk assessment?
2.	What is the scope of the assessment? Is it large, complex, and/or critical?
3.	What is the nature of the potential negative events (risks) to be assessed? Physical and tangible hazards, system or process failure modes, deviations or nonconformance with quality systems procedures, others?
4.	Are the risks and their causes well-known or are there substantial unknowns?
5.	Are the causes of the risks likely independent or interdependent?
6.	What levels of data or understanding exist for these risks? Alternatively, where is the current product/process/system in its lifecycle?
7.	Are available data sets predominantly qualitative or quantitative?
8.	Do methods or data exist that may rate the risks from the standpoint of classical factors such as probability of occurrence, severity of impact, and/or capability to detect?
9.	What is the expected output type for the risk assessment (rank-ordered risk register, hazard control plan, design of experiments plan, etc.)?
10.	Who will the risk assessment be submitted to (or likely reviewed by)?

Table A. Key Prerequisite Questions in the QRM Tool Selection Process.

QRM tool selection is rarely a purely objective process. While each QRM tool has unique attributes that may immediately qualify or disqualify the tool as a compatible match for a particular problem statement, it is rarely the case that these attributes immediately point to a single tool as the sole choice to address the problem statement. It is much more likely that several tools may merit consideration and that a degree of subjective judgment will be required in the final selection. In order to accommodate the objective and subjective considerations in the QRM tool selection process, job aids that model these considerations within simplified formats, such as decision trees and analysis matrices, have proven useful.

An example decision tree and associated analysis matrix are illustrated in Figure 2 and Table B respectively. These job aids represent just one of the many ways that QRM tool selection may be facilitated and standardized. The flexibility and broad range of application for common QRM tools makes generalization of tool attributes (such as relative strengths and weaknesses) a subjective exercise, and different pharmaceutical firms may have experiences with these risk management tools that may differ from some of the generalizations presented in these figures.

The decision tree in Figure 2 begins with some of the typical prerequisites required to initiate the QRM tool selection process. The decision flow then includes pathways that direct risk assessment teams toward (or away from) particular QRM tools based on information gleaned by answering the key questions listed in Table A. The first decision point focuses on the nature of the risks being evaluated (e.g., are they tangible hazards or more likely to be undesirable events such as failure or fault modes). If the team has undergone a preliminary risk identification exercise, a common understanding of the risk types will be readily available, thus allowing the team to further navigate the decision tree. From there, the team will leverage their knowledge of the types of data available for the assessment or the nature of the relationship between the failure or fault modes to continue to work through the tool selection process. Objective attributes of certain QRM tools may quickly lead to selection of a tool as depicted by the green terminator symbols in Figure 2. However, it may be the case that the exercise of this decision flow will not lead to a definitive QRM tool recommendation, and further analysis of potential tools will be required according to the QRM tool analysis matrix in Table B.

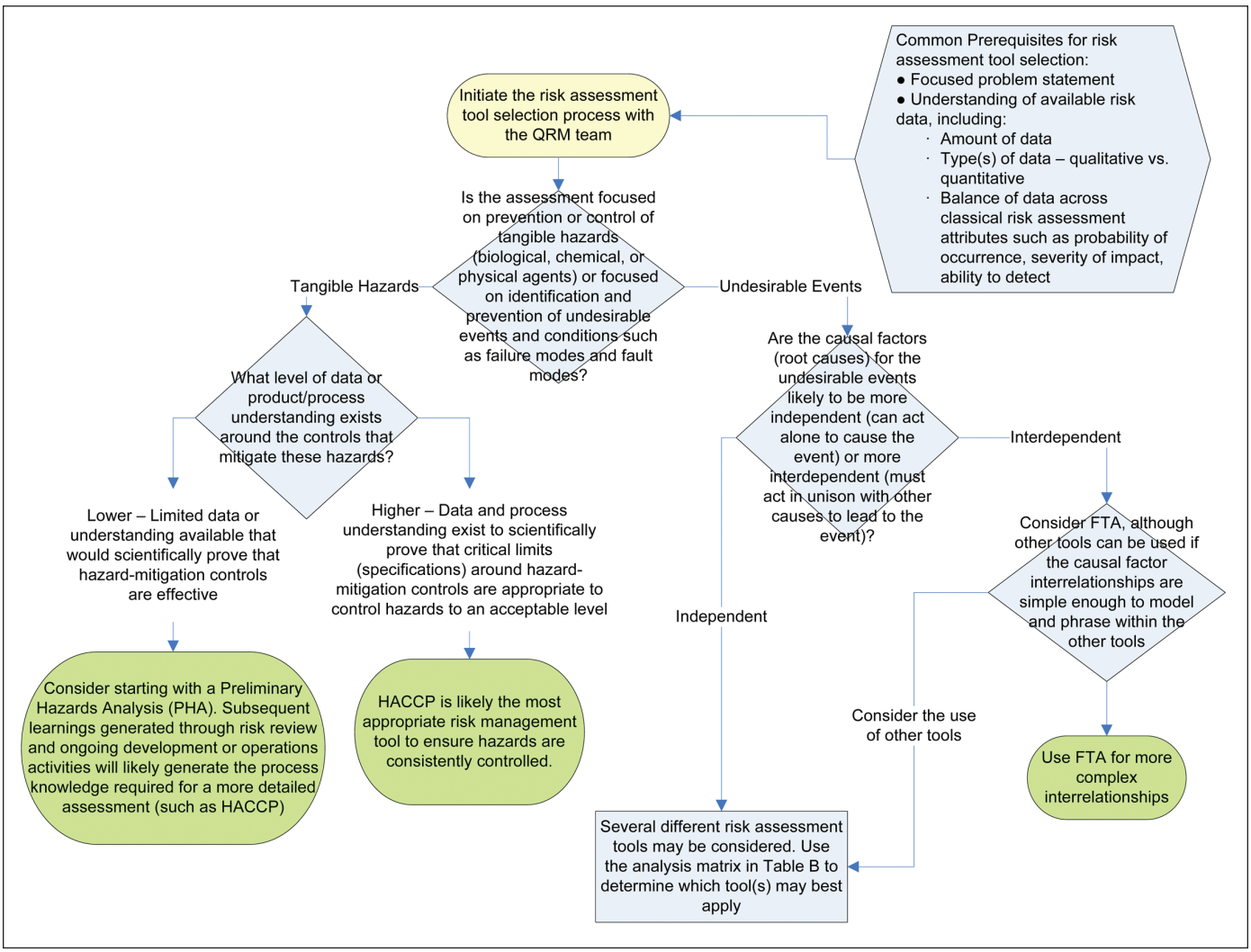


Figure 2. QRM Tool Selection Decision Tree.

"The full benefits of QRM are consistently realized only when the best tools are selected for the job."

Considerations	FMEA	FTA	Fishbone/ Ishikawa	HACCP	HAZOP	PHA	RR&F
If process/product/system knowledge is limited (ex: early lifecycle phases)	X	✓[1]	✓	X	✓[1,2]	✓	✓[2]
If process/product/system knowledge is advanced (ex: later lifecycle phases)	✓	✓	✓	✓	✓	X	✓
If problem statement is simple or if an elegant assessment is appropriate	✓[2]	✓	✓	✓[2]	✓[2]	✓	✓
If problem statement is highly complex or if a detailed assessment is required	✓	✓[1]	X	✓	✓[1]	X	X
If risk ranking is desired	✓	X	X	X	X	✓	✓
If risk detection capability is limited	X	✓	✓	✓	!	!	!
If risk data is more qualitative in nature	X	✓	✓	X	✓[2]	✓	✓
If risk data is more quantitative in nature	✓	✓	X	✓	✓	✓	✓
If demonstration of the effectiveness of risk controls is required	✓	X	X	✓	X	X	X
If risk identification is a challenge, if hidden risks need to be revealed, or if structured brainstorming is desired	X	✓	✓	X	✓	X	X

✓ Tool is likely a suitable fit under this consideration and is designed or capable to perform this way.
X Tool may have less (or no) capability to deliver under this consideration or may be either overly complicated or too simplistic for the task.
! Tool may be suitable, however effectiveness may be limited due to challenges in rating some probabilities of occurrence. It may be challenging to rate risk probabilties if there is limited means to detect those risks in the first place.
[1] Brainstorming capability of this tool may be particularly beneficial for this type of assessment.
[2] Capabilities of this tool can be scaled back to accommodate qualitative or more simple assessments.

Table B. QRM Tool Analysis Matrix.

The QRM tool analysis matrix in Table B lists seven of the most frequently utilized QRM tools that are referenced within ICH Q9. The rows list considerations that are largely derived from the key prerequisite questions from Table A. The seven common QRM tools are rated across the columns for their general compatibility with the listed considerations. QRM tools that cumulatively score higher degrees of compatibility (more check marks) are more likely to be selected for use by the team. It is important to note that a QRM tool should not necessarily be disqualified for use if it scores reduced compatibility (indicated by an "**X**") for one or more considerations. In those instances, the team should understand the limitations of the QRM tool for the particular problem statement and explore if approaches may be taken to mitigate those limitations (e.g., couple the tool with supporting statistical methods, couple the use of the tool with another QRM tool, etc.).

It is possible that the exercise of the QRM tool analysis matrix in Table B may yield multiple preferred tools that score similarly. In this event, teams may consider several approaches to reach a final decision. Often, tabulation of "pros" and "cons" for each tool in relation to the risk problem statement, scope, and available data helps to bring clarity around which risk management tool may be the best fit for the problem statement. Another more intensive approach to final tool selection is to pilot test each tool under consideration using some representative risks that were noted during preliminary risk identification. This hands-on approach often gives risk assessment teams a deeper appreciation for the true compatibility (or lack thereof) between the QRM tool and the problem statement. Finally, teams also may want to consider which regulatory bodies are likely to audit or review the risk assessment since particular agencies may have higher degrees of familiarity or have preferences around the use of particular tools.

Conclusion

There is an understandable temptation to standardize QRM efforts around a single or limited subset of risk management tools in order to build internal risk management consistency, minimize training, and facilitate knowledge transfer and comparison of risks across different locations, products, and processes. However, disciplined QRM training, expert facilitation, and knowledge management programs may allow these benefits to be attained in an organization that embraces flexibility and espouses to use the best QRM tools to match the risk problem statement. The full benefits of QRM are consistently realized only when the best tools are selected for the job. In this regard, organizations should endeavor to standardize around the process of intelligently considering, debating, and then selecting the best QRM tool each time they commence a risk-based initiative. Methodologies and job aids such as those presented in this article may facilitate this endeavor and ensure consistent right first time QRM tool selections.

References

1. ICH Harmonized Tripartite Guideline, *Q9 – Quality Risk Management,* International Conference on Harmonization, 2005, www.ich.org.

2. Q9 Briefing Pack Web page. International Conference on Harmonization Web site. http://www.ich.org/products/guidelines/quality/q9-briefing-pack.html, Accessed 9 February 2011.

About the Authors

Kristin S. Murray is an Associate Director in the global CMC Regulatory Affairs Department and oversees global regulatory submissions for both investigational and commercial products within Pfizer Biotech. Murray has 20 years of experience working in the biotech industry in various functions supporting development and manufacturing. Murray has provided the regulatory leadership for the execution of Quality Risk Management across Pfizer's Biotech sites. Her risk management experience includes providing leadership, training, and facilitation efforts in many areas, including process design and controls, manufacturing facility design, operations and controls, process containment, and cross-contamination prevention and control. Before her tenure in regulatory affairs, Murray was a manager of a bioanalytical laboratory, overseeing clinical, nonclinical, and impurity analytical method development and qualification. She frequently represents Pfizer at conferences, community symposia, and within industry working groups. Murray received a BS in biochemistry from Bates College and a MS in biochemistry from Harvard University. She can be contacted by telephone: +1-978-247-4543 or email: kristin.murray@pfizer.com.

Pfizer, 1 Burtt Rd., Andover, Massachusetts 01810, USA.

Stephen Reich is Risk Management Principal, within Global Quality at Pfizer Pharmaceuticals. He leads Pfizer's Quality Risk Management community of practice, and facilitates development and harmonization of Quality Risk Management best practices across a global network of locations. He routinely provides organizational leadership, project management, training, and facilitation for risk management programs and initiatives. He also provides Quality Assurance leadership in designs, controls, and risk management for novel and highly flexible multiproduct and multihost biologics manufacturing facilities. His technical leadership in this field is founded in the expertise that he developed during more than a decade as a validation engineer at Pfizer (Wyeth). Reich received his BS in chemical engineering from Cornell University, and his MS in quality assurance and regulatory affairs from Temple University. He can be contacted by telephone: +1-978-247-1177 or email: stephen.reich@pfizer.com.

Pfizer Global Quality, 1 Burtt Rd., Andover, Massachusetts 01810, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

This article presents a three phased approach to implementing a Manufacturing Systems Solution using real life examples to demonstrate the benefits.

Manufacturing Systems Solution – More than Manufacturing Execution System (MES)

by Gilad Langer

Learning From the Past About Our Current Manufacturing System's State

In 1985, the Computer and Automated Systems Association of the Society of Manufacturing Engineers (CASA/SME) published its vision of enterprise-wide teaming or as it was known the "CIM Enterprise Wheel" - *Figure 1*.[1] Computer Integrated Manufacturing (CIM) presented a vision in which manufacturing operations are managed and enabled by one software system with a common information model at its core.[2] The vision was targeted at addressing the problem of managing production operations, its materials, resources, and information. A novel idea at the time – so it seemed, but if we reflect on current day manufacturing solutions it looks like we are still struggling with some of the same issues and that this vision is still very relevant.

The original CIM wheel concept was focused on automation and integration inside the enterprise. The concept was revised in 1993 and took a more holistic approach to include the manufacturing organization as a whole. This newer model (from 1993) puts the customer at the center, which is an idea that is not much different from modern operational excellence approaches. For example, Lean Thinking advocates focusing on adding value to the customer and the central concept in Process Analytical Technology (PAT) is achieving process understanding.

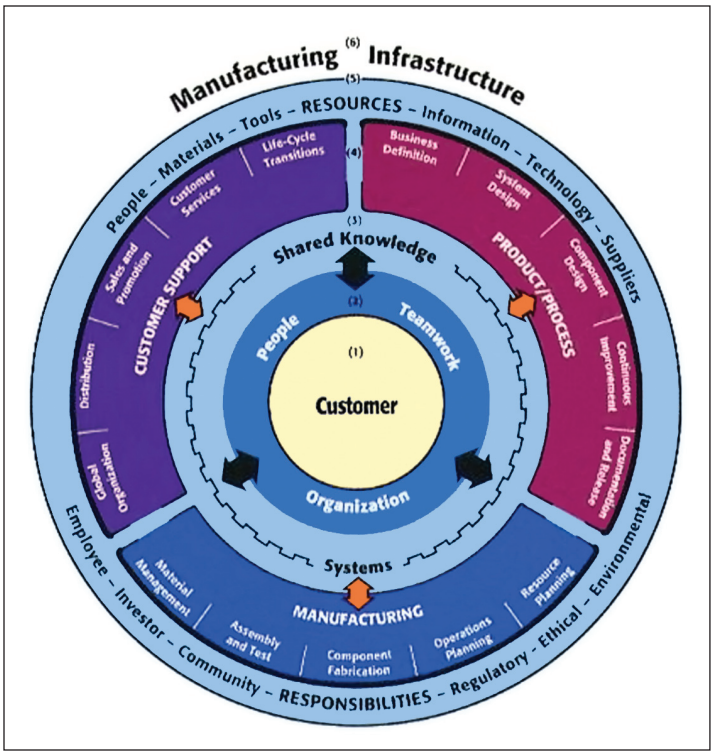


Figure 1. SMEs CIM Enterprise Wheel.

Over the last three decades, companies across a variety of industries have been implementing solutions in an attempt to conform, at least in part, to the CIM concept. These "Manufacturing Systems" solutions have provided companies with some of the benefits that the CIM concepts suggest, but many challenges still remain. The CIM concept is less known in the pharmaceutical industry; however, some of its elements have trickled into more popular concepts such as ISA-95.[3] In both models, the software system that provides the fundamental functionality is a Manufacturing Execution System (MES).

A Manufacturing System solution is comprised of all the manufacturing resources (ap-

plication, equipment, and people) and associated information working together to create a quality product, or Manufacturing System. This Manufacturing System solution concept is very similar the "MES Domain" concept presented in the *ISPE GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach*.[4] Ruklic and deSpautz defined it as follows:[5]

> *"The concept of Domain recognizes that inherent functionality within applications and systems often span the Enterprise-Control system Integration layers."*

The MES Domain concept seems to be similar to the CIM vision of the 90s. They all point to a solution composed of different systems driving manufacturing operations that are based on information and have customer value as their goal. It seems that we are re-inventing the wheel – the CIM wheel.

The goal of this article is to review the current state of MES solutions and the challenges that they present. In addition, the term "Manufacturing System" is used rather than Manufacturing Execution System (MES) to differentiate between MES – a software system that can be purchased, and Manufacturing System – the solution that is provided by integrating a variety of shop floor software systems. This perspective will bring some clarity to the selection and design process of these solutions focused on addressing the challenges of enabling successful deployments and realizing the true value from these solutions.

Understanding the Manufacturing Systems Challenge

Typically, a Manufacturing System solution involves a multitude of systems each aimed at addressing a specific functional need, such as quality, operational efficiency, compliance, batch records, etc. These systems are sometimes referred to by the specific function that they serve or the problem that they are implemented to solve, e.g., electronic Batch Record (eBR), Batch Management, Recipe Manager, Barcoding, Deviation Management, etc. The naming is not important, but it does reflect a common reality that systems sometimes have been implemented to solve a particular problem or provide a specific function. For example, using a system that provides an eBR replacing the paper based batch record is a common and valuable solution implemented by many companies. It addresses the issue relating to compliance and most importantly, enables release by exception. However, the electronic batch record is just one piece of a full Manufacturing System solution. This scenario where systems are used for specific and sometimes isolated functions is referred to as "Islands of Information" and interestingly the CIM concept, drafted more than three decades ago, already recognized this as a shortcoming.

In most cases, companies realize that they have challenges in managing the wealth of information and operations in their manufacturing shop floor, as well as specific challenges in supporting process and operations. Yet, to clearly define the relevant Manufacturing Systems solution it is important to have a clear understanding of the problem as a whole. This holistic approach is a central element in understanding the objectives of a Manufacturing System and also sometimes referred to as the "Shop Floor Management Problem."

Some definitions of Manufacturing System are focused on describing a solution or more precisely the functionality and architecture of the solution. For example, the Manufacturing Enterprise Solutions Association (MESA) model6 presents a number of functional categories from a business perspective, whereas the ISA-95 model7 provides solution architecture based on functional decomposition. These models have been successfully used in many cases by companies seeking to explore and standardize their Manufacturing Systems, such as Pfizer, Merck, Genentech, and Amgen.[8] They are most effective when the system's objective is clear and where a specific functionality set has been identified. Yet, these models do not adequately address the fundamental challenges of defining the problem and scoping a solution.

In an attempt to aid in the definition of the "Shop Floor Management Problem," a specific model is present here that is referred to as the "Integration of Flows." This model provides a perspective that is targeted at defining and scoping the objectives of the Manufacturing System. The model assumes that a manufacturing organization can be described as a composition of two information flows and one physical flow as depicted by Figure 2.

Product Information Flow

This flow represents the business processes that manage and generate product information including R&D, product design, process engineering, quality engineering, etc. This product information is required by the production processes and may include formulations, recipes, SOPs, BOMs, etc. It is important that this information is delivered to the shop floor in an effective and timely manner. In addition, these processes rely on accurate feedback from the shop floor processing activities.

Logistical Information Flow

This flow represents the business processes that manage and generate the information, relating to order and material man-

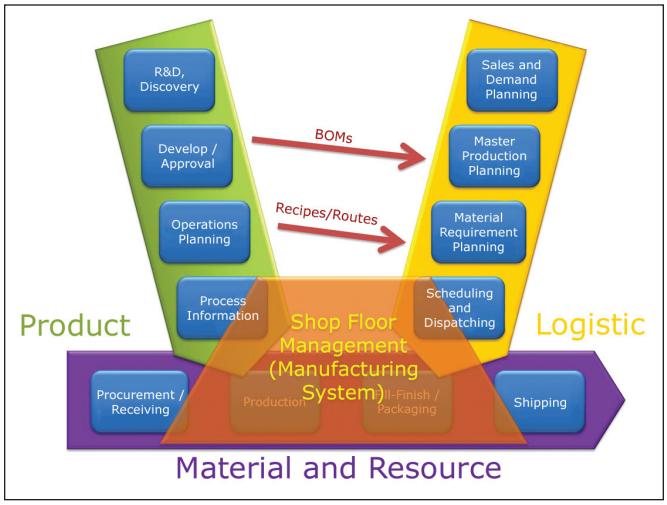


Figure 2. Manufacturing systems and shop floor management.

agement. This includes master scheduling, demand management, capacity planning, MRP, etc. The resulting information includes manufacturing schedules and plans in the form of production, work, and shop orders. Here again, it is important that the information is delivered to the shop floor in an effective and timely manner. In addition, these processes rely on accurate feedback from the shop floor processing activities.

Material and Resource Flow

This flow represents the physical flow of material and resources on the manufacturing shop floor. It is the actual manufacturing process and includes the equipment, automation systems, and people. The outputs of this flow are the finished products or batches.

The intersection of the three flows represents an important and complex integration and coordination challenge. It is where information converges with the real-world, where models, specs, and schedules are put to use. This intersection of the virtual and the real is the puzzle that Manufacturing Systems attempts to solve and can be described as:

> *How to make best use of the information provided by the Product and Logistical flow to efficiently and effectively manage the physical flow of Materials and Resources (also known as the production process).*

Although it may seem as a simplistic definition, it really embodies what a Manufacturing System is designed to do. It is analogous to the job of a production supervisor or plant manager. Imagine a scenario where a seasoned and effective production supervisor or plant manager is running a simple operation and think about how increasingly complicated and hard this task becomes when it is scaled both in volume, complexity, and product variance – this is what the Shop Floor Management problem is.

The "MES Domain" concept as introduced in the ISPE GAMP® Good Practice Guide[4] has some significant similarities to the "Integration of Flows" model. It defines the Manufacturing System space (MES Domain) as all the systems that are currently in place, as well as new ones that may be implemented as part of a solution. The guidance describes the Manufacturing System problem as one of the fundamental aspects of systems implementation where MES is involved. These set of systems and the interoperable solution that they provide to the overall problem is what the focus should be, not a specific system or isolated problem and that is essentially the same as the CIM model's definition.

Analyzing Current State of a Manufacturing System – An Example

Why do all these different models and their history matter? Well, they help gain a perspective about the current state of systems in the manufacturing landscape and importantly they exemplify the fact that in most cases, there is no cohesive solution to the "Shop Floor Problem." The realization that a solution is more than the sum of its parts is important and is a fundamental element in the design process of a Manufacturing Systems solution.

Experience shows that a relatively common challenge that many life sciences companies face is that they may have a variety of different systems on their manufacturing shop floor. Many of these systems are "Commercial Off The Shelf" (COTS) with home grown custom solutions built on top of these or even stand-alone custom solutions. Sometimes a Manufacturing Execution System (MES) is also implemented, but commonly to address a specific process or function, such as Weigh and Dispense (W&D) or to manage the Batch Record electronically (eBR).

When the manufacturing plants for a BioPharmaceutical company were analyzed to determine their current state using the "Integration of Flows" model, it was clear that their solution was not ideal. A multitude of enterprise level systems and an even more complex landscape of site level systems existed. In addition, they had identified some major deficiencies in one of their manufacturing sites. This site was geographically isolated and with time had a host of different systems implemented including both custom home-grown systems and COTS. They identified specific problems around batch release and tracking and had some fixes in place with the existing solution landscape.

To illustrate the different solutions in this example, the "Integration of Flows" model was used and the systems mapped on top of the flows. This provides a perspective to the functionality that each system provide for the Manufacturing Systems or System Landscape - *Figure 3*.

Looking at the model in Figure 3, it is apparent that the current state fits the description from CIM about "Islands of Information." The systems and solutions that were in place are point solutions each intended to provide specific functionality for a specific need, yet they are all part of the MES Domain. The solution for this specific organization was to implement a COTS MES product that would replace the home grown MES and could effectively interoperate with the other systems to provide a complete Manufacturing Systems solution. This solution did not only provide the needed traceability and efficient release by exception, it also provided the capability to better manage Work In Process (WIP) materials, information that could be used for Nonconformance (NC) analysis, and a way to directly implement and measure the impacts of Corrective Actions and Preventative Actions (CAPAs). In addition, the solution provided more accurate and frequent information about the progress of production orders to ERP that was invaluable both for financial performance and for production planning and scheduling.

In this example, the new Manufacturing Systems solution became much clearer after the system was commissioned and in operation. The challenge is to convey this value and benefit in the initial assessment phase. Ultimately, the difference was in using a modern COTS MES not as another localized system, but as the central system with effective interoperation with the other systems. In addition, the MES was made responsible for all process execution and material tracking, including data collection of pertinent information to product quality and process compliance.

One of the important lessons learned from this exercise was that using this approach that included an initial assessment phase, with an analysis to determine the "As-Is" state of the system landscape, was instrumental in developing a common understanding of the problem at hand. It was an invaluable tool that helped everybody in the organization gain a common understanding and gain alignment with the objectives of the solution. This is not to say that it was an easy accomplishment. There were quite a few compromises that had to be made both with objectives and functionality that makes the final solution far from ideal and as in many implementations involving MES, it was "painful" at times. Yet, it was a big step in the right direction and provided a valuable solution with a substantial impact to improving process efficiency, product quality, and risk of regulatory exposure. Hopefully this company will use this solution to drive even more efficiencies and improvements, and in the process let the solution evolve.

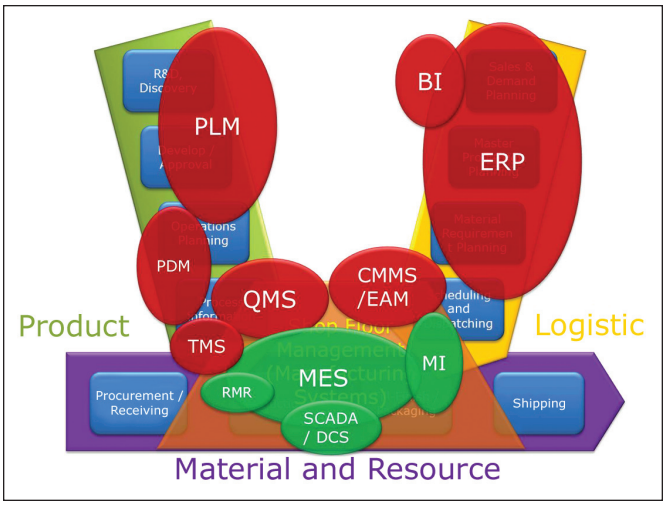


Figure 3. Example of system landscape.

Abbreviation		Description
ERP	Enterprise Resource Planning	SAP with substantial customizations.
BI	Business Intelligence	Only used for financial data
PLM	Product Lifecycle Management	Not implemented
PDM	Product Data Management	Mainly with Documentum but other file based and paper passed records existed.
QMS	Quality Management Systems	Custom home-grown system that was used to manage nonconformance information (NCR) and Corrective Actions – Preventive Action (CAPA) information.
MES	Manufacturing Execution System	Custom home-grown system with very limited tracking capabilities and implemented on a legacy platform. Batch Records were mostly paper based, no eBR (electronic Batch Record).
SCADA/ DCS	Supervisory Control and Data Acquisition/ Direct Control System	Automation systems included a variety of disparate mostly SCADA systems.
CMMS/ EAM	Computer Managed Maintenance System/ Enterprise Asset Management	Only calibration management was implemented using legacy system that was no longer supported and did not manage all of the relevant equipment calibration.
TMS	Training Management System	Training/Certification management was implemented in an SAP module, part of ERP.
RMR	Raw Material Receiving	Raw material receiving was managed by a home-grown system that communicated with ERP.
MI	Manufacturing Intelligence	Not implemented, basic reporting used from whatever the standards systems provided. Much of the data and information visualization was performed in Microsoft Excel spreadsheets.

Table A. System landscape abbreviations and descriptions.

Why Do We Need a Manufacturing Systems Solution?

To most, the question of why is there a need for a Manufacturing Systems solution is evident. The simple answer is that a Manufacturing System solution provides substantial value to a manufacturing organization, yet it is seemingly difficult to convey the specifics. In Table B there is an example of the specific benefits and value that a cohesive Manufacturing System solution provides. These are only a subset of the benefits and specifically relate to the example described in the previous section.

Selecting an MES Product and Justifying the Manufacturing Systems Solution

In the example above, it seems that the benefits are apparent and can be easily quantified. Unfortunately, that is only recognizable after the fact, in other words, it is not typically easy to provide that level of clarity regarding the benefits before the solution is in place. In addition, the quality and efficiency gains are inherently tied to the process and may be perceived as part of the process improvement and not necessarily the Manufacturing Systems solution. It is a "chicken and egg" scenario where the process improvement could not be achieved without a system, yet consequently, the benefits are attributed to process improvements.

It is not surprising that Manufacturing System solutions, involving an MES, are typically the last ones to be implemented in the Manufacturing Systems landscape. They are notoriously difficult to justify and rationalize based on ROI. They are inherently tied to the value adding process and it is hard to attribute benefits to a system by itself. In some cases, it is straightforward to provide quantifiable benefits when there is a specific, and typically catastrophic, event that needs to be remedied, such as a recall, 483 (FDA warning letter), detrimental quality issues, etc. In most other cases, the Manufacturing System should really be perceived as an enabler and its justification has to be rooted in the process that the solution is intended to support. The MES system needs to be considered as a platform that enables operational excellence, i.e., more efficient process, better quality, effective material management, traceability, etc. This brings clarity to

Category	Value Description
Release by Exception	The ability more effectively "Release by Exception." The burden of batch record review is minimized to a bare minimum. The system configuration and recipes are "qualified." This means every batch, lot, or order executed is guaranteed to be performed exactly as prescribed. If anything is not as prescribed an exception is logged with relevant e-signatures and approvals.
Compliance	Ensure compliance through elimination of paper, and availability of quality records. More effective and error-proof data entry reduction in batch record creation and review time, and reduction in incident and rework handling.
Process Execution	Effective process execution including order dispatching, tracking and execution that enables improved Work In Process (WIP) management of all raw material, intermediates, and final product. In addition the system can provide real time inventory reporting to ERP.
Quality	Minimizes risk to product quality, such as risk of losing a batch and other scrap of material. Ensure quality by increased use of in-line QC and more effective SPC. Visibility into quality sources to localize and disposition materials in process and post-process.
Data Integrity	Seamless integration with automated equipment and automation system allowing download batch information, recipes and set-points. Recording of order and batch information in context and not only in time-series and capture of data for engineering analysis and investigation work.
Intelligence/ Reporting	Provides the data and information fundament for Manufacturing Intelligence and Performance Management.
Employee Satisfaction	Increase employee satisfaction and reduce operator training time by eliminating redundant data entry and paper handling as well as empowerment through better visibility to the production operations.
Process Standardization	Drive operational excellence across the organization by effectively propagating operational improvement and efficiency gains to different sites and processes.

Table B. Specific benefits from a Manufacturing Systems solution.

the benefits of the solution and also helps in aligning people around the solutions and its objectives.

Once the solution's objectives are defined and the system landscape is mapped, the next element in the process is the requirement analysis and development of a User Requirement Specification (URS). In this phase, it is common practice to use formal (true and tested) models, such as the MESA model or the ISA 95 standard. This is the tedious, but necessary part of the preparatory and selection phases for the MES platform. The detail involved in the process is important and these models provide a beneficial tool; as the saying goes, "the devil is in the details." However, using these models with no clear focus is risky since the significance of each requirement may not be clear and their prioritization is even more difficult. The models should assist to ensure that all aspects of the required solution have been examined and that the scope of the solution is valid.

Based on the experiences and finding conveyed so far in this article, a three phased approach to Manufacturing System solution design appears evident. In most cases, elements of this approach are performed to some extent; however, the value of executing these three phases correctly and in sequence should not be underestimated. Each successive step builds on the previous one helping to acquire knowledge, gain understanding, align the organization, and disseminate the value of the solution. Experience shows that companies that have adhered to this simple process have been able to realize a complete Manufacturing Systems solution faster and more efficiently, minimizing the "painful" experience that typically accompanies these initiatives.

Once the three phases in Table C have been completed successfully, the next steps that may include MES vendor selection and on to commissioning and go-live become much more streamlined. In most cases, MES products are aligned with specific industries and hence it is straightforward to make an initial short list. But, this may not always be the best approach and it may be valuable to broaden the search for a suitable product. For example, in some scenarios a vendor may

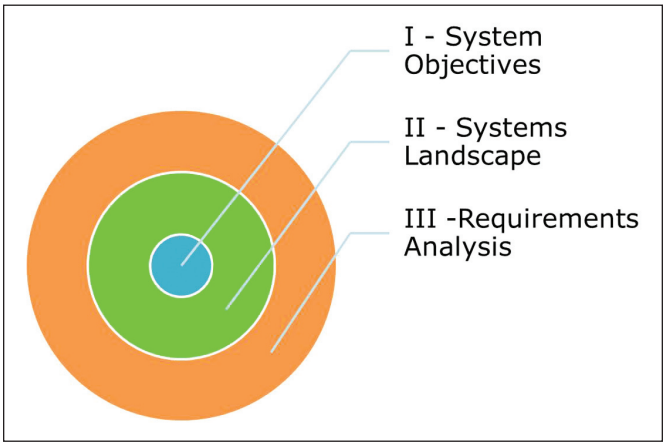


Figure 4. The three phases of solution design.

I – System Objectives	What is the solution for? Gain a clear understanding of the specific Manufacturing Systems problem with focus on determining existing system or "As-Is," and the future solution's objectives or "To-Be." What are the goals of the system? i.e. Release by exception, reduce bottlenecks, lowering scrap, improve quality, etc. Use objectives to streamline the decision process, implementation process, and also to align the organization around a solution.
II – System Landscape	Draw up the "MES Domain." This is a map of process and current state of the system solution landscape. Use this to get a clear understanding of what already exists in the MES Domain including production systems, business systems, automation systems, and interoperability solutions. It is also valuable to define a long and short term strategy based on the goals for the existing system landscape and future solution.
III – Requirement Analysis	Using accomplished industry best practices and standards such as ISA-95 embark on a detailed requirements analysis to develop a URS. The URS scope and detail should be driven by the solution's objectives and understanding of system landscape. The URS should also include requirements for interoperability, deployment, compliance, scalability, and upgradability.

Table C. Description of the three phased approach for solution design.

be trying to penetrate the pharmaceuticals or biopharmaceuticals industry, which could provide a unique opportunity to potentially influence the particular vendor or collaborate with them to obtain a solution that fits well to a specific company or process needs. There are many other factors that can and do play into system selection and "It depends" is always a true statement when talking about fit of a specific MES product to the specific environment. A clear understanding of your particular needs, specifically your "Shop Floor Management Problem" or "MES Domain" is invaluable.

Conclusion

The nature of Manufacturing System calls for a solution design process that involves not only flexibility and ingenuity, but also a great deal of good engineering. The MES Domain is inherently complex and this complexity means that providing a clear and concise return on investment is challenging, given that MES typically involves a substantial capital investment. The result of this is that MES implementations are commonly surrounded with uncertainty and implementation experiences that typically are described as "painful."

It is therefore important to consider that a Manufacturing System is not a single system or software from one vendor. It involves a composition of all the different systems in the manufacturing environment, interoperating to solve the "Shop Floor Problem." The focus should be on the solution and not the software system. This may be challenging since it involves many different applications and different parts of the organization, each with somewhat differing goals. Understanding this problem or MES Domain is crucial and the more time that is devoted to describing it the better the solution gets.

Therefore, using a regimented approach that focuses on the three elements of the solution including objective, systems landscape, and requirements in a sequential manner is invaluable as the initial stage of the solution design. This approach not only provides superior technical perspective, but is also invaluable in aligning the organization with the solution. It helps in generating interest in the solution and establishing its importance in the organization. Experience shows that a key element in a successful Manufacturing Systems solution deployment is that people in the organization believe in the solution.

Learning from experience is an important aspect of any engineering exercise and Manufacturing Systems solution design is no different. Considering the history behind these systems designs over the last three decades from the CIM concept to current day standards, such as ISA-95 and GAMP MES GPG, there should be ample fundament to design such a system. Yet, it seems that it is still a challenge and one that is becoming more and more important as companies attempt to deal with the dynamics of modern manufacturing environments. The three phased approach described in this article presents an answer to this challenge, one that has been tested in industry and has so far shown great success. Hopefully, it will serve many other companies that are working to design and deploy a Manufacturing System solution.

References

1. SME Blue Book, *Process Reengineering and the New Manufacturing Enterprise Wheel,* SME, 1994.
2. Langer, G., Sørensen, C., Schnell, J., Larsen, M. H., Jacobsen, P. and Lenau T., *Computer Integrated Production,* DTU Course no. 80206, Pub. no KPD-18-99, Lyngby 1999, ISBN 87-90855-28-0.
3. ISA Standard, ISA-95 Enterprise Control Systems, ISA, 1998.
4. *ISPE GAMP® Good Practice Guide: Manufacturing Execution Systems – A Strategic and Program Management Approach,* International Society for Pharmaceutical Engineering (ISPE), First Edition, February 2010, www.ispe.org.
5. deSpautz, J.F., Ruklic, G., "Domain Methodology for Computer System Specification and Verification Applied to Manufacturing Execution Systems (MES)," Pharmaceutical Engineering, May/June 2008, Vol.28, No.3
6. Langer, G. and Alting, L., "An Architecture for Agile Shop Floor Control Systems," *The Journal of Manufacturing Engineering,* Vol. 19, No. 3, 2000.
7. MESA, The MESA Model, Manufacturing Enterprise Solutions Association, http://www.mesa.org/en/modelstrategicinitiatives/MESAModel.asp, 2008.
8. World Batch Forum (WBF), ISA-88 and ISA-95 in the Life Science Industries, Chapters 13 - 14, Momentum Press, Vol. 4, 2011.

About the Author

Dr. Gilad Langer has more than 15 years of experience in the manufacturing and quality system domain and spans a variety of industries where he has spearheaded projects involving strategic complex software solutions in both Europe and the Americas. He has served as trusted advisor and business consultant in the areas of technology directions, industry strategy, and manufacturing systems implementations for companies such as GE, Caterpillar, J&J, Bang and Olufsen, Abbott, Maersk, Roche, Zimmer, Novo Nordisk, BioMarin, and Amgen. He is an accomplished leader with experience from military, academic, and multiple manufacturing industries. Dr. Langer has a MS in manufacturing, industrial and software engineering, and a Doctorate from the Technical University of Denmark, one of the top technical institutes in Europe. His research was focused on advanced concepts for highly agile manufacturing systems, where he has pioneered agile methods for software development and has been involved in major European research projects. He can be contacted by telephone: +1-919-763-1800 or by email: gidl@nnepharmaplan.com.

NNE Pharmaplan, 150 Executive Park Blvd., Suite 4550, San Francisco, California 94134, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Computer Aided Process Engineering at Chemagis

by Wayne Genck, Michal Hasson, Efrat Manoff, Roberto Novoa, and Moshe Bentolila

This article presents a detailed analysis of how one generic pharmaceutical manufacturing company implemented computer aided process engineering for process development, design, and scale-up from the beaker to the plant.

Chemagis Ltd. is a pharmaceutical company manufacturing generic APIs. The company is a subsidiary of Perrigo. Recently, Chemagis has incorporated Computer Aided Process Engineering (CAPE) techniques and programs for new Active Pharmaceutical Ingredient (API) projects. This effort was designed to improve research, pilot, and full scale manufacturing efforts. CAPE has become an integral part of the Development Program for the Pilot Department (DPPD).

In order to facilitate the integration of CAPE, a new Process Simulation Engineer position (PSE) was established. The two main CAPE simulation programs that are utilized are Mixing Simulator[1] and Process Simulator.[2]

Knowledge of the programs and capabilities has been disseminated in the R&D and Pilot Departments and the skill set is a requirement for all professional staff. Thus, the engineers are capable in using the simulation models in order to analyze the impact of variable operational process parameters.

Introduction

Active Pharmaceutical Ingredients (APIs) are usually produced by organic synthesis reactions. Normally, the synthesis process development begins in the R&D laboratory, continues in the Pilot Plant, and culminates in the large scale Production Plant.

The company produces more than 30 generic APIs and initiates R&D for another four to six new products per year; the personnel have to constantly strive to develop and use new technologies and processes to meet the rigorous scientific and regulatory demands and challenges to support today's global markets. To this end, computer technologies are frequently employed by the company.

During the last 15 to 25 years, several diverse computational software tools have been developed to aid chemists and chemical engineers to quickly calculate and understand the chemical and physical processes involved in chemical reactors. Being an API producer, the main focus is on Batch and Semi-Batch chemical reactors.

After investigation and testing of several programs, it was decided to use the following computational tools:

Mixing Simulator *– Mixing Simulation and Calculation Software*

This program can be utilized to simulate agitation conditions and achieve the following:

- mathematical modeling of mixing phenomena
- determination of average and local hydrodynamic and turbulent mixing parameters
- impact of mixing on solid-liquid phenomena

Process Similator *– Chemical Dynamic Simulation Software*

Results that can be achieved:

- fitting of chemical reactions experimental data, model of the process
- optimization of the process
- process Scale Up
- simulation of the process: effect of scale dependent physical phenomena
- reactor equipment process general characterization

Even though these programs are relatively easy to use, the personnel have to be trained. In order to initiate and launch these programs quickly, the above mentioned Development Program for the Pilot Department (DPPD) as part of the company's Development Strategy was established.

The PSE position was created whose func-

tions involve Simulation, Optimization, and Scale Up of all new generic API projects plus training of the R&D plus pilot personnel.

Methodology Employed to Implement and Develop the Use of CAPE in the Pilot Department

The PSE individual manages the generation of experimental data, while performing all necessary calculations using the CAPE Programs to generate possible results for Simulation, Optimization, and Scale Up of the process. In addition, this person recommends operational support and/or solutions to problems related to mixing systems, reactant feeding, and other challenges linked with reactor and process operations.

This effort, which is called Simulation, has five stages from the beginning of a new API project to the end. The project development is managed by a Chemical Engineer, while simulation is performed by the PSE. These two departments are in contact with the Project Manager and other appropriate personnel. At the end of the project, the PSE issues a report concerning the Simulation results which is discussed with the Project Manager, the Engineering Development Group Leader, and the Pilot Department Director. The finished document is incorporated in the Project Manager's final report.

Obviously, if the Pilot Department engineers have to understand the Simulation proceedings and results, they have to be trained in CAPE methodology along with being knowledgeable in chemical reactions, chemical process engineering, reactor performance and operation; all of which are related to Process Simulation and Scale Up.

Process Simulation Stages

As discussed, five simulation stages are performed for each new API project. All new projects have to undergo simulations and scale up.

First Simulation Stage – Laboratory R&D

This is considered to be the most important stage for the simulation process. It initiates when the R&D laboratory has a new API project to begin in the Pilot Department.

The following procedure is employed:

- The Project Manager, PSE, and Pilot Engineer Development Group Leader visit the R&D Laboratory to observe how the Development Chemist carries out and controls the chemical reactions.
- During this launch, the Team meets with the researcher to gain an understanding of the raw materials, properties and physical-chemical characteristics; reaction characteristics and possible reaction schemes, mixing performance, and other engineering considerations. The Team may suggest additional experiments.
- A final visit report is issued noting the findings and important issues for the process.

An initial approach for the Process Scheme has been identified. If kinetic data for the chemical reactions is available from the R&D laboratory, it is possible to perform the first Simulation/Scale-Up to initiate work in the RC–1 reactor to improve upon the laboratory findings. A technical meeting is held to achieve consensus on the Experimental Program and Data Collection in the 2 liter RC–1[3] reactor.

The participants are normally the Pilot Department Director, Process Development Director, Pilot Engineer Development Group Leader, Project Manager, PSE, and QA Laboratory Manager.

This meeting is intended to attempt to update the Process Scheme according to the following results from Process simulator:

- What are the main reaction steps? Are these chemically realistic? Are they balanced?
- In which phase(s) do they occur?
- What data are available to support model development?
- Which steps are believed to be fast (at lab scale) and which are slow (you may be able to focus on fitting only the slower, rate determining steps)?
- What are the likely rates of each physical transport process (e.g., can you assume that mixing was thorough enough to not be rate-limiting at least at lab scale)?
- How are these rates likely to vary on scale-up?
- Based on Process Scheme, are such variations likely to be important?
- Should a simpler Process Scheme be used as a basis for initial modeling?

After this meeting, the Project Manager is ready to prepare the experimental plan and summary of information to initiate the Development Project phase in the mini pilot RC–1 reactor. The PSE prepares to process the experimental data obtained from this step.

Second Simulation Stage – Mini Pilot, RC–1

At this stage, experimental data is acquired (kinetics and thermo chemical if necessary) from the reactions performed in the RC–1. This data is processed using Process simulator according to the Process Scheme to prepare curves fitting the experimental points. This exercise generates the following values:

- Reaction rate constant for each reaction of the scheme, k (1/s, L/mol.s, L^2/mol^2.s, etc.)
- Activation Energy for each reaction of the scheme, Ea (kJ/mol)
- Mass Transfer Coefficients (for liquid-liquid, liquid-solid, liquid-gas, etc)
- Other information characteristic to the process (crystallization, distillation, etc.)

When good curves and correlations are achieved, it is required to have an accurate Simulation Model for the API project. This model is analyzed with the Project Manager with the participation of the Engineer Development Group Leader and Pilot Department Director. If necessary, the model will

be restructured. The Final Simulation Model is then used for Process Simulation, Optimization, and Scale Up.

Third Simulation Stage – Mini Pilot Design Of Experiments (DOEs)

With the Simulation Model finished, CAPE Process simulator tool is used to study the influence of each process operational parameter on the chemical reaction behavior. It is possible to simulate, for example, the process at different reactor temperatures, at different stirrer velocities, and the use of different feed rates. This yields a response concerning what will be different, if anything, in the process result.

If the Model is accurate enough, this simulated study can replace experimental work for a DOE. Regardless, the simulated results are a good starting point to program the experiments in a DOE program. The contribution is to reduce the number of experiments.

This investigation facilitates the procedure to achieve Optimization of the process. The goal of the Optimization is to achieve the best operational parameters to obtain maximum product yield and/or minimum impurity concentration along with productivity.[4]

Fourth and Fifth Simulations Stage – Scale Up

The Pilot Department has numerous reactors of different materials of construction, different shapes, capacities, and mixing systems. Projects include production ranging from samples to multiple kilos of GMP and non-GMP materials. The engineer can start the Scale Up process at the beginning of the project.

The team performs a Scale Down of the API process to ensure that the work done in the RC–1 reactor will reproduce in the bigger vessels. Essentially, it is determined for the larger reactor (according to the maximum production required) the best mixing hydrodynamics and energy distribution to employ in the smaller ones.

Summarizing, a process engineer can use this stage to make a complete analysis and modification (if necessary) of the Simulation Model and its results.

Finally, a summary report is generated based on the API Project Simulation results with comments and recommendations concerning the operational parameters to use in different reactors to achieve the optimum final result. An example of this report is presented in this article.

As seen above, from the beginning of the new Generic API Project, a thorough investigation was initiated employing a continuous teamwork style to achieve the simulation.

Results and Discussions

Using the Process and Mixing programs as part of CAPE efforts, the company has completed Simulation and Scale Up for more than 15 new generic API projects and existing products. The tools have been very helpful to analyze the process parameters that will be critical for a good performance in the production step; specially, regarding problems related to distillation, mixing and crystallization.

The following is an example of a Simulation Program. The need to maintain confidentiality does not allow us to disclose the reactants and product.

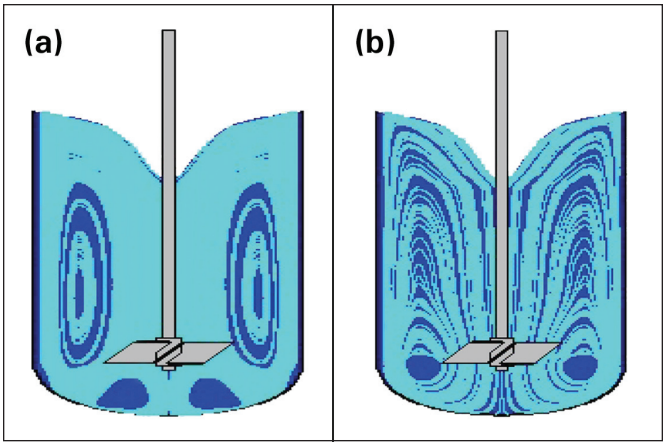


Figure 1. RC–1 General flow – pattern picture, (a) pumping down and (b) pumping up.

Simulation Report Example: Generic API P Project

Project: P

Report Corresponding to: P Reaction, Simulation and Scale-Up Results

Using the P reaction experimental data from RC–1, a fitted model for the simulation and scale-up and/or scale-down for the P preparation process was achieved.

The Objective was to develop a good kinetic model for the P reaction in RC–1. With this model, the development engineer can simulate the process for the next reactor stages, including safety issues, scale-up, and required processing parameters.

Laboratory Investigations

As discussed, the process development team visited the R&D laboratory in order to see the preparation and performance of the P reaction. The reaction took place in a 1L Reactor with paddle blade stirrer at (250 to 500) rpm.

The following was observed for the P reaction process:

- Reaction is performed in two steps. The first one consists of mixing A and B (solids) with solvents (T + S) to obtain a solution. During a 45 minute timeframe and mixing at 250 rpms, the reactor temperature was raised to 60°C. Final solution is clear and without suspended solids.
- In the second step, in order to obtain P, C (solid) was added to the solution. Reactor temperature and stirrer velocity were raised to 80°C and 500 rpm respectively. Reactor kept at 1 to 1.5 hr under these conditions. During this process, the C solid appears to be suspended.

When analyzing Technical Transfer Documents and HPLC results, the following initial conclusions concerning simulation and scale-up work were made:

- P reaction process at laboratory level seems to be relative simply. Reaction occurs in a Heterogeneous Liquid (solution T – P – A – B) – Solid (C) phases with mass transfer considerations.
- The main impurities present with product P are its isomer (IP) and D.
- The solid C properties (large medium particle diameter of around 735 µm and density of 2400 kg/m^3) and from previous experience when C was used, it was predicted that it would be difficult if not impossible to suspend C in the RC–1 and other Mini Pilot reactors.
- Process Scheme is Batch Heterogeneous Liquid – Solid Reaction, as shown in Figure 2a.

Up to this point, the simplest possible reaction scheme is the following:

1. Equilibrium Reaction: E ↔ F
2. Main Reaction: A + E + C → P
3. Secondary Reaction: A + F + C → IP
4. Impurity Reaction 1: P + C → D

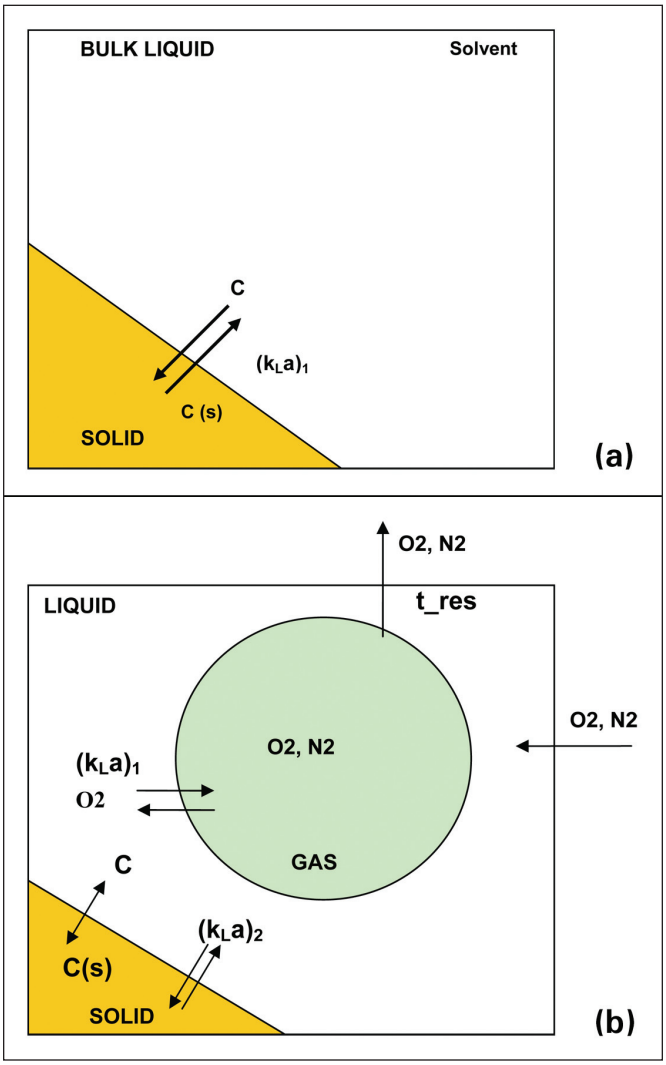


Figure 2a. Process scheme liquid – (a) solid reaction and (b) gas reaction.

Stirrer Velocity rpm	Solid Suspension Characteristic	Max. Non Uniformity Axial Solid Distribution %	Max. Non Uniformity Radial Solid Distribution %
700	Complete Suspension is Questionable	**110**	10.7
800	Complete Suspension is Questionable	**91.6**	10.7

Table A. RC–1 Stirrer velocity – solid liquid mixing performance.

5. Impurity Reaction 2: IP + C → D

First Simulation

Next, the best operational parameters to achieve a good P reaction performance is estimated (at least similar to that obtained in the R&D laboratory) in RC–1 while employing four baffles.

Principal input data used for the simulators were: reaction recipe, properties of the reaction components, reactor and stirrer dimensions and geometrical characteristics along with C solid particle characteristics. C concentration during the reaction is 46.4 kg/m^3. Mixing parameters results are presented in Table A, while employing two different stirrer speeds.

In both cases, partial settling of the solid phase is predicted. The Average concentration of solid phase in continuous flow predicted at these stirrer velocities is 22 to 23 kg/m^3 (50% of the initial solid concentration in the reactor). According to these results, good uniformity and adequate solid suspension distribution in the reactor is not expected and poor mass transfer would influence the reaction. It is known that the small C solubility (3.62E-04 mol/L) in the chosen solvent would necessitate a large End of Reaction (EOR) time to achieve acceptable results.

Comments and Changes during RC–1 First Simulation Stage

The first P experiments in RC–1 (MH025, 26, 27, 31) with normal stirrer operation (pumping down) demonstrate the mentioned difficulties and relatively long EOR time (8 to 13 h) to achieve acceptable final reaction results. In an effort to resolve this problem, the RC–1 stirrer was adapted to pump in an upward direction between 700 to 800 rpm. The experiments (MH033, 35, 37, 39) demonstrate better results with EOR time considerably shorter (2.5 to 4 h).

Reaction	Reaction Rate Constant (K)	Units	Activation Energy (Ea)	Units
1. Equilibrium Reaction	K_{eq} = 9.87E+5 K = 5320.32	L/mol 1/s	264.58	kJ/mol
2. Main Reaction	13400	L^2/ mol^2 s	324.50	kJ/mol
3. Secondary Reaction	2.63	L^2/ mol^2 s	82.50	kJ/mol
4. Impurity Reaction 1	3.68	L^2/ mol^2 s	15.90	kJ/mol
5. Impurity Reaction 2	3.62	L^2/ mol^2 s	240.60	kJ/mol

Table B. Reaction rate constants and activation energy fitted values.

The above results may be due to the observed difference between the "general flow patterns" for the reactor media introduced by change in the stirrer pumping direction as depicted by Mixing simulator Figure 1 (a) and (b). No other explanation was theorized since the calculated quality values of axial and radial solid distribution in the liquid-solid mixing is the same regardless of the pumping direction.

Working with the R&D laboratory, it was found that feeding air to the reactor reduced IP at EOR. The Oxygen (Ox) from the air reacts with IP and P to form D. In the crystallization operation D level is more easily reduced versus IP. After all these changes, the conditions were established to obtain a kinetic model of the P reaction.

The new Process Scheme (Figure 2b) will be a more complex one: Heterogeneous Batch Reaction in Three Phases, Liquid (T+S + A + E ↔ F) – Solid (C) – Gas (Ox from Air).

Second Simulation

The new reaction scheme is now as follows:

1. Equilibrium Reaction: E ↔ F
2. Main Reaction: A+ E + C → P
3. Secondary Reaction: A + F + C → IP
4. Impurity Reaction 1: P + C + Ox → D
5. Impurity Reaction 2: IP + CA + Ox → D

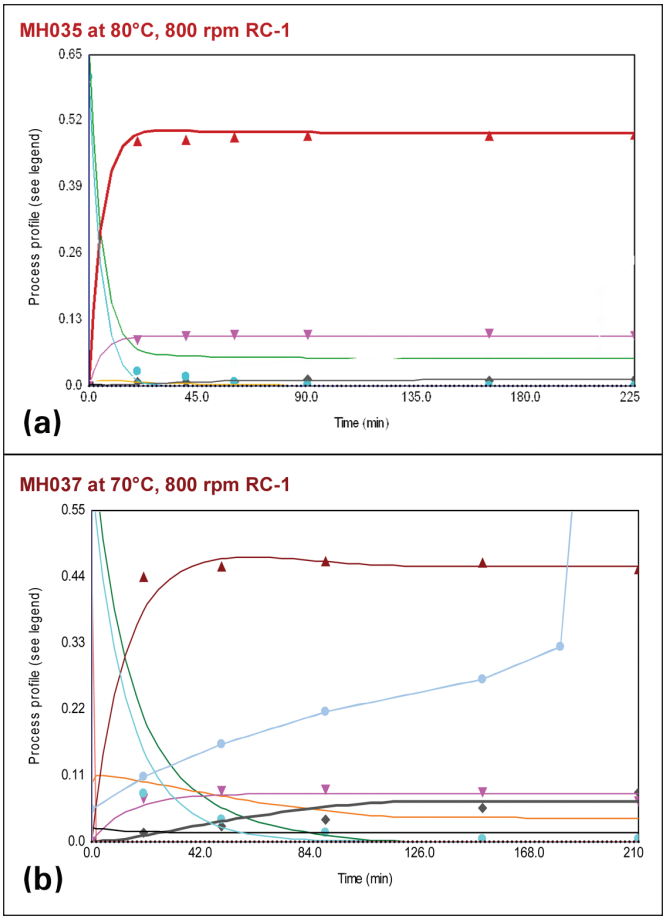


Figure 3. P Fitting result (a) and (b).

Oxygen enters with air into the reactor by two ways; first, air is kept in the vapor head space and second, by feeding it straight into the solution at a specific moment of the reaction.

The main task here is to obtain a better fitted model for the P reaction, for the new reaction scheme. The fitted model was obtained using RC–1 operation parameters, the recipe, and laboratory kinetic results for the following experiments:

- MH033, 70°C, 700 rpm, EOR = 240 min
- MH035, 80°C, 800 rpm, EOR = 225 min
- MH037, 70°C, 800 rpm, EOR = 210 min

The following Reaction Constants and Activation Energy were obtained - *Table B*:

The Mass Transfer Coefficients (solid and gas) for each experiment were obtained using Process simulator and adjusted in the kinetically fitting process are:

- For MH033 at 700 rpm, K_{La} = 119.891/s and KLc = 1.48 1/s, solid and gas respectively.
- For MH035 and MH037, at 800 rpm, KLa = 256.85 1/s and KLc = 2.16 1/s, solid and gas respectively.

The gas Henry value and C solubility also were estimated and fitted:

- At 70°C: Henry = 3995 Pa. m3/mol; C solubility = 2.611E-04 mol/L
- At 80°C: Henry = 5000 Pa. m3/mol; C solubility = 4.715E-04 mol/L

Figure 3 (a) and (b) demonstrates the goodness of fit of the Model obtained for the P Liquid – Solid – Gas Feed Batch Reaction. (Points are the measured data and the lines are the fitting and simulation results; all represented in mmol of materials in the system.)

Our main operational parameters are: Stirrer velocity (700 – 800 rpm); Reactor Temperature (70 – 80 °C) and Air (Ox) Feeding (1 – 60 min).

After reviewing all possible combinations of these parameters using the fitted model, it was noted that variations of the final results are greatly influenced by the Reactor Temperature. Air (Ox) feeding times do not show any remarkable influence on the final results.

The impact of Stirrer Velocity and Reactor Temperature is shown in Table C and charted Figure 4 for EOR and Air Feeding constants.

EOR = 225 min		P,	IP, D	in mol		
RPM	P, 80°C	P, 70°C	IP, 80°C	IP, 70°C	D, 80°C	D, 70°C
800	0.49	0.51	0.098	0.08	0.012	0.01
700	0.49	0.51	0.098	0.08	0.012	0.01

Table C. Stirrer velocity and reactor temperature influence over final results.

At expected, between 700 to 800 rpm, there is no appreciable influence over the final value of P in the reaction. At constant Stirrer Velocity as Temperature increases, P is reduced and impurities increase.

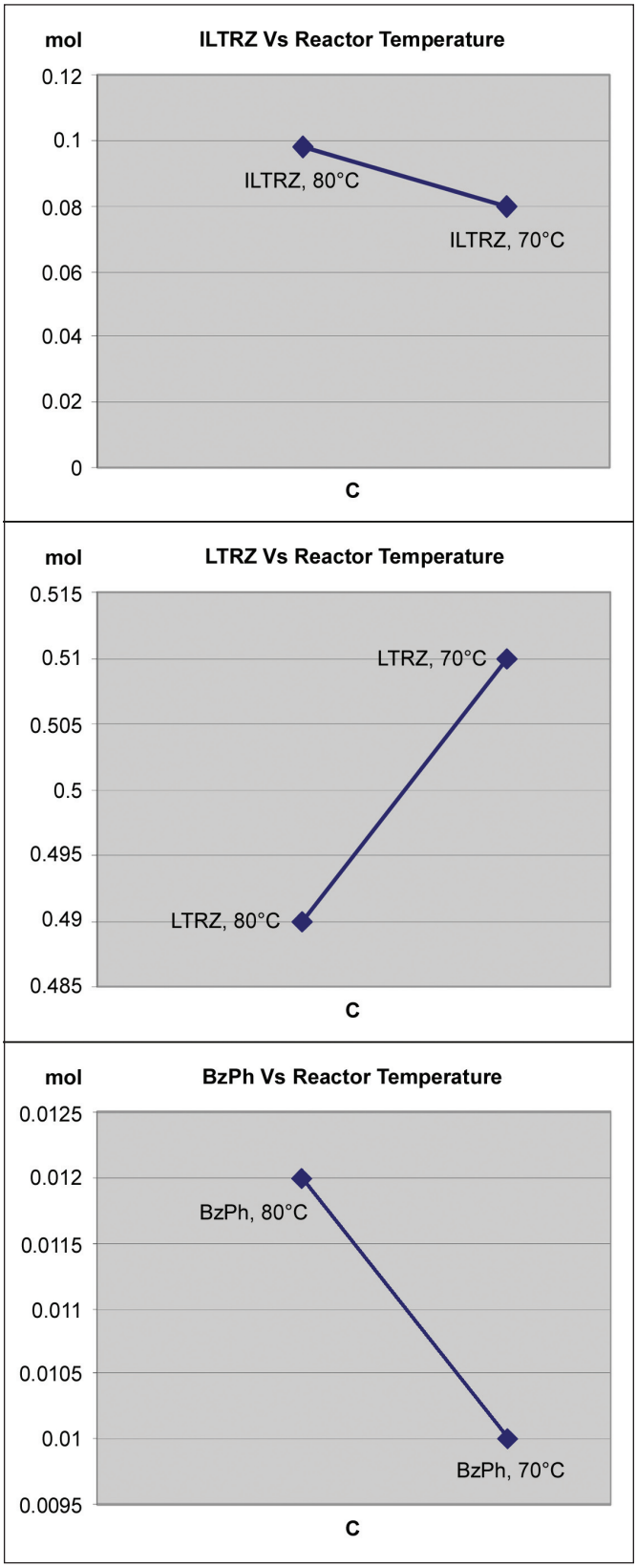


Figure 4. Stirrer velocity and reactor temperature influence over final results.

Temp. °C	EOR min	With the following results >>>	Yield, %	P, mol	IP, mol	D, mol	D, mol
62	231		75	0.455	0.068	0.07	0.008

Table D. Simulated optimization results.

Optimization of P Reaction Process

According to final amounts established for each component at EOR time the optimization targets were:

IP < 0.062 mol
D < 0.072 mol
A < 0.009 mol

Operational parameters fixed for optimization

Reactor temperature = 60 to 80 °C
Reaction Time: 110 to 450 min
Stirrer Velocity: 800 rpm
Air Feeding: as in MH037

Optimum results are presented in Table D. Compared to MH037, the final results are very close.

Fourth – Fifth Simulation – Scale Up

During the experimental – simulation work, it was demonstrated that two important factors are required to achieve a good reaction result:

1. Milled C is required to suspend the reactant and properly carry out the reaction. Milled C particle size: 300 to 430 µm; Medium Particle Size = 360 µm.

2. Air addition is necessary. Feeding Air constant, equivalent quantity to 43L Oxygen/mol D; 60 min of feeding should be sufficient if gas inlet subsurface under impeller and a satisfactory gas distribution is achieved.

With these findings, it is possible to calculate the main Liquid – Solid – Gas operational characteristics for all possible reactors in two of the Plants. For Plant 75, none of the reactors were adequate to perform the reaction. For this reason, several modifications were proposed to Reactor 7501 (100 L, maximal operational capacity). For Plant 76 only in Reactor 7610 (10 L, maximum operating capacity), the expected mixing is satisfactory. Experiments determined that good reaction results could be achieved in this small vessel. Table E shows the main operational characteristics predicted in each of these reactors.

As seen in Table E, it was found that the Hydrodynamics, Turbulence, and Air Additions were superior in the modified Reactor 7501, when compared to the small R7610. Liquid-Solid characteristics are similar in both reactors. Based on these calculations, one would expect good performance in the modified, larger vessel.

The Plant Scale-Up trials confirm the projections from the computer modeling and a successful scale up was achieved.

Operational Parameter	R 7610	R 7501 Modified
Operation Initial Conditions		
Reactor Volume, L	8	100
Reactor Temperature, °C	70	70
Stirrer Velocity, rpm	450	300
Hydrodynamics		
Mixing Power, W	17	335
Reynolds for Flow	73200	249000
Turbulence Main Characteristics		
Energy Dissipation – Average value, W/kg	2.29	3.61
Energy Dissipation – Maximum Value, W/kg	103	122
Liquid-Solid Mixing Main Characteristics		
Solid Suspended Condition is Expected	OK	OK
Maximum Degree of Non-Uniformity – Axial, %	14	15
Maximum Degree of Non-Uniformity – Radial, %	5	4
Average Concentration of Solid Phase in Continuous Flow, kg/m^3	39	39
Gassing Characterization		
Gas Hold – Up*	0.00024	0.16
Specific Mass Transfer Coefficient Gas – Liquid, 1/s	0.0015	0.655
Gas Mass Transfer Rate*, kg/h	0.0011	6.84
Gas Distribution: Satisfactory, Flooding Not Expected	OK	OK

* Gas Hold-up: represents the average value of volume fraction of gas in the gas-liquid mixture.
* Gas Mass Transfer Rate: rate of gas dissolution corresponding to specific mass transfer coefficient.

Table E. Mixing simulation-scale-up result.

Crystallization Considerations

Both Chemagis and Genck International have found Mixing to be a powerful simulation tool for crystallizations, precipitations, and scale-up.[4]

For example, often secondary nucleation is a controlling factor for the ultimate product size distribution. When employing geometric similarity for scale-up, it can be shown that the nucleation rate due to crystal-to-impeller contact decreases by a factor of D-0.67 while maintaining a constant P/V and decreases even more, D-2, while maintaining tip speed constant. At higher slurry densities, crystal-to-crystal secondary nucleation becomes controlling. It can be demonstrated that secondary nucleation in this case can be reduced by reducing P/V, and in particular, impeller speed. Low shear, efficient hydrofoils often assist in this goal.

Table F demonstrates the results of a typical scale-up from a 50 gallon Pilot Plant to a 6,250 gallon Production unit employing geometric similarity. The final slurry contains 15% solids with an average particle size of 125 µm and a maximum size of 350 µm. The vessels are baffled with dished heads and have 45° pitch blade turbines.

A summary of definitions for the predicted parameters is as follows:

1. **Maximum value of energy dissipation – microscale phenomena – energy dissipation behind the agitator blades** – controls breakage, nucleation, and micromixing in this zone.
2. **Local values of energy dissipation – microscale phenomena – average energy dissipation plus energy dissipation in bulk slurry and at baffle** – controls breakage, nucleation, and micromixing in these zones.
3. **Characteristic time of micromixing – time of microscale degradation of non-homogeneous concentrations** – important for precipitations.
4. **Shear rates – characteristic shear rate at the microscale level** – scale-up governs mass transport process for growing and dissolving solids.
5. **Maximum energy of collisions at zone of maximum turbulence near impeller blades – collisional energy of particles** – higher values increase breakage and secondary nucleation.
6. **Energy of collisions in bulk – collisional energy of particles** – although less than the maximum value, the large number of collisions in the bulk can affect breakage and secondary nucleation.

	50 gal. Pilot Plant	Constant P/V 6,250 gal. Plant	Constant Tip Speed 6,250 gal. Plant
Hydrodynamics			
P. mixing power, hp	0.086	10.73	2.20
NRe for flow	70,300	5.75 e+05	3.39 e +05
Average circulation velocity, m/s	0.311	0.517	0.305
Mean circulation time, s	3.79	12.7	21.6
NRe, impeller	1.3 e + 05	1.11 e + 06	6.53 e + 05
Tip speed, m/s	3.20	5.44	3.21
Turbulence			
Energy dissipation average, W/kg	0.356	0.319	0.0655
Energy dissipation max. W/kg	110	110	22.4
Volume of Zone for maximum energy dissipation, cubic meter	0.000213	0.0268	0.0268
Characteristic micromixing time, s.	4.18	4.43	9.79
Energy dissipation at baffles, W/kg	0.147	0.130	0.0267
Energy dissipation in bulk, W/kg	0.147	0.130	0.0267
Microscale of turbulence near blade, m	1.24 e-05	1.24 e-05	1.84 e-05
Microscale of turbulence near baffle, m	6.46 e-05	6.66 e-05	9.89 e-05
Microscale of turbulence in bulk, m	6.46 e-05	6.66 e-05	9.89 e-05
Turbulent shear rate near blade, l/s	8970	8960	4050
Turbulent shear rate near baffle, l/s	327	309	140
Turbulent shear rate in bulk, l/s	327	309	140
Liquid-Solid Mixing			
Maximum degree axial, non-uniformity %	13.8	9.20	15.9
Maximum degree radial, non-uniformity %	0.558	0.237	0.236
Maximum Energy of collisions, J	7.25e-11	7.24 e-11	2.51 e-11
Characteristic time between two strong collisions, s.	38.3	42.5	72.0
Energy of collisions in bulk, J	8.77 e-13	8.11 e-13	2.82 e-13
Frequency of collisions of maximum energy l/s	0.0261	0.0235	0.0139

Table F. Mixing programming.

7. **Frequency of collisions of maximum energy** – predicts how often the slurry particles see the maximum collisional energy – if higher, more breakage and secondary nucleation.
8. **Time between two strong collisions** – average period of uninterrupted crystal growth.

Conclusion

1. It has determined that the use and implementation of the CAPE program can aid in process development and Scale-Up from bench scale through the Pilot Plant and into the full production units.

2. Training is essential to assure the best utilization and ultimate results from the CAPE program.

3. The CAPE program requires substantial interaction by the various functional groups in the organization in order to yield optimal results.

References

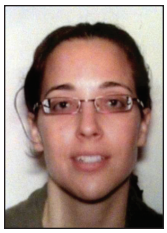
1. Levin M., Process *Scale-Up in the Pharmaceutical Industry,* Marcel Dekker, Inc., New York, 2001.
2. Bright R., Dale D., Dunn P., Hussain F., Kang Y., Mason, C., Mitchell, J., and Snowden, M.,"Identification of New Catalysts to Promote Imidazolide Couplings and Optimisation of Reaction Conditions Using Kinetic Modelling," *Org. Proc. Res. Dev.,* 8 (6), pp 1054–1058, 2004.
3. Bentolila, M., Kennet, R., "Scale-up Optimization Using Simulation Experiments," presented at the American Institute of Chemical Engineers (AIChE), Palm Springs California, 11-16 June 2006.
4. Genck, W., "Optimizing Crystallizer Scale-Up," *Chemical Engineering Progress,* June 2003, pp. 36-44.
5. Genck, W., "Crystal Clear – Part 2, Scale-Up, Simulation and New Technologies," *Chemical Processing Magazine,* December 2003, pp. 37 – 42.

About the Authors

Wayne Genck, PhD, President of Genck International, has an extensive background in the areas of crystallization and precipitation. The consulting firm of Genck International assists pharmaceutical, specialty chemical and commodity chemical manufacturers in crystallization and precipitation issues. This includes matters involving design, troubleshooting, polymorphism, and scale-up of crystallization and precipitation issues. He has consulted for more than 240 industrial firms and has written numerous articles for Chemical Engineering Progress. In addition, he authored the chapter on crystallization for the recent 8th Edition of Perry's Chemical Engineers Handbook. He is the recipient of the Professional Achievement Citation in Engineering for Alumni from Iowa State University from which he earned a PhD in chemical engineering. He is a frequent lecturer for courses on industrial crystallization. He can be contacted by telephone: +1-708-748-7200 or email: genckintl@aol.com.

Genck International, 3 Somonauk Court, Park Forest, Illinois 60466, USA.

Michal Hasson received her degree in chemical engineering from the Ben Gurion University of the Negev, Beer Sheva, (Israel) in 2002. Thereafter, she joined Chemagis Ltd. (Perrigo subsidiary) as a Engineering Regulatory Manager. She received her MSc in environmental engineering also from Ben Gurion University in 2006. In 2005, she joined the Pilot Department in Chemagis as a pilot engineer and she is currently a laboratory manager of the process technology characterization area.



Efrat Manoff received her degree in chemical engineering from the Ben Gurion University of the Negev, Beer Sheva, (Israel) in 2005. Thereafter, she joined Chemagis Ltd. (Perrigo subsidiary) as a Pilot Engineer in the R&D Department. In 2009, she received her MSc in environmental engineering also from Ben Gurion. In 2009, she moved to Enzymotech (Kfar Baruch, Israel) as a process engineer. Currently, she is the production plant manager of Enzymotech Biotechnology and in charge of implementing GMP procedures in the company.

Roberto Novoa received his MSc and PhD degrees in chemical engineering from the "Universidad de Oriente," Santiago de Cuba, Cuba. His professional experience includes working in Cuban sugar factories and in R&D projects of sugar cane by-products. From 1974 to 1998, he was a chemical engineering professor at U.O. Santiago de Cuba, Cuba. Since 2003, he has been a simulation engineer of API R&D - production in Chemagis, API Division of Perrigo, Ramat Hovav, Beer Sheva, Israel.

Moshe Bentolila received his degree in chemical engineering from the Israel Institute of Technology – Technion, Haifa, (Israel) in 1994. Thereafter, he joined with Tami – IMI institute for R&D Ltd. (ICI Israel Chemicals), as a pilot engineer. In 1997, he received his MSc in reactor design from Israel Intitute of Israel – Technion Haifa. In 1998, he moved to Chemagis Ltd. (Agis group – Ramat Havav, Israel) as a Pilot Department Manager. During his work is Chemagis, he developed a methodology for scale-up processes in the API industry. Recently, he joined to VisiMix – Software as a chemical engineer in Customer Support. He can be contacted by telephone: 972-2-5870123 or email: mosheb@visimix.com.

Visimix Ltd., PO Box 45125, Jerusalem, Israel 91450.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

This article presents a comparison of sampling methods used to validate data migrated onto IT systems.

Validating Data Migrated onto Information Technology (IT) Systems

by Mark Nightingale

Introduction

The implementation of an IT system inevitably raises issues concerning the management of previous records, often referred to as legacy or heritage data. Such data is ideally migrated onto the new system to provide immediate access, effective back-up, and avoids the requirement for alternative archives or maintenance of the heritage system. The decision to migrate all or part of the legacy data may be influenced by regulatory and medico-legal requirements, frequency of access, the need to update legacy records, effect on performance of the new database and availability of resources to support the migration process. For blood services, data migration has helped address recent EU blood safety legislative requirements for long term maintenance of a full and accessible audit trail from donor to recipient.[1]

The process of automated data migration shown in Figure 1 may require specialist software (a data migration tool) developed by suppliers of the heritage and new system. Alternatively, and less frequently nowadays, a manual migration process may be deployed through specialist "data take-on" personnel or suitably trained existing employees. Alternatively, the process may involve the migration of data onto an intermediate database to provide a more suitable format prior to migrating to the new system or to consolidate several diverse databases. Each of these processes is subject to differing types and magnitude of error and all require the data to be validated after migration.[2] Data migration validation is a specialized part of the wider acceptance testing of IT systems that includes ensuring that the physical and logical database architecture, security, functionality, and performance are as specified.[3]

Data migration errors can affect data transfer and data integrity (accuracy). These include systematic errors, such as failure to migrate a data field or all of the data within a field, data rounding and truncation errors (exact numeric value not stored), corruption of data when merging fields and data mapping errors, e.g., blood group "A" on the heritage system assigned as group "B" on the new system. The risk of systematic errors can be reduced by carefully specifying and agreeing the fields to be migrated, testing mapping relationships enforced by the migration tool, and applying data validation rules during transfer. Such rules include data type, format, permissible range of values, character length, and referential integrity (consistency with data elsewhere on the system). The ability to count, preferably by electronic means, data items on the heritage and new system after migration can confirm that all records have been migrated (although complicated when there is not a 1:1 relationship between data items). Random errors can occur during manual data entry, due to incorrect transcription. They also can occur during automated migration through corruption and loss of links between data items, e.g., due to migrating databases which lack proper indexing (primary and foreign key constraints), through interruption by automated database management activities (the firing of triggers), and using incorrect delimiter syntax.[3] Random errors are by definition more difficult to prevent and detect. Data integrity errors are generally detected by checking an appropriate sample of migrated data.

In the absence of widely accepted standards for data migration validation, sampling plans have historically used an intuitive (*ad hoc*) approach to sampling based on perceived risk (henceforth referred to as an "intuitive sampling plan.") For NHSBT, the assessment of risk and conversion to the required sample size for checking, although successful in its outcome, was qualitative and lacked the objectivity to assist in its transfer between IT projects or use by other staff. Intuitive

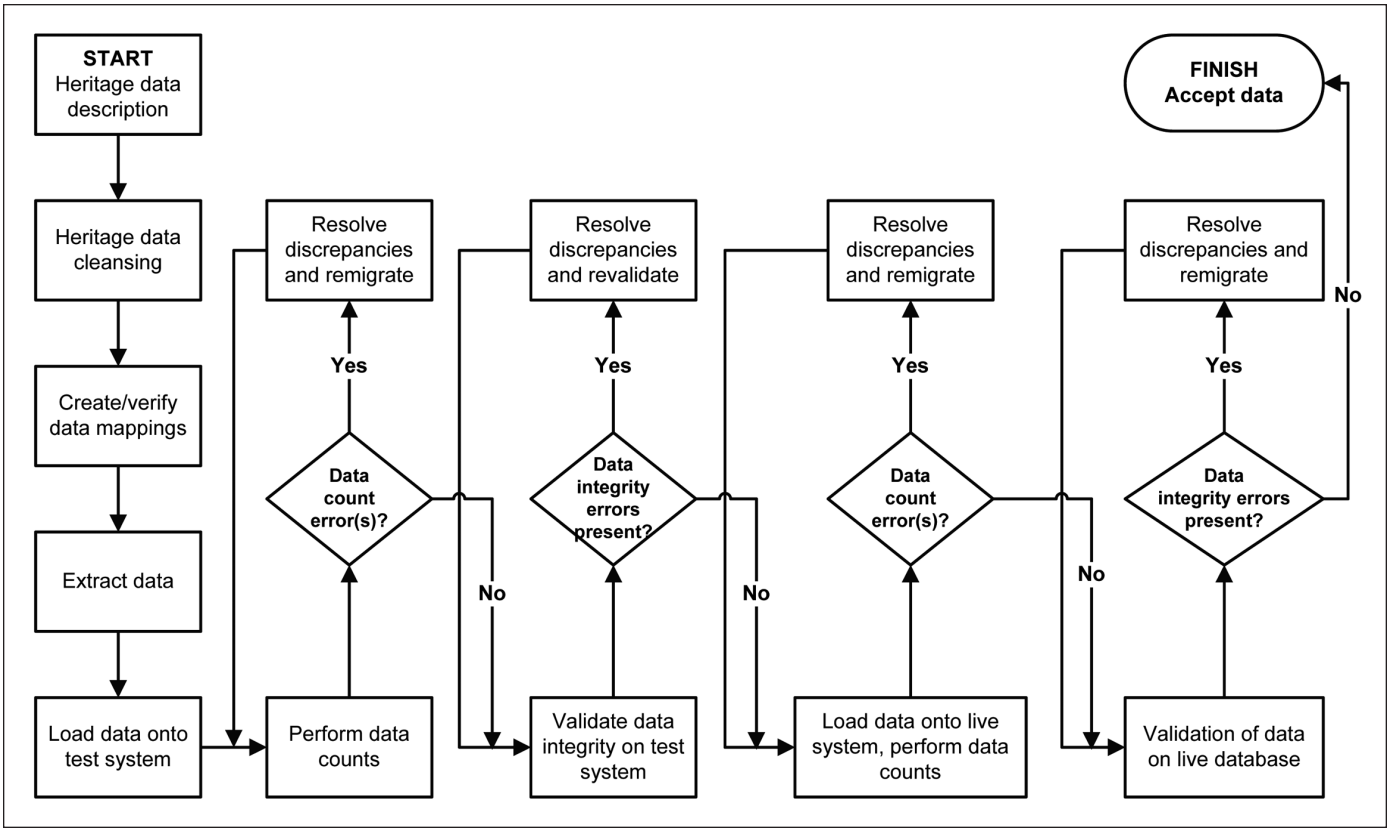


Figure 1. The data migration and validation process.

sampling plans typically required the sampling of fixed percentages of heritage records for each category of data followed by verification of their accuracy on the new system. Sample size was typically assigned on a sliding percentage scale from 0.1% to 100% based on an arbitrary assessment of the criticality of the data and the fallibility of the data migration method. The enormity of the data checking task for national systems when several million records are to be migrated is obvious, even based on modest fixed percentages.

Alternative sampling plans based on probability theory could be used for data validation, e.g., those defined in standards, such as the ISO 2859 (BS 6001) series.[4] ISO 2859-2 (BS 6001-2), Specification for sampling plans indexed by Limiting Quality (LQ) for isolated lot inspection appears the most appropriate (although GAMP® 5 has since recommended ISO 2859-4 – see discussion).[5-6] Each migrated data field can be considered an isolated lot of size "n" with erroneously migrated data being "non-conforming items" that can be counted and analysed as an "attribute." Use of this standard requires those involved to establish a pre-agreed LQ defined as: "A quality level in percentage non-conformity for which the purposes of sampling inspection is limited to a low probability of acceptance." This model is henceforth referred to as the "ISO 2859-2 sampling plan." Of note, ISO 2859-0 (BS 6001-0) does not recommend an *ad hoc* sampling method as "it will lead to the calculation of risks that may be unjustifiably high, furthermore there being no formal basis for either the acceptance or rejection of the lot."

Risk analysis is extensively applied during validation planning to determine the degree of testing required.[6-8] It is typically based on the product of the scores for impact, probability of occurrence, and ability to detect the consequences before they cause an adverse impact (detectability.) The British Committee for Standards in Haematology (BCSH) recommends that risk analysis be carried out as part of data migration validation.[9] "The level of validation required will depend upon several factors and should be determined through a risk assessment process." However, this and other publications appear not to reference an objective method for correlating the output of such analyses with a numerical sampling plan. We aim to provide a straightforward sampling plan based on the assessment of various risk factors by those with knowledge of and experience in using the data. These include the migration process, data complexity (heterogeneity) and the impact of, and ability to detect an error. The proposed methodology henceforth referred to as the Risk-Based Sampling Plan (RBSP) is compared with the alternatives described above.

Materials and Methods

Data Migration Validation Process

Risk-Based, ISO 2859-2, and intuitive sampling plans were applied to the validation of three complex data migrations which were necessitated by NHSBT's requirement for new software from alternative suppliers providing substantially increased functionality, configurability, and GxP compliance. The intuitive sampling plan was applied prospectively to two migrations of demographic, clinical, and laboratory test data. First, from patients referred by hospitals for laboratory investigations (red cell immunohaematology – RCI) and second, blood donor data. The other methods were applied retrospectively for comparison. The RBSP was then applied prospectively to

		Sample Size (%)		
Data Category	No. of Records	(A) intuitive prospective	(B) ISO 2859-2 retrospective	(C) Risk-based retrospective [risk calculation]
Low impact demographic details verified at each donation	196,000	200 (0.10)	800 (0.41) Accept if no errors	98 (0.05) [0.1X0.1X0. 1X0.5= 1/2000]
Medium impact laboratory results verified at each donation	196,000	200 (0.10)	800 (0.41) Accept if no errors	490 (0.25) [0.5X0.1X0. 1X0.5= 1/400]
High impact donor medical history updated if donor re-attends	1200	60 (5.0)	380 (76.92) Accept if no errors	60 (5.0) [1.0X0.1X0. 5X1.0= 1/20]

Table A. Sampling plans for a migration of blood donor data.

a migration of transplant patient histocompatibility data with the other methods applied retrospectively. The data categories, numbers of records, and sample size required by each plan are shown in Tables A, B, and C. Data migration in each case was by an automated method using validated software (by visual confirmation of specified mapping relationships and the trial migrating small samples of known data). Following that, data migration validation was performed with a full data load to populate the new database and the chosen sampling plan was then applied.

The RCI data migration validation was carried out at each site that contributed data while the blood donor and patient histocompatibility validations were carried out centrally. Validation was carried out by pairs of Biomedical Scientists using printed heritage system reports as the primary record with each data item verified and retained as a permanent record. Errors were recorded on an Exception Report and passed to IT staff for investigation and resolution prior to the next data load. Having applied the chosen sampling plan and checked the required number of records, any corrective action indicated was agreed, recorded on the Exception Report, implemented, and verified as effective during the next validation exercise. This process was re-iterated until no further errors were detected.

The Intuitive Sampling Plan

The intuitive sampling plan for each of these data migrations was derived by the migration team based on an arbitrary assessment of the criticality of the data and migration method. Validation sample size for each category of data is shown in column A of Tables A, B, and C.

The ISO 2859-2 Sampling Plan

The sample shown in column B of Tables A, B, and C was derived using the ISO 2859-2 sampling plan (procedure A for single lots). These samples are based on an LQ value of 0.5% (the lowest LQ in ISO 2859-2 statistical tables).

		Sample Size (%)		
Data Category	No. of Records	(A) intuitive prospective	(B) ISO 2859-2 retrospective	(C) Risk-based retrospective [risk calculation]
Low impact demographic details verified on each new sample	1,900,000	770 (0.04)	1,250 (0.07) Accept 3 errors	950 (0.05) [0.1X0.1X0. 1X0.5 = 1/2000]
Low impact sample ID data verified on each new sample	5,330,000	440 (0.01)	1,250 (0.02%) Accept 3 errors	2,665 (0.05) [0.1X0.1X0. 1X0.5 = 1/2000]
Medium impact historic laboratory test results verified on each new sample	25,000,000	6,100 (0.02)	1,250 (0.005%) Accept 3 errors	62,500 (0.25) [0.5X0.1X0. 1X0.5 = 1/400]

Table B. Sampling plans for a migration of patient red cell reference data.

The Risk-Based Sampling Plan

The sample shown in column C of Tables A, B, and C was derived using the RBSP as follows. Three risk factors were assessed for each category of data to be migrated: 1. the impact of an error in the data, 2. the likelihood of the error occurring, and 3. the ability to detect the error in migrated data after the IT system is in routine use.

1. Error impact was assigned as "high risk" to data items that could directly affect patient safety or prognosis, e.g., clinical data and critical laboratory data. "Medium risk" was assigned to data that could indirectly affect patients, e.g, historic records of treatment or laboratory investigations

		Sample Size (%)		
Data Category	No. of Records	(A) intuitive retrospective	(B) ISO 2859-2 retrospective	(C) Risk-based prospective [risk calculation]
Low impact demographic details verified on each new sample	289,144	200 (0.07)	800 (0.28) Accept 1 error	146 (0.05) [0.1X0.1X0. 1X0.5 = 1/2000]
High impact basic laboratory results verified on each new sample	75,683	400 (0.53)	800 (1.06) Accept 1 error	378 (0.5) [1.0X0.1X0. 1x0.5 = 1/200]
Medium impact HLA types verified before clinical use	56,000	1000 (1.79)	800 (1.43) Accept 1 error	1400 (2.5) [0.5X0.1X1. 0X0.5 = 1/40]

Table C. Sampling plans for a migration of patient histocompatibility data.

		Likelihood of Error				
Data Type	Impact of Error	Migration Method	Heterogeneity of Data	Detectability	Overall Risk	Sample Size (%)
E.g. 1	1	1 (manual)	1	1	1	All / (100)
E.g. 2	0.5	0.1 (automated)	0.5	0.1	0.0025	1/400 / (0.25)
E.g. 3	0.1	0.1 (automated)	0.1	0.1	0.0001	1/10,000 / (0.01)

Table D. Example risk analysis template.

that might be used for research purposes and demographic details not required for identification purposes. "Low risk" was assigned to any other data (and should require its migration to be carefully justified).

2. The likelihood of an error occurring was assessed by the following two factors:

   First, migration method: "high risk" was assigned to manual data entry with no second person check, "medium risk" to manual migration closely monitored by experienced staff or migration via a validated intermediate database or spreadsheets, and "low risk" to automated migration using a validated migration tool.

   Second, heterogeneity of data: "high risk" was assigned to complex and variable data involving multiple "mappings," e.g., for transplant patients, their tissue type (Human Leucocyte Antigen – HLA), "medium risk" to a data string such as patient medical history or laboratory comments, and "low risk" to simple data (e.g., a patient's gender or date of birth).
3. The ability to detect an error in the data after the new system is implemented. "High risk" was assigned when migrated data (e.g., test results) are destined to be issued directly from the database without being re-validated, "medium risk" when data will be manually checked before use/issue, and "low risk" when data will be electronically verified against new findings.

The risk analysis for the RBSP was carried out using an Excel template shown in Table D. For each category of data to be migrated, each of the four risk factors above was assigned a value: 1 for high risk; 0.5 for medium risk, or 0.1 for low risk. The value assigned to each risk factor was multiplied to give an overall risk factor ranging from 0.0001 to 1. This was correlated directly with the sample size for data validation. Therefore, for a manual migration of critical, highly heterogeneous data with a low probability of error detection, validation requires 100% of migrated records to be checked. An automated migration using a validated migration tool with simple, non-critical data with a high probability of error detection requires 1 in 10,000 (0.01%) records to be checked. A minimum sample of 30 records (or all if less than 30) is recommended regardless of overall risk factor to compensate when relatively small numbers of records are being migrated (<10,000).

Targeting Records Within the Sample

The methods described above were used to establish the overall number of data items/records to check in each data category of data. The prescribed sample for the intuitive and RBSP was carefully selected from within the range of data in each category. This was to ensure that the data sample represented: the oldest and newest data; data entered by each contributing clinic or laboratory; all categories of patient; all investigation types and outcomes. The intention was for selection criteria to be accommodated from within the overall sample required by each of the sampling plans. This is practical because highly heterogeneous data with complex mapping requirements prompts for a larger sample when using the RBSP.

Validation of the Risk-Based Sampling Plan

The residual risk of an error in migrated data was calculated by two methods. First, a retrospective measurement of data errors revealed since the 2006 migration of patient data in Table B. Second, by statistical inference applying both a random and systematic error model to the sampling plans and patient data in Table C. The systematic error model was developed for this application and assumes that records in each category are stratified with the number of strata times the stratum size equal to the total number of records. For example, Patient Demographics has 289,144 records which are assumed to comprise 41 strata, each of size 7,052. Any error will affect all 7,052 records in the stratum. This is a simplification of the true situation, but allows a plausible calculation of the residual error rate, for comparison with the conventional independent error model. A fuller explanation is provided in the sidebar "Statistical Model for Assessing Residual Risk."

Results

The patient RCI data migration validation (intuitive sampling plan) identified the following data migration errors: four incorrect mappings, three owing to the data migration routine, and eight "bugs" in the data conversion routine. No errors attributable to the migration process have been detected to date since implementation. The histocompatibility data migration (RBSP) identified: seven mapping errors, one data specification error, 13 errors in the data migration routine, 12 migration software errors, and 13 errors in the host system configuration.

Table E shows for the migration of patient RCI data, the validation effort associated with each sampling plan (measured in hours taken to sample, verify, and document the data validation checks). This has been correlated with the residual risk of an error for the intuitive sampling plan based on subsequent live use of the data where it is estimated that a total of 300,000 (15%) of records have been accessed for update, an activity where errors might reasonably be expected to be highlighted.

Table F shows for the migration of histocompatibility data the residual risk of error for the three sampling plans based on statistical inference. In Table F(a), errors are assumed to be random and F(b) systematic. The entries in each cell are

	Sampling Plan			
	Intuitive		ISO 2859-2	Risk-based
Category of Data	Validation Effort (hours)	Measured Residual Risk of Error Since Routine Use (see Note)	Validation Effort (hours)	Validation Effort (hours)
Demographic	10	$< 1 / 3.0 \times 10^5$	16	12
Sample ID Data	10	$< 1 / 8.2 \times 10^5$	28	59
Test Results	8	$< 1 / 3.8 \times 10^6$	1.6	80
Note: Based on number of errors detected in migrated patient records accessed since routine use (none to date).				

Table E. Correlation between validation effort and residual risk of an error in the migrated data.

upper 95% one-sided confidence limits for the error rate given that no errors were observed in a sample of the size shown in Table C.

Discussion

In designing the RBSP, the aim has been to correlate validation effort (and corresponding data sample) with the risk of error in migrated data. An assessment of the impact of data errors and their "detectability" has, in common with typical risk analyses, enabled the overall risk score and sample to be reduced by two orders of magnitude. The predicted likelihood of an error occurring, (depending on the migration method and data complexity) has, based on a comparison of error rates, conservatively enabled a further two orders of magnitude reduction in sample. For example, error rate in the manual entry of complex data has been estimated at 1/300 characters whereas for automated data transfer, two or more orders of magnitude less can be expected.[10] Thus, for a "full house" of high risk factors, our risk impact analysis requires the accuracy of all migrated data to be checked. This coincides with Good Pharmaceutical Manufacturing Practice (GMP) for validating manually entered critical data.[11] Conversely, for a "full house" of low scores, sample size can be reduced by four orders of magnitude to 0.01% of records.

The allocation of risk values to each of the four risk factors dictates the sensitivity of the RSBP in detecting errors. The definitions and examples provided under "materials and methods" help inform this decision. The four categories of risk factor (impact of error, etc.) and their three associated risk values divide the overall risk score into 15 increments. Figure 2 shows the relationship between the risk increment and sample size which increases approximately exponentially from 0.01 to 100%.

The impact of a change in risk factor can be seen when applied to the patient data migration in Table B. Validation of demographic data required a sample of 950 records. Using the risk increments, either side would have increased the required sample to 1900 (for no apparent improvement in error detection) or have reduced it to 190. This smaller sample would not have allowed adequate representation of contributing laboratories, patient types, and date ranges.

The sample required by the RBSP, as a percentage of records migrated, was close to the intuitive plan for straightforward data such as demographics and patient comments. However, ISO 2859-2 required a significantly larger sample for these categories which was not justified by the finding of additional errors during validation or live running. The most notable disparity was seen with the RBSP for patient RCI sample and test results - *Table B*. Owing to the large amount of data being migrated and higher error impact the RBSP prompted for a significantly larger sample than both the intuitive and ISO 2859-2 plans. This together with the increased validation effort was justified as the intuitive plan (used during the migration) required an additional two data validation and corrective action cycles to eliminate the errors. Additionally, a single low impact error was detected during the final data validation exercise (in preparation for live running), which required correction by database amendment.

Figure 2 shows the main advantage of the BPSC over ISO 2859-2 (and the GAMP 5 recommended ISO2859-4) in its gradual increase in sample as the risk of error and its impact increases (e.g. Table B sample ID and test data). For small migrations (< 3000 records), ISO 2859-2 requires a sample varying from 13 to 100%. Sampling at this level is not justified for automated migration of simple, non-critical data. For the above reasons, we do not recommend using ISO 2859-2 for

	(A) Intuitive	(B) ISO 2859-2	(C) Risk-based
F(a)			
Patient Demographics	0.015	0.0038	0.021
Basic Laboratory Results	0.0075	0.0038	0.0079
HLA Types	0.0030	0.0038	0.0021
F(b)			
Patient Demographics	8.8×10^{-6}	0.0019	1.2×10^{-5}
Basic Laboratory Results	2.2×10^{-6}	0.00093	2.2×10^{-6}
HLA Types	0.00016	0.0019	0.00011

Table F. Upper 95% estimates of residual risk, when no errors are found for the sampling plans detailed in Table C. (a): random error and random sample selection. (b): systematic error and targeted sample selection (ISO2859-2 plans A and B only.)

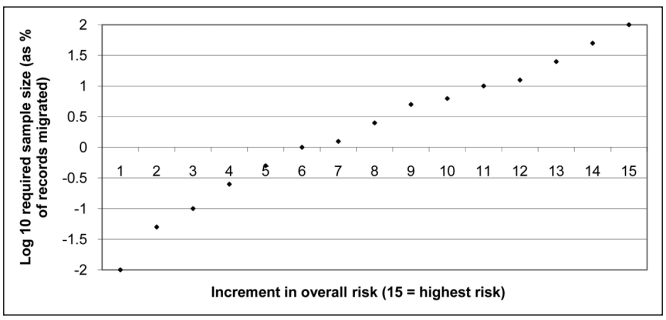


Figure 2. Relationship between increasing risk and sample size for the RBSP.

this application and imply no criticism as it was not written for this purpose. ISO 2859-4 uses a fixed sample that does not depend on the quantity of data being migrated. This might be considered a disadvantage in that the chance of detecting random errors present at a fixed proportion decreases as the number of migrated records increases. Significantly, this situation is more likely to be associated with an increased incidence of random error as exposure to risk factors in the migration process (see introduction) also increases with time.

Table F indicates that sampling at the specified levels cannot entirely eliminate a small residual risk of data errors. Systematic errors should be detected by the process of checking mapping relationships and data integrity. Random errors are by definition more difficult to detect, but tend to be associated with higher risk manual migrations for which the RBSP requires a tenfold larger sample. The difference between residual risks in Tables F (a) and (b) gives an idea of the improvement obtained by judicious targeted sampling, provided that errors occur systematically.

When errors are detected during validation, the approach should be to identify the root cause, correct the error(s), and reapply the sampling plan (to the data that contained the errors plus a new sample). Sample selection is an important aspect of any sampling plan. Records could be chosen at random from among legacy data (as required by ISO 2859-2) such that any record has an equal chance of being selected. However, this strategy fails to take into account that some tests are seldom requested and some blood characteristics comparatively rare. Therefore, random sampling is not recommended for this reason. Instead, we favor careful targeting of records as described above and recommended by BCSH.[9]

The phased migration trials deployed here had the benefit of successively correcting and reducing errors so that by the live migration, confidence was gained that no additional errors would be detected that might delay the "go-live." The patient data migration validation proved difficult to manage across multiple sites. Twelve reported errors that proved unfounded were owing to misunderstanding by the data "validators" of

Statistical Model for Assessing Residual Risk

In general, the number of records migrated is denoted by N of which an unknown proportion p still contain errors distributed at random. A sample of ρN records is checked, and r of them are found to contain errors. The number of errors has the hypergeometric distribution $r \sim \text{Hyp}(N, pN, \rho N)$, which if the sampling and error rates are small, can be approximated by the Poisson distribution $r \sim \text{Poiss}(\rho Np)$. We shall normally only consider inference from an observed $r = 0$. Let there be f strata each of size g so that $fg = N$. Any error is replicated in all g records of the stratum. θf strata are represented among the records examined. The number of strata containing errors is a Poisson random variable $s \sim \text{Poiss}(\theta fp)$. What is observed will actually be t, the number of records in error, rather than s, the number of strata containing errors. However, t and s will be almost equal as long as they are small.

The intuitive and RBSP are both targeted in that each record is chosen from a different stratum. Given that ρN of the N records are screened, representing θf of the f strata, targeted sampling means maximizing θ so that $\theta = \rho g$. On the other hand, the ISO 2859-2 scheme chooses records at random with the result that θ is less than ρg. For example, $\theta \approx 0.63$ if $\rho g = 1$.[12] When θ is as large as this, the Poisson approximation is no longer accurate, and the reduced variance of the hypergeometric model should be used, $\text{var}\, s \approx \theta fp(1 - \theta)$. A notional random variable equal to s divided by $(1 - \theta)$ is regarded as Poisson distributed, $u \sim \text{Poiss}(\theta fp/(1 - \theta))$. A 95% upper one-sided confidence limit for p when $u = 0$, i.e., no errors were found, is given by $\theta fp/(1 - \theta) = 3.00$, where 3.00 is log 20.[12] For example, if $f = 41$ and $\theta = 0.999$ the upper confidence limit is $p_U = 7.3 \times 10^{-5}$. This is for targeted sampling of 41 strata where 99.9% of the strata are represented. If the sampling were random instead of targeted about 63% of the strata would be represented and p_U would be 0.0027. If errors were thought to be random (and therefore independent), among 289,144 records, p_U when no errors are found in a sample of 41 would be 0.073. Results are shown in Table F(a) and F(b). For example, the intuitive demographics sample was of 200 records. The confidence limit is 3.00/200 = 0.015.12 In Table F(b), the data are assumed to be stratified. The numbers of strata and the coverage of strata by targeting are assigned according to the owners knowledge of their data. For example, Patient demographics is considered to have 41 strata of which 99.9% are covered by targeted selection. The remaining 159 records in the sample of 200 are supposed to be chosen at random. The expected number of strata covered by them is given by the Arfwedson occupancy distribution with parameters $N = 159$ and $k = 41.041$. This is a coverage rate of 0.884 .[12] Applying this rate to the 0.041 so far unrepresented strata we find the total coverage to be $41 + 0.884 \times 0.041 = 41.036$ strata out of 41.041. Hence, the upper 95% confidence limit p_U is $3.00(1 - \theta)/(\theta f) = 3.00 \times 0.001 \div 41.036 = 8.8 \times 10^{-6}$.

The residual risk calculations for Table F(b) use the assumed numbers of strata (41, 2, 5, 83 and 15 for the five data categories) and the assumed coverage of strata (99.9% for all except HLA Type which has been conservatively estimated at 90%). The estimated residual risk is not particularly sensitive to the number of strata, but sensitive to the coverage because of the factor $1 - \theta$ in the expression for p_U. We have used the dispersion-adjusted Poisson approximation to the true hypergeometric distribution throughout. Our calculations are based on the last, error-free iteration (Figure 1), and ignore the earlier times round the loop. We have constructed a model of the iterative process, rather like maximum probable number estimation with serial dilution. This gave similar estimates to the much simpler error-free test, so we did not consider it worth including in this article.

the data migration specification (data not intended for migration or displayed in an unexpected field). Training was more difficult to deliver, communication slower, and many of the inappropriate Exception Reports duplicated across sites as a result. The centralized donor migration validation enabled IT, laboratory, and quality assurance staff to be readily available to address any such misunderstandings.

By applying this Risk-Based sampling plan, the data owner can, through an assessment of the risk to their organization increase their validation effort in a justifiable and predictable manner to maximize the benefit of this costly and time consuming task. This is vital during the implementation of an IT system when there will be numerous competing tasks and priorities.

For some data items, NHSBT has begun to augment the RBSP with direct electronic comparisons of heritage and migrated data extracted into Microsoft Access. Although very promising, the method currently appears limited to straightforward data (string), does not confirm that the data is correctly displayed, requires additional expert IT support, and each new application has to be extensively validated.

References

1. *Directive 2002/98/EC of The European Parliament and Council*, Commission of European Communities, "Setting Standards of Safety and Quality For Collecting, Processing Testing, Storage and Distribution of Human Blood and Blood Components,"2003.
2. Morris, J., *Practical Data Migration*, British Computer Society (ISBN 1-902505-71-9), Chapter 2, 2005.
3. Microsoft, *Solution Guide for Migrating Oracle on Unix to SQL Server on Windows*, Chapter 8 – Developing: Databases – migrating the database and Chapter 9 – Developing: Databases – Unit testing the migration, 2005. <http://www.microsoft.com/technet/itsolutions/cits/interopmigration/unix/oracleunixtosql/or2sql08.mspx, accessed March 2011.
4. *Sampling Procedures for Inspection by Attributes – Part 0: Introduction to the BS 6001 Attribute Sampling System*, British Standards Institute (BSI), BS 6001-0, 1996.
5. *Sampling Procedures for Inspection by Attributes – Part 2: Specification for Sampling Plans Indexed by Limiting Quality (LQ) for Isolated Lot Inspection*, International Standards Office. BS/EN/ISO 2859,1985.
6. *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, www.ispe.org.
7. *Guidelines for Validation and Maintaining the Validation State of Automated Systems in Blood Banking*, International Society of Blood Transfusion (ISBT), Vox Sanguinis, 85 supplement, 2003.
8. *ICH 09 Quality Risk Management*, Medicines and Health Care products Regulatory Agency (MHRA), MHRA EuroDirect Publication No. 24235/2006 (EXT), 2006.
9. *The Specification and Use of Information Technology (IT) Systems in Blood Transfusion Practice*, Revill et al, British Committee for Standards in Haematology (BCSH), 2006. http://www.bcshguidelines.com/pdf/computer_guide_220506.pdf, accessed March 2011.
10. Palmer, RC, *The Barcode Book*, Helmers Publishing Inc. (ISBN 0-1911261-02-8), 1989.
11. *Rules Governing Medicinal Products in the European Union*, EU GMP, Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 11, Computerised systems, clause 6, Accuracy Checks, 2007.
12. Johnson N.L., and Kotz S., *Discrete Distributions*, John Wiley, New York, 1969.

Acknowledgements

The author wishes to acknowledge John Ord, Gordon Burgess, Delordson Kallon, Ian Britton, Phil Stamp, and Chris Harpur of NHSBT for their expert input to the data migration processes described, all NHSBT staff involved in data migration validation, and especially Dr. Andrew Grant, Statistics Unit, Health Protection Agency, Colindale for the statistical modelling and residual risk calculation and Margaret Reed, NHSBT for the extraction of invaluable IT system reports.

About the Author

Mark Nightingale qualified as a bio-medical scientist in 1977, worked in hospital and Blood Transfusion Service laboratories and became a laboratory manager in 1984. His qualification route included HNC in Haematology and Blood Transfusion, BA (honors), in biological science, a higher degree in Transfusion Science and B.Tech in Health Service Management. Work experience includes immunohaematology, transfusion microbiology; histocompatibility, blood component, and IVDD preparation. Since 1990, he has worked as a quality professional in the same field and posts have included QA Manager NHSBT Southampton, NHSBT Midlands and Southwest Zone Quality Manager. His current role is NHSBT Quality Specialist providing input to national projects and task forces, including the implementation and validation of national IT and laboratory test systems and their data, critical consumables contracting, UK Blood Service Standing Advisory Committees for Blood Components, and IT. International duties include representing the UK Blood Transfusion Services on ISO TC76 WG1 and BSI/CH212 for transfusion equipment, participating in an EU project to harmonize Blood Service Auditing (EUBIS), and development of a European Blood Alliance purchasing specification for blood bags. Membership of professional bodies includes, Fellow of the Institute of Biomedical Sciences; founding member of British Blood Transfusion Society, Associate member of Institute of QA. He is a IRCA Lead Auditor and have participated as a visiting Lecturer for BSc and MSc biomedical and transfusion science. Research interests include transfusion science, quality management, and control and statistical techniques and to date include 22 publications in peer reviewed journals.

National Blood Service, Coxford Road, Southampton SO16 5AF, United Kingdom.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

A visible player in the development of FDA's 2011 Final Guidance on Process Validation, Grace McNally shares her experience on the effort it takes to shape such policy and her perspective on the Guide's key recommendations.

PHARMACEUTICAL ENGINEERING Interviews

Grace McNally, Senior Policy Advisor, FDA CDER Office of Compliance, Division of Manufacturing and Product Quality

by Rochelle Runas, ISPE Technical Writer

Grace McNally is a Senior Policy Advisor in CDER's Office of Compliance, Division of Manufacturing and Product Quality, Guidance and Policy Team. She is active on several working groups dealing with process validation, combination products and revisions of the CGMPs, as well as developing training for FDA and industry. She has served as Compliance Officer handling CGMP cases and as a field Investigator in ORA (Office of Regulatory Affairs) specializing in drug and medical device inspections. Prior to coming to CDER she worked in Denver District and Philadelphia District. She graduated from Boston College, Chestnut Hill, MA.

Q Can you please give us an overview of your role and responsibilities as Senior Policy Advisor in CDER's Office of Compliance, Division of Manufacturing and Product Quality, Guidance Policy Team?

A The Guidance and Policy (GAP) team manages the development of regulations, enforcement policy, guides/inspection programs and guidance for industry related to drug CGMPs and other adulteration issues. Additionally, GAP members consult on cases under review by our pre-approval, domestic and foreign case management branches, develop ORA inspection guides, provide input on ORA training courses, and comment on external documents impacting drug quality (e.g., USP, ISPE, PDA, and PIC/S). Other responsibilities include managing division procedures, coordinating responses to external inquiries, and providing input on international agreements impacting on surveillance and enforcement of drug quality.

My responsibilities within the GAP team include developing guidance for industry, participating in the Combination Product workgroup and the CGMP regulation revision workgroup, and developing training courses/materials for FDA investigators and DMPQ personnel. Also, I provide CGMP case consultations to Division compliance officers and field personnel. I am the Division's representative on a couple industry committees and advisory boards. I chaired the workgroups that developed the process validation guidance. Since its publication in January 2011, industry outreach and internal FDA training associated with the final PV Guidance for Industry has been a focus.

Q Process Validation is a hot topic for ISPE Members and the pharmaceutical manufacturing industry in general. What was your direct involvement in the final *Guidance for Industry – Process Validation: General Principles and Practices*?

A I was Chair of the original and revision working group. CDER Office of Compliance led this effort which was initiated as part of the CGMPs for the 21st Century initiative. One workgroup created the original 2008 draft, and a second one convened to finalize it based on comments to the draft. Many of the original members were on the second workgroup but we also benefited from new members and their fresh perspectives.

I led meetings, drafted language, helped edit text, and facilitated discussions to resolve differing opinions and keep us moving forward. I also handled the administrative tasks, e.g., create agendas, maintain document versions, and summarize progress. The drafting was truly a group effort; my colleagues from CBER, CVM, ORA and other Offices (Pharmaceutical Science, Generic Drugs and Biotechnology Products) were excellent contributors. I also had great support from my colleagues in Office of Compliance. Brian Hasselbalch, GAP Team Leader, initially co-chair, continued to participate and provide input through to the completion of the project. Two Compliance Officers (Tamara Felton and Steve Hertz) and one of our Regulatory Counsels (Paula Katz) in Office of Compliance also were enormously helpful in organizing and summarizing the comments from the 2008 draft and editing the final version. The Division Director, Rick Friedman, stayed informed and was very supportive.

Q Do you believe the guidance's recommendations will change industry's approach to process validation in general? If yes, how? If no, why not?

A Yes, I do. This guidance reinforces several foundational principles of the CGMP regulation essential to long term process validation success. First, this guidance advocates "lifecycle" thinking as opposed to a "once and done" process validation mentality. Lifecycle thinking fosters better planning and knowledge management and incorporates feedback for process improvement.

Secondly, this guidance highlights process design, including understanding process parameter and material attribute interactions, as part of the lifecycle. Good design work increases the odds of a successful commercial scale qualification and robust process overall.

And, finally, the lifecycle comes full circle in Stage 3 which reflects in part the requirement in 211.180(e) which obligates manufacturers to periodically evaluate their manufacturing experience and determine the need for changes. The recommendations about measuring process performance and process variability with statistical tools and data analyses are directly related to several key CGMP requirements, e.g., 21 CFR § 211. 110(a), 211.110(b), 211.165(d).

I think the guidance will cause manufacturers to rethink a "one-size-fits" all PV approach. This guidance promotes scientific and risk-based approaches that incorporate, rather than overlook, the different or unique aspects of the particular product and process under study. Ultimately, routine oversight should be aligned with the normal behavior of the process in order to detect shifts or drifts, etc. The root cause of any unexpected behaviors will likely be easier to determine because of the greater degree of process knowledge.

Q From your experience working on the Guidance, what challenges did the FDA face in developing the Guidance?

A The workgroup members had different regulatory responsibilities, scientific backgrounds, and industry experience. Initially, our diverse backgrounds were challenging but ultimately proved to be our greatest strength. Over the course of our collaboration, we gained broader insight into the inspectional, review and compliance issues surrounding process validation. We had to consider the differences in statute and regulation, as well as any historical conventions, between the different drug types covered by the Guidance. The diversity of the workgroups made for productive discussions about these issues and contributed greatly to the strength and scientific standing of the principles and recommendations in this Guidance. I learned a great deal and have tremendous respect for my colleagues with whom I worked on this project.

Q What do you think were the main concerns industry voiced from the 2008 draft of the Process Validation Guidance and how are those concerns addressed in the final version?

A We received comments concerning applicability of the Guidance to legacy products and processes, and also issues surrounding statistical sampling, statistical data analysis and measures of process performance.

Regarding legacy processes, the final version includes some clarifying language stating that implementation of the recommendations of the Guidance would likely begin in Stage 3. The programs manufacturers already have (or should have) to collect and analyze product and process data can be used to evaluate the state of control of the process. These evaluations may trigger a return to some of the activities described in Stages 1 and 2.

From a lifecycle perspective, validation is an ongoing activity and manufacturers should establish a program(s) that regularly assesses the state of control regardless of when or how the process was developed. Changes to correct or improve the process and control strategy should be proactively pursued as increasing process knowledge and experience dictates.

The industry also expressed concern about the emphasis on statistics – applying statistical tools, metrics and analyses to manufacturing data, and objectively measuring the performance of their processes. The gist of the concern was mostly where and how to begin implementation rather than objections to the need for it. I believe there is recognition that the CGMPS have long required this.

During conferences and other interactions with industry, I am hearing

"Seek to understand, in a methodical, scientific way, the interactions between process parameters and raw material attributes."

that some industry groups, individual companies and consultants are initiating task forces or committees, internal projects, or writing papers to share ideas and information about this topic. This is very encouraging.

The use of statistics is not a new discipline or field of study. Many resources are available in the literature and manufacturers need to move forward in this area. I am hopeful this will lead to more meaningful studies and criteria during Stages 1 and 2 as well as more targeted and value added Stage 3 programs.

Consumers expect the drug to have the same quality every time they ingest, inject or apply it. This Guidance is promoting better measurement of intra-lot and lot-to-lot consistency. The appropriate level and frequency of routine sampling and monitoring should be tied to that knowledge.

Q You delivered a presentation on the Guidance at ISPE's Tampa Conference in February. Considering the 2008 draft release was met with mixed reviews and interpretations, Tampa Conference audience members were relatively quiet and had few follow-up questions. What is your opinion on how the final Guidance has been received by industry?

A My Office has received positive feedback. Many welcome the emphasis on a scientific, well reasoned approach to design, demonstration at commercial scale, and monitoring and maintenance in accordance with some reasonable and measurable confidence.

The Guidance also created some anxiety. While some saw the opportunities and value added, others felt concern about losing what they perceived as 'certainty' in PV expectations. People naturally seek standards, and uniform approaches in the interest of efficiency and regulatory certainty. The agency supports that if the science is there for the product/process in question. In our past experience we saw (and, disturbingly, still do) more than a few instances where design work and process understanding was minimal, qualification efforts were rote and devoid of truly meaningful acceptance criteria and a thoughtful, scientific process monitoring program(s) was altogether missing.

This guidance emphasizes the necessity of comprehensive design work, meaningful process performance criteria, data collection and analysis, and a solid process monitoring program.

Q What is a main takeaway message from the Guidance you feel could serve as a beacon to industry as it considers and implements concepts within the Guidance?

A Seek to understand, in a methodical, scientific way, the interactions between process parameters and raw material attributes. Understand their impact on the important safety, efficacy, and quality attributes of the drug. For the initial qualification, build a scientific and comprehensive approach around those key aspects. Past protocol(s) may or may not be appropriate for the new product/process under study. Consider its uniqueness first; then consider if existing platforms or approaches make sense for this new process.

Q Is there a coordinated global effort between agencies to align the process validation/requirements/regulations? If so, what is your role in this?

A FDA has been involved in international harmonization efforts on a variety of issues. The ICH collaboration is a well-known example. However, a formal initiative to globally align process validation requirements is not underway at this time. Nevertheless, during meetings or other occasions where FDA and other regulators convene, the issue is being discussed. Through these discussions in which several of my colleagues and I participate, we hope to better understand the various perspectives and share ours as well. This may lead to a coordinated effort in the future.

Q In your career, what are the most significant issues or changes you have seen in the pharmaceutical environment, domestically and globally, and what changes or challenges do you anticipate in the next few years?

A Outsourcing and the increasing globalization of the industry are the biggest changes I've witnessed in my career. A move from all-under-one-roof to a contracting environment may bring industry greater efficiency but also creates new challenges. For example, separation of process design and development from the commercial manufacturing site may raise some difficult issues regarding the process and product knowledge. Those parties who are qualifying and maintaining the process need access to certain information and knowledge. Companies will need to examine their knowledge sharing practices with contractors and their quality agreements. I expect there will be an emphasis on figuring this out in the next few years.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Controlling Service Oriented Architectures in Support of Operational Improvement

by David Stokes

This article presents an approach to leverage GAMP® good practices to facilitate the qualification and validation of IT middleware and Service Oriented Architecture in support of efficient business operations.

Information Technology (IT) middleware and specifically Service Oriented Architecture (SOA) has the ability to transform business operations within the pharmaceutical and other life sciences industries. Middleware consists of multiple functional and technical components, operating in an integrated manner as part of the IT infrastructure. SOA provides functional software based services via the network to defined groups of users or to other software components.

The use of re-usable and integrated components makes it easier, faster, and less expensive to integrate computerized systems and to more efficiently automate business processes. Partly due to concerns about compliance and control, the life sciences industry has been slower than other industries to leverage this rapidly maturing technology, which is one of the reasons why the industry lags behind similar non-regulated industries in terms of performance benchmarks.

What is needed is a flexible and risk-based approach that allows the IT Department to leverage the power of middleware and SOA, while at the same time addressing regulatory compliance concerns.

Based on practical experience in the pharmaceutical sector and keeping technical details to a minimum, this article provides non-technical users and IT Quality personnel with an outline of what middleware and SOA is and a suggested approach to how it can successfully be controlled.

The Advantages of IT Middleware and SOA

Traditionally control systems and business systems were integrated using custom developed interface software. This was (and is) time consuming to develop and validate, but from a technical perspective the disadvantages are that:

- Every connection between two systems needed to be developed as a custom interface - *Figure 1*.
- There was little, if any, re-use of the software.

At a time when the business "silos" in life sciences are starting to be broken down, it is necessary to think about integrated end-to-end business processes rather than discrete transactional software applications.

This need to streamline business operations and take a common view of shared data, such as product information, patient information, and customer data, means that it is more necessary than ever to integrate different software applications and databases. Rather than using a custom developed point-to-point model, the use of SOA allows software components to be developed based on standards, allowing them to be efficiently re-used - *Figure 2*. This has several business advantages:

- Development time is reduced, allowing the IT Department to more quickly meet the service requirements of the business.
- Development costs are reduced, because components can be re-used and the scope of any new development is limited to the development of new components or new functionality for existing components.
- Upgrading business applications becomes simpler, because the "plug and play" nature of the software components allows easier

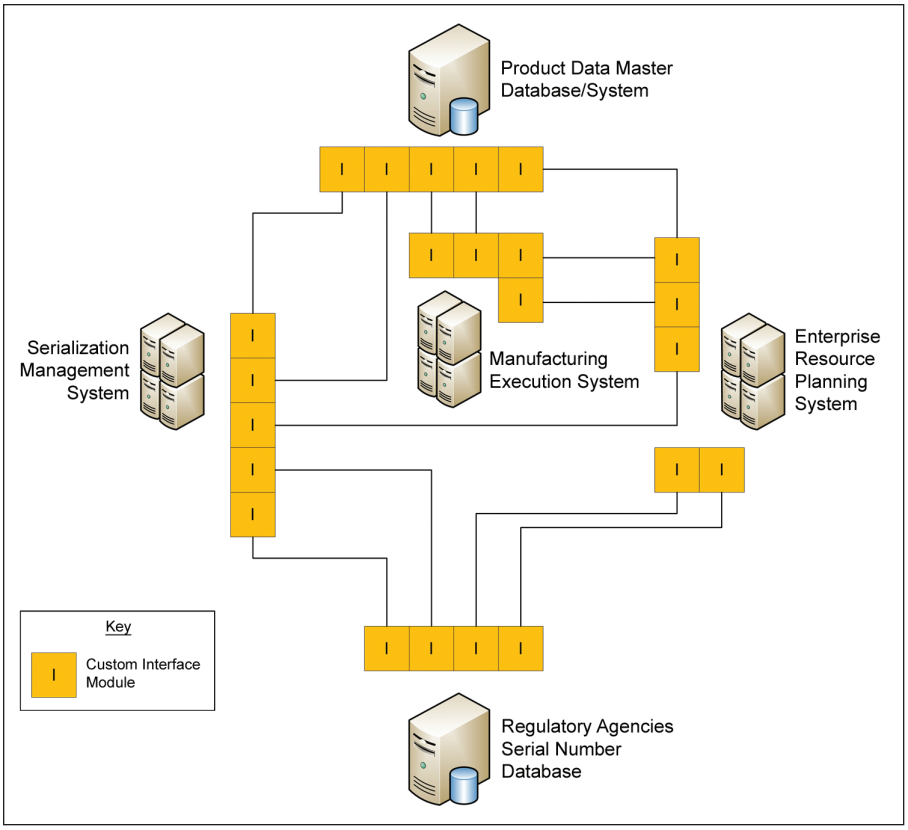


Figure 1. Traditional interfaces with monolithic applications.

upgrades to new versions and faster integration of new applications.

- Business processes are more easily integrated, streamlining operations, reducing costs, and allowing more effective collaborative working.

Service Oriented Architecture

IT middleware is a prerequisite for the use of a Service Oriented Architecture (SOA). In a SOA architecture, various software components provide "Services" (i.e., they do something) for users, as part of a wider middleware environment.

These are commonly referred to as Service Providers – the software that does the "something" – and the Consumers – who need the "something" to be done and which may be another piece of software or a real human user. A simple example would be a Service that takes a product name and product ID from a Consumer, checks against the product master database that it is a valid product name/product ID combination, and then returns a response to the Consumer – which may be a confirmation that the input was correct, an error message to say that the input was incorrect, or a list of suggested legal combinations in the case of an erroneous query.

This means that a variety of software applications – such as those used to enter customer orders, support product recalls or build bills of material – no longer need to access the product master data base themselves. A single Service Provider can provide this Service to all Consumers – including human users via a suitable Web interface – with the advantage that the next time the product master database application is updated only one piece of code needs to be used (the Service Provider). Another more complex example of this might be in the management of serial numbers for medical devices or – with pending regulations requiring unique identification – drug products.

Such applications require the management of tens of thousands of product/package codes and millions of serial numbers. In order to retain consistency and assure product traceability, this data will need to be exchanged and synchronized between various applications within the life sciences organization (labeling systems, label checking systems, MES and ERP systems, Warehouse Management Systems, etc.) and with third parties, such as distributers, re-packers, and regulators.

As initial trials in the medical device sector have discovered, entering this data manually is both time consuming and error prone.[1] Some would say that this is impossible with realistic production volumes. However, with a Service Oriented Architecture, it becomes possible to develop a relatively small number of software Services which are able to fulfill requests from multiple Consumers to generate, process and return serial numbers, product/package combinations, shipment status, and so on. Indeed some current serialization products now on the market are developed using SOA components specifically to facilitate the provision of services to users via the user interface or, more commonly to external systems through web services.

This is typical of the increasingly common, multiple interface requirements that are needed to integrate and streamline the modern life sciences organization and IT middleware and SOA are increasingly seen as the most efficient solution.

The Qualification/ Validation Issue

At a time when life sciences companies are looking to reduce costs, comply with stricter regulatory expectations, and to collaborate more effectively internally and with third parties, middleware and SOA appear like a good idea.

However, adoption has been hampered because neither the IT or Quality organizations know how to make middleware and SOA compliant. With multiple interfaces, the process of validating a traditional "monolithic" software application is generally well understood and there is plenty of industry guidance on the subject.

However, neither the FDA or PIC/S guidelines address the specific issues of IT middleware or SOA and even

"…adoption has been hampered because neither the IT or Quality organizations know how to make middleware and SOA compliant."

the GAMP® Guide and GAMP® IT Infrastructure Compliance and Control Good Practice Guide are silent on the subject.[2-5]

At the heart of the issue is that IT middleware and SOA are very flexible – it can provide almost any Service for any Consumer. In one case, the Service may have no regulatory significance (e.g., simply providing a messaging Service with no understanding of the message content) and in other cases the Service provides functionality which may or may not have regulatory significance.

According to GAMP® guidance, software applications are validated on the basis of risk and that IT infrastructure is qualified. However, before following this basic guidance, it is necessary to understand when SOA components should be considered as part of the IT infrastructure and qualified and when the SOA components provide regulatory significant functionality and should be validated as a software application.

In the case of the product name/product code look up, in some cases, the data may have no regulatory impact (a query by the Marketing Department to check to see if a product name has already been used elsewhere in the organization). In other cases, there may be some regulatory risk (building a new bill of material for a new product formulation) or even a high regulatory risk (checking all product name/product ID combinations to determine the scope of a product recall).

This leads to a situation where life sciences organizations have struggled to understand whether middleware and SOA needs to be qualified as IT Infrastructure or validated as a software application. In many such organizations, the technology is starting to be used for non-regulatory business purposes, but not in support of regulatory significant business operations.

By extending well established principles, it is possible to develop an approach to address this problem and allow IT middleware and SOA to be used across the life sciences organization.

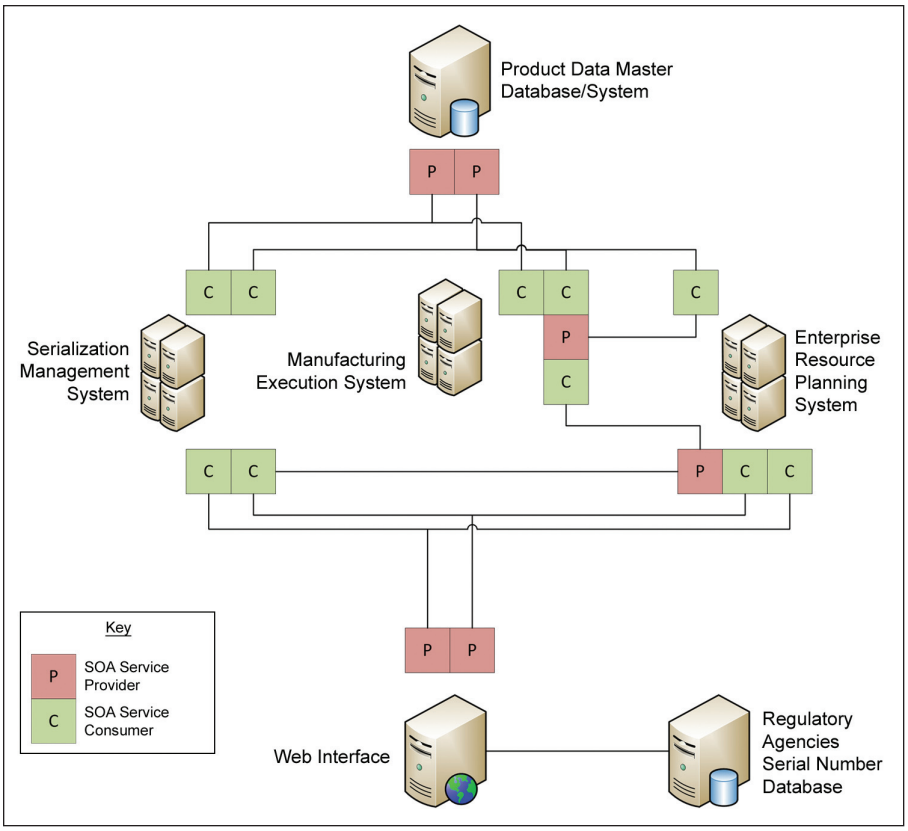


Figure 2. Applications integration using service oriented architecture.

Implementing IT Middleware and SOA

Before looking at a recommended process for verifying IT middleware and SOA, it is useful to consider some of the IT operational and project management issues that also need to be considered.

Key to compliant IT infrastructure software applications is the need to ensure that infrastructure is built and installed in accordance with specifications and designs and that applications software meets documented user requirements. This is a clear regulatory expectation, but is usually defined in terms of developing a monolithic software application (a single tiered software application that "does everything" including providing the user interfaces, database access, data processing, etc.) to meet specific requirements.

However, with IT middleware and SOA, the objective is to develop a software architecture where components are developed to meet the requirements of all possible Consumers, which in theory means that the requirements of all human users' need to be considered as part of the design of the Service.

There are two possible approaches to developing middleware or SOA components – the first of which is to try to identify all possible users and meet their requirements in developing the first version of the Service (common requirements definition). The second is to identify and meet the needs of a

	Advantages	Disadvantages
Common Requirements Definition	• Leads to the development of a more flexible and useful Service • Fewer subsequent releases reduces the ongoing burden of impact assessment, risk assessment and regression analysis	• May be difficult to reconcile the needs of multiple groups of Business Users • Difficult to engage Business Users with no immediate requirements or need
Project-by-Project Requirements Definition	• Allows the needs of one set of Business Users to be focused on • Initial Services tend to be simpler and faster to develop • Faster Return on Investment	• On-going need for impact assessment, risk assessment and regression analysis • Can lead to the development of additional project specific Services rather than the flexible re-use of existing Services

Table A. Requirements definition advantages and disadvantages.

subset of users with the first version of the Service with subsequent versions of the Service meeting the needs of additional groups of users (project-by-project requirements definition). Table A describes some of the advantages and disadvantages of each approach.

The challenge of getting all of the possible users of a Service together to define their requirements is considerable, especially when some users may not yet realize that they need the Service. This leads most IT organizations to adopt a project-by-project approach which has challenges in many organizations, especially where there is little or no experience in developing software in an iterative develop-and-release basis.

Such development approaches lend themselves more easily to agile software development techniques, but this can lead to conflict where the IT Quality Management System or the Quality Unit assumes that a traditional type of "V" model approach will be used in the development of software or computer systems.

To successfully use IT middleware and SOA in support of regulatory significant operations, it may well be necessary to review and update project management and software development life cycle models to allow for the use of the most appropriate and efficient development techniques.

Where a project-by-project approach is adopted, there are also two additional problems that need to be considered:

- In certain circumstances it may be necessary to have two versions of the same Service "live" at the same time – because not all Consumers can be updated to use the new version of the Service at the same time.
- Without careful management of the scope and functionality of each Service, it is likely that new Services will be developed to meet new user requirements, when a better solution would be to extend the scope and functionality of an existing Service.

This complexity needs to be managed, but unlike a traditional system, which has a clear project and operational phase, there is no discrete "project team" in place for SOA, and the software has a life cycle which is linked to, but separate from the life cycle of traditional monolithic applications. Therefore, this requires the establishment of an architecture group responsible for the management and control of the SOA. This also needs the use of suitable tools, which is discussed in detail below.

It is also necessary to redefine the role of what GAMP® 5 defines as the System Owner and the Process Owner. Although the SOA architecture group will clearly need to fulfill the role of the (technical) System Owner, there is obviously no single Process Owner from the business side for shared components. This means that someone from within the SOA architecture group also must represent the needs of the wider user community and fulfill the role of Process Owner (this "voice of the customer" is defined as the Product Owner in certain software development techniques).

Utility vs. Business Services

In order to help with the task of controlling and appropriately qualifying/validating a SOA, it is useful to break it down into its constituent parts and to consider each part. To aid this process, Services can generally be divided into different categories and classes as shown in Table B.

Category	Class	Description	Example
Utility Service		Provides a utility function, usually with little business specific functionality. Can be considered as IT infrastructure (GAMP® Software Category 1).	File transfer between applications across an Enterprise Service Bus. The service will handle errors and retries, but does not check or manipulate any file contents.
Business Service	Data Service	Provides data related services, such as data storage, data lookup, data retrieval or data deletion. May impact upon regulatory significant data and may be considered to be GAMP® Software Category 4 or 5.	Extract of a subset clinical data from a clinical data warehouse.
	Application Service	Provides software functionality, usually described in terms of functional requirements. May be considered to be GAMP® Software Category 4 or 5.	Application to check valid product name and product ID combination.
	Business Process Service	Provides business functionality, usually described in terms of business requirements. May be considered to be GAMP® Software Category 4 or 5.	Workflow to facilitate transfer of customer compliant from CRM system to Adverse Events Report system.

Table B. Service categories and classes.

This categorization and classification provides a useful way to not only understand the architecture, but to think about what controls should be applied and how a risk-based approach may be applied, rather than begin every risk assessment from a blank sheet of paper. With SOA, it is useful to create a default working model which can be challenged and reviewed as each Service is developed or updated. Using such a default model, it is possible to develop general guidance which states that Utility Processes are generally qualified as part of the IT Infrastructure and that Business Services are generally validated.

SOA Risk Management

Assuming that a GAMP® type risk assessment model is being used, one of the challenges in using a risk-based approach to the qualification/validation of SOA is that the risk severity of the Service may change depending upon how the Service will be used by various Consumers.[6]

Where a common requirements definition approach is used, it is possible to consider every use of the Service by every Consumer and to determine the worst case risk severity. However, as discussed above, Services are usually developed on an iterative basis to meet the needs of successive groups of users and in this case, risk assessment can take one of two paths:

1. Assume that at some point in the life of the Service a Consumer will have a high severity requirement, and assess the Service accordingly, i.e., the default risk severity for every Service Provider is high.
2. Assess the risk severity of the Service version by version (based upon the risk severity of the version specific Consumer requirements) and accept that in some cases, the risk severity will increase from one version to the next and additional verification may then be required.

Although the first option is the simplest in terms of conducting risk assessments, the disadvantage is that every Service will be verified as if it is high risk severity. In many cases, this will be inappropriate and a waste of resources, but this can be useful with respect to Data Services where the risk severity can be associated with the data rather than the Consumer.

In the second case, resources can be focused on the verification of Services that are of higher risk severity, but this will need a much more rigorous change control impact assessment process and a willingness to revisit and review previous risk assessments. This is perhaps a more useful approach for Application and Business Process Services and in these cases, the risk severity should be taken from risk assessments conducted in support of the consuming service.

With respect to risk likelihood, this can be considered partly as a function of the novelty of the Service. Newly developed or updated Services should be considered to be GAMP® Software Category 5 (custom software) and verified accordingly, using suitable Functional and Technical Design Specifications, design review (including code review), and risk-based Unit Testing.

More mature Services Providers (versions that have been in use for some time, working with multiple Consumers) can be considered to be GAMP® Software Category 4 (configurable software), or rarely as GAMP® Software Category 3 where there are no configurable parameters for the Service.

This will help developers to think about risk likelihood, but it should be noted that there are other factors that also will determine the determination of risk likelihood, including the use of standards (see below), the experience of the development team (internal or via an external supplier), the maturity of the software development life cycle, and quality management system, etc.

Unlike monolithic software applications, where it is possible to consider the wider business process context in determining the detectability of a risk (e.g., the failure of a dissolution test will detect that a risk has occurred before final patient safety is placed at risk) it is not possible to consider the downstream risk detectability via all possible Consumers. Therefore, risk detectability will largely be a function of the error checking routines that are built in to the Service or which are an inherent function of the supporting middleware.

Standards Based SOA

As inferred above, risk likelihood can be reduced (and the task of software developers made easier) where standards are leveraged in the development of a SOA. These standards may either be:

- Industry standards, agreed between multiple software vendors to aid in the interoperability of middleware and SOA, supported by major software vendors, such as Oracle, Microsoft, IBM, etc. These also may include life sciences industry specific standards, such as those designed to aid in the exchange and analysis of clinical data, for example.
- Vendor specific standards, which are specific to the supplier of the specific middleware/SOA technology.
- Internal standards, which are specific to the individual Regulated Company. These may often be internal data standards (using a so-called canonical data model which defines a superset of all necessary data object attributes) or where industry or vendor standards are insufficient, architecture design and coding standards.

Wherever possible, it is recommended that standards are followed and in keeping with GAMP® 5 Key Concepts, it is much easier and cost effective to leverage supplier standards than reinvent your own. This also can significantly ease the task of verification, as discussed below.

Code Review

Regulatory significant SOA components should be subject to code review. Although a well understood principle, code review can itself be scaled dependent upon risk. A low risk priority SOA component may be

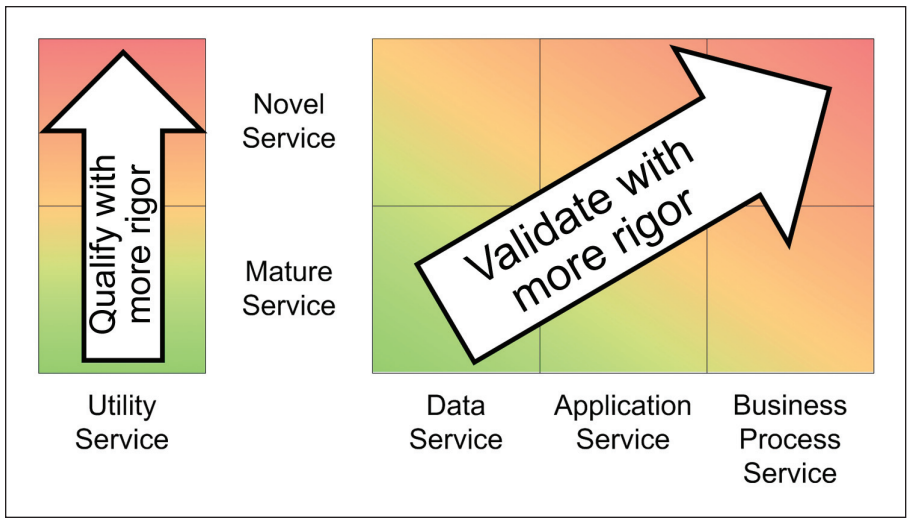


Figure 3. Default assumptions for SOA qualification/validation.

subject to desk review by a single, qualified peer reviewer but for a high risk priority (high risk severity and/or novel) SOA component, a more formal code walkthrough with the broader development team is more appropriate. It is important to review the code against the input requirements and specifications, as well as ensure that SOA components are developed in accordance with SOA standards.

Security Model

One of the advantages of SOA is the ability of a Service Provider to service the needs of any Service Consumer. However, from a security perspective, this isn't always a good idea. While it's obvious that internal researchers and collaborative research partners need easy access to previous research results, you wouldn't want that same information made available to the general public (or competitors) across the Internet.

In order to assure data integrity and compliance with regulations such as 21 CFR Part 11, it is therefore necessary to develop and implement a robust security model which defines exactly which Consumers are allowed to make a request of which version of each Service Provider.

In certain circumstances, this will need to be taken to an even lower level, defining not only which classes of Consumer can make a request on each Service Provider, but also which specific (machine or human) Consumers can make requests, or can read, write, or delete defined subsets of data. If this is a design concern, it is often better to define new Services to handle the specific requests rather than over-complicate the design of a general Service.

This security model not only needs designing, but needs to be updated and maintained as new Services are developed and as new Consumers are added and obviously needs to be tested as part of the verification of the Service.

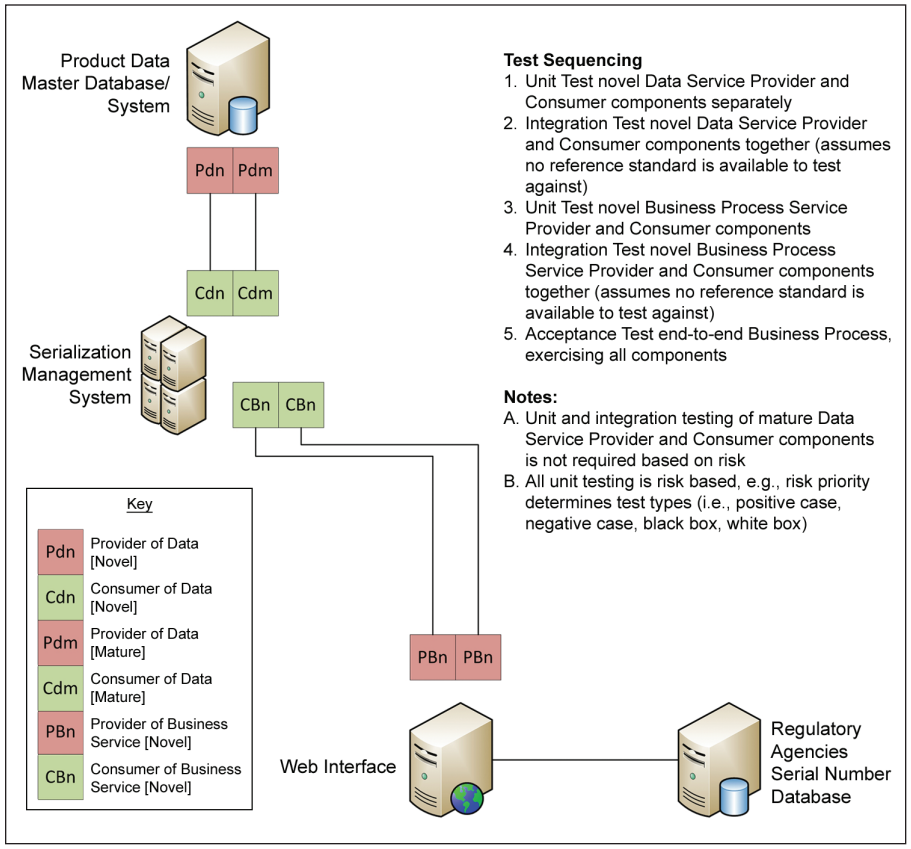


Figure 4. Example of SOA verification dependencies.

Testing Middleware and SOA

Based upon risk, SOA components can then be tested with the verification usually handled at two levels.

At the lowest level, traditional Unit Testing of both the Service Provider and Consumer will need to be conducted with the scope and rigor of testing determined by risk assessment. While the risk severity of a Consumer is relatively easy to determine, because it is much more closely related to a business requirement, this is not the case with a Service Provider and a suitable approach to risk assessment will need to be used, as discussed above. Different types of testing (black box, white box, positive case, negative case) should be used as appropriate and as described in the GAMP® Good Practice Guide: Testing of GxP Systems.[7]

Some form of integration testing will

"While regulatory compliance concerns have been a barrier to adoption, it is possible to establish processes and tools that allow SOA to be used for both general business and regulatory significant processes."

also be required, but there is a need to sensibly limit the interoperability testing between every Provider and Consumer. Where standards are leveraged it should be possible to review and/or test individual Service Providers and Consumers against a reference model, which can significantly reduce the scope of interoperability testing.

For many Utility Services, this level of basic functional testing will be all that is required to consider the Service to be qualified. For Business Services, it will still be necessary for individual groups of users to perform some testing of their functional or business requirements.

For Data Services and Application Services this level of functional testing may be conducted by the SOA architect group based Product Owner on behalf of the user community, remembering that any regulatory significant use of the Application Service should still be subject to some level of testing by each group of users as a part of their own validation exercise.

For Business Process Services there will almost certainly be some level of user testing of the business process as part of the acceptance of the Service. In order for testing to be efficient and cost effective, it will be necessary for all stakeholders to understand and leverage the testing that was performed at a lower level and what the test interdependencies are. As an example, if a new version of a Business Process Service relies upon a new Data Service, the new Data Service will need to be unit and integration tested before the new version of the Business Process Service is tested.

Figure 4 shows an example of a Business Process Service supplied by the Regulatory Agencies product serial database via way of the Regulatory Agencies Web service – this could be uploading a set of unique serial numbers and product codes to the regulators database, processing a receipt message, and updating the status to indicate that that data has been uploaded and received.

However, before submitting the serial numbers and products codes to the Regulatory Agencies, the Serialization Management System checks that the details are correct and it does this by consuming Data Services provided by the Product Master System. To do this, it uses a mature Data Service, i.e., the basic product name and product ID lookup and also via a new Data Service, i.e., one that checks valid ranges of serial numbers that can be assigned to various product classes. In this case it makes sense to test the Data Service first, test the Data Service integration next, test the Business Process Service Components, and finally the end-to-end business process.

Where SOA components are developed by external third party developers, this will best be facilitated where the Regulated Users SOA architect groups and the external development group work closely together and where there is full transparency with respect to the testing that has been conducted at all levels.

While it is not recommended that classic IQ, OQ, and PQ terminology is employed for the qualification and validation of SOA, it is possible to map different levels and types of test against IQ, OQ, and PQ if required.

Leveraging Supplier Tools

With any SOA, there are a lot of "moving" parts, and unlike a traditional monolithic applications project, there is no clear distinction between a project phase and an operational phase. Rather, each component has its own development, test, and release cycle with the expectation that each component will have many versions and releases. There may be multiple versions of the same Service live at any one time and there will certainly be complex interrelationships to define which Consumers are allowed to call which version of which Service Provider.

In a regulated industry, issues concerning release management, configuration management, "systems" inventories, security, etc., are very important and traditionally the control of SOA required the use and integration of many different processes or tools. The overhead of managing the SOA landscape was also a barrier to adoption in a number of cases.

However, most of the major SOA software vendors have realized that the complexity of managing the SOA was preventing the adoption of the technology in smaller organizations and increasing costs in larger organizations, regardless of the industry. Most suppliers are now providing comprehensive SOA management suites to manage and control the development, verification, security, and deployment of the SOA components and the better suites can certainly be relied upon to meet regulatory expectations in this regard.

When looking to leverage SOA, it is recommended that life sciences organizations look not only at the middleware tools and SOA technologies, but also carefully consider the management tools that are available. Use of the right management tools can significantly reduce the cost of ownership.

Conclusion

The use of middleware and SOA offers significant advantage to any life sciences organization looking to reduce software integration costs or streamline business processes. While regulatory compliance concerns have been a barrier to adoption, it is possible to establish processes and tools that allow SOA to be used for both general business and regulatory significant processes. For some organizations,

this will mean a change in approach to IT project management and software development life cycles. For all organizations, this also will require a good understanding of the technology.

Once the technology is well understood, it is then possible to break down the SOA landscape into its constituent parts, develop guidelines for the qualification, validation and control of the SOA, and leverage current industry guidance to cost effectively adopt middleware and SOA in an efficient and compliant manner.

References

1. Griffey, S., Martin,A., Odle, M., Wylie, M.J., *SSS-GHX Development of the Prototype Unique Device Identifier Database: Report of a Pilot Test on Usability and Feasibility,* 20 November 2009, www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentifiers/UCM191772.pdf.

2. U.S. Food and Drug Administration (Center for Devices and Radiological Health, Center for Biologics Evaluation and Research), *General Principles of Software Validation,* 11 January 2002, www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126955.pdf.

3. Pharmaceutical Inspection Convention and Pharmaceutical Cooperation Inspection Scheme/(PIC/S) PI 011-3, *Good Practices For Computerised Systems In Regulated GxP Environments,* 25 September 2007, www.picscheme.org/publication.php?id=8.

4. *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, www.ispe.org.

5. *ISPE GAMP® Good Practice Guide: IT Infrastructure Control and Compliance,* International Society for Pharmaceutical Engineering (ISPE), First Edition, August 2005, www.ispe.org.

6. *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, Appendix M3, www.ispe.org.

7. *ISPE GAMP® Good Practice Guide: Testing of GxP Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2005, www.ispe.org.

About the Author

David Stokes qualified in the United Kingdom as a process control engineer in the early 1980s and validated his first control and automation systems in 1985. He is an active member of the GAMP® Community of Practice and has contributed to the GAMP® Guide and several GAMP® Good Practice Guides. Stokes is currently Global Head of Life Sciences for Business and Decision, a multi-national Consultancy and Systems Integrator. His recent projects have included the development of pragmatic approaches to the control of IT middleware for a number of strategic clients. He can be contacted by telephone: +44-(0)-191-525-7700 or email: david.stokes@businessdecision.com.

Business & Decision Life Sciences, 7, Camberwell Way, Doxford International Business Park, Sunderland SR3 3XN, United Kingdom.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Online Particle Size Analysis for Optimal Spiral Jet Milling

by Alon Vaisman

This article examines the principles of operation of industrially important mills and how real-time laser diffraction particle size measurement facilitates optimization and automated control.

Despite the extensive use of spiral jet mills in the pharmaceutical industry and elsewhere, correlations between milling parameters and the particle size of the final product are often not fully understood. Appropriate Process Analytical Technology (PAT) incorporates real-time particle size measurement that provides insight into the milling process, and a firm foundation for effective optimization and control.

All industrial sectors share the need to optimize production to meet competitive, environmental, and legislative pressures, but for the pharmaceutical industry the manufacturing model itself is currently the subject of intense scrutiny. Traditionally, this sector eliminates variability in the final product by closely defining and fixing every step of the manufacturing process, using analysis to verify success at each stage. Unfortunately, this approach removes the flexibility to respond to variability in the feed, simply translating it through to variable product quality. Therefore, lost or out of specification batches are a common problem.

Recent regulatory guidance (ICH Q8, Q9, Q10) is intended to stimulate a transformational switch to knowledge-based product development and manufacture. Relevant PAT tools are fundamental to this shift since they supply the data needed to understand the process and product in detail, supporting the implementation of Quality by Design (QbD). More broadly integrated PAT systems provide the timely continuous measurement, statistical data analysis capability, and functionality necessary for automated process control, a critical building block toward the goal of real-time release.[1]

Within the pharmaceutical industry, milling or micronization, especially of an active ingredient, is commonplace because of the impact of particle size on important product properties, such as bioavailability, dissolution time, and flow properties.[2] Spiral jet mills are an appealing choice for such applications, offering a range of valuable features.

Principles of Operation of a Spiral Jet Mill

Spiral jet mills:[3]

- deliver fine materials with a narrow particle size distribution
- are suitable for temperature sensitive materials
- are easy to clean and have no moving parts
- allow milling in an inert atmosphere for materials sensitive to oxidation

This makes the technology an attractive option for many pharmaceutical applications; however, productive use of these mills demands a detailed understanding of the relatively complex principles governing design and operation.

In a spiral jet mill, comminution is achieved through particle-particle collisions promoted by turbulent air flow in the mill chamber. The comminution and classification functions are combined, particle size reduction occurring primarily at the outer edges of the chamber, while separation on the basis of size takes place toward the center. Particles with a certain fineness pass out of the mill via the vortex finder, while coarser material is propelled by centrifugal force toward the outer edges for further milling. Figure 1 shows a schematic of a spiral jet mill that illustrates these operating principles.[3]

Feed is accelerated into the flat cylindrical milling chamber of the unit using an injection system, which fluidizes the particles with pressurized air. Air also is introduced, at very high velocity, through a series of tangential nozzles positioned around the mill at a defined angle to the outer wall. This circulating air picks up the

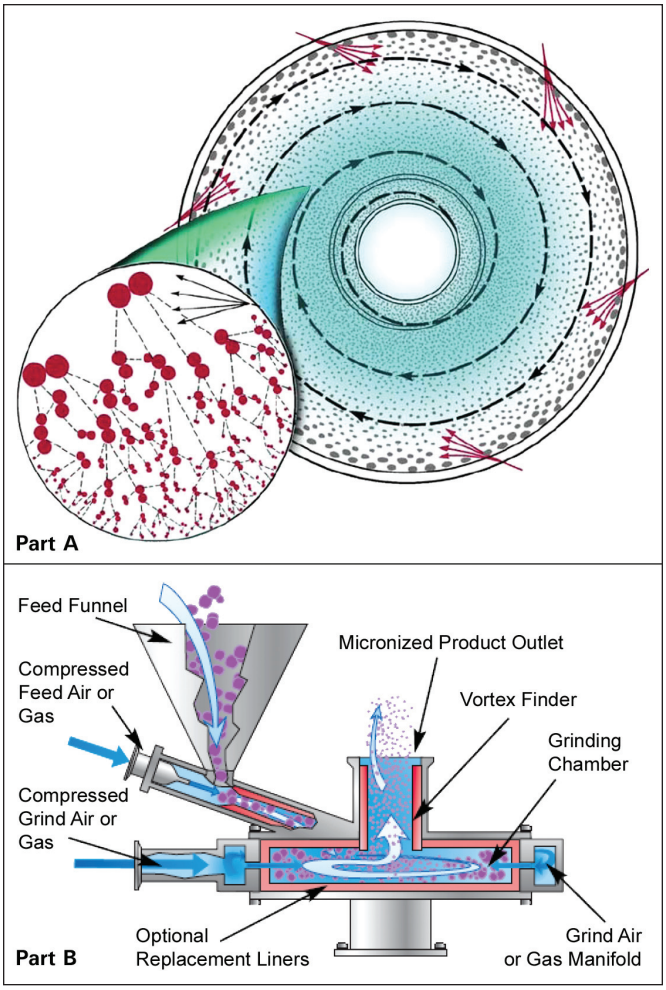


Figure 1. Schematic of a spiral jet mill showing operating principles (Part A and Part B). *Published with permission from Sturtevant Inc.*

feed and creates a flow regime that promotes particle-particle collisions, especially toward the edge of the chamber where large particle concentration is relatively high. At the vortex finder in the center of the mill, the balance between the drag and centrifugal forces acting on each particle determines the size of material exiting the mill.

At the design stage, an array of variables can be manipulated to target a specific product cut size. The geometry of the milling chamber impacts collision behavior, while volume is a controlling parameter for hold-up, the time the material will spend in the mill. The distance of the vortex finder from the base of the unit, and its diameter, both affect classification efficiency, while the number, diameter, and angle of the air nozzles strongly influence the flow regime that develops inside the mill. If the nozzle angle (α) is too small, material moves very close to the wall, friction then inhibiting adequate particle acceleration. On the other hand, if the angle is too great, larger particles will tend to enter the classification zone and exit via the vortex finder, giving a broad product size distribution. Therefore, the choice of angle size is always a compromise between milling and classification.

Once the unit is specified the degrees of freedom are drastically reduced, far fewer variables remaining for the manipulation of product particle size. In the manufacturing environment particle size control is usually achieved by varying parameters such as milling and injector pressure, and material feed rate.

Using Online Analysis to Develop Process Understanding

In an ideal world, the feed to a process would be fixed, making it possible to develop just a single set of operational parameters to consistently deliver in-specification product. This is the basis of the fixed process manufacturing model. Unfortunately, in real life, the feed may vary, but the specification on the product remains rigid. Therefore, with a manually controlled process, the operator needs to modify process parameters on a regular basis to maintain beneficial production. With batch manufacture, it is typically the case that a milling process, taking feed from, for example, an upstream crystallization process, is re-tuned for each new batch.

Without real-time analysis, this tuning process can be lengthy and wasteful, in terms of time, energy, and material. A key benefit of online particle size analysis is that it allows the operator to identify an optimal operating point as quickly as the process dynamics allow, and to maintain it. Furthermore, over the longer term, real-time measurement makes it easier to learn about the process and quantify the correlations between processing variables and product quality. Such correlations scope the operational range of the mill. This permits the development of models that describe the output particle size in terms of those operational variables which can be manipulated easily in order to achieve it. The following case studies provide a practical illustration of these points.

Case Study: Investigating the Impact of Feed Rate on Particle Size

Figure 2 shows real-time particle size data measured during a trial designed to investigate the impact of feed rate on jet mill performance for several different materials. Here, particle size was measured using an online laser diffraction analyzer,

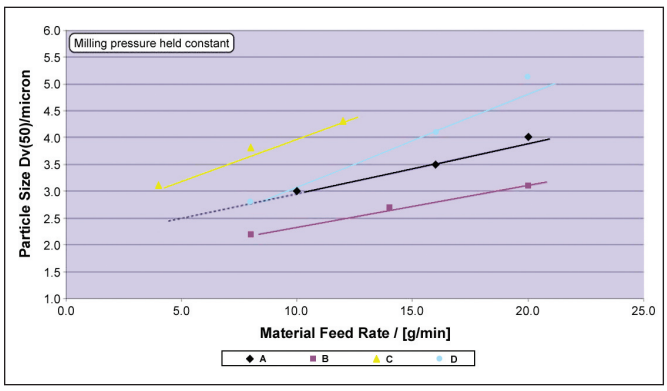


Figure 2. Investigating how feed rate to a spiral jet mill influences particle size for a range of materials of different hardness, brittleness, and particle density (A, B, C, and D) (mill pressure constant).

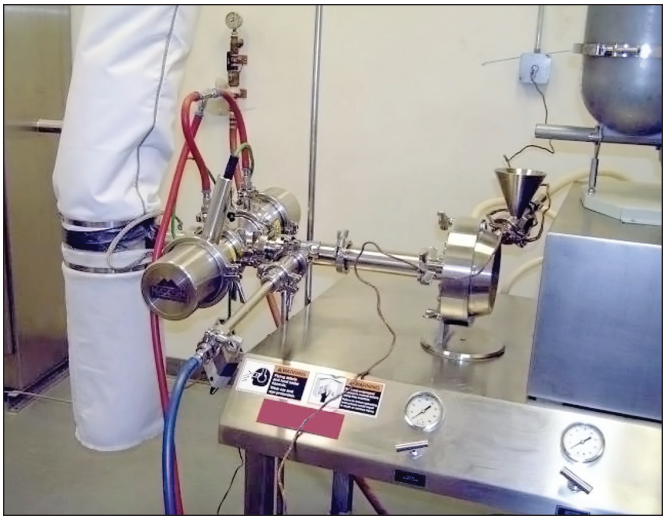


Figure 3. An on-line particle size analyzer installed on the exit line from a spiral jet mill.

capable of reporting complete size distributions at a rate of up to four per second - *Figure 3*.

These initial data quantify the link between feed rate and Dv50, median particle size, for a number of different materials. Samples A, B, C, and D differ in terms of hardness, brittleness, and particle density. Material C, for example, is lactose, quite an elastic material, difficult to dose at a constant feed rate and not so easily reduced to a fine particle size by the mill. The trends with feed rate are as expected and suggest that further reductions would produce even finer particles; however, Figure 4 indicates that this may not necessarily be the case.

When all other conditions are kept constant, reducing feed rate below a certain point increases the Dv50 of the exiting material. This behavior is straightforward to rationalize by referencing the operating mechanism of the mill. With a spiral jet mill, comminution arises from inter-particle collisions promoted by the circulating air. At higher than optimal feed rates the particles are packed closely together and force of impacts is low. At low rates, on the other hand, milling becomes inefficient because particle concentration is so low. Low concentrations decrease not only the likelihood of impact, but also the velocity (energy) with which particles collide. Therefore, efficiency falls.

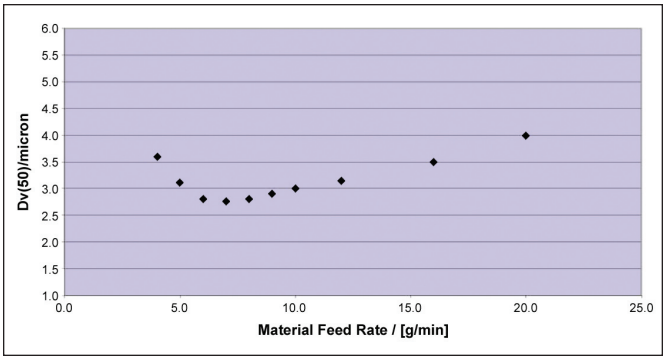


Figure 4. Demonstrating how the Dv50 of material exiting a spiral jet mill changes with feed rate, passing through an optimum (all other mill variables kept constant during the trial).

Case Study: Tuning Multiple Variables to Target a Particle Size Specification

The preceding study provides useful data for the optimization of one operational variable, but tuning the process ideally involves simultaneously varying all the levers that the operation team has at its disposal. Figure 5 shows results from such a trial investigating the milling of lactose. The aim of this study was to rapidly identify a set of operating conditions able to yield lactose with the required particle size distribution. In this respect, it reflects a common situation within the pharmaceutical sector where it is often necessary to rapidly tune operating variables to process a new batch of feed to the given specification.

Here, injector pressure and feed rate are both being varied, the magenta curve highlighting the conditions that produce the finest, most tightly distributed product. Perhaps the most important thing to notice though is the timescale over which the measurements were recorded. This optimization study was completed in just eight minutes.

With spiral jet mills, the process dynamics are typically extremely fast; residence times may be very short, around a minute or less. As long as data acquisition is sufficiently rapid, it is possible to move to an advantageous operating point extremely quickly, as this example demonstrates. Doing so minimizes the amount of material wasted and maximizes plant throughput/utilization. Being able to establish optimal operating conditions for each batch in just a few minutes, rather than several hours as may be the case with off-line analysis, delivers significant economic return, offsetting initial capital investment. Furthermore, with real-time measurement in place, this "tuning" process can be fully automated. For example, a leading pharmaceutical manufacturer has validated a fully automated milling system that consistently delivers to a defined set point by automatically varying mill parameters to compensate for batch-to-batch variability.[4]

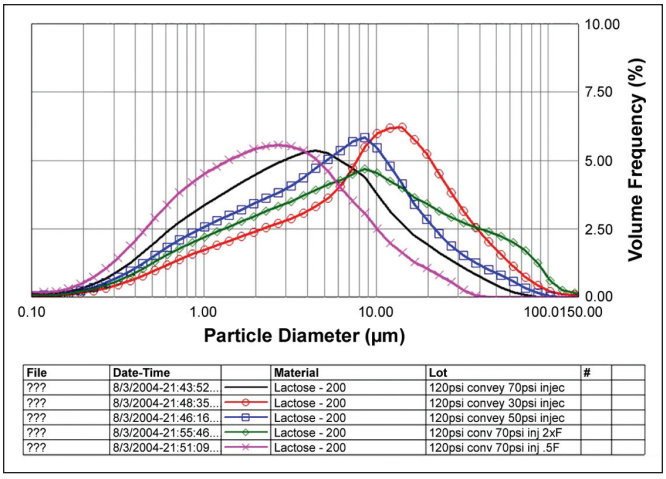


Figure 5. Investigating the impact of injector pressure and feed rate on particle size distribution for the milling of lactose with a spiral jet mill. (Note: F is the baseline feed rate so the 2F and 0.5F conditions represent a doubling and halving of the baseline rate respectively.)

Case Study: Determining Process Time Constants and the Causes of Process Instability

Results from a second, similar optimization study are shown in Figure 6, this time in the form of a trend that very clearly draws attention to the ability of the analyzer to swiftly detect process changes.

In this study, injector pressure and feed rate were optimized as the customer took the plant through five sets of operating conditions over a period of just 15 minutes. Once more, the objective was to rapidly identify optimal operating conditions for processing a batch of material. Dv50, Dv90 (the particle size below which 90% of the particle population lies) and transmission, a measure of the amount of light passing through the sample, and consequently sample concentration, all reflect alterations to the operating parameters. The ability of the analyzer to rapidly detect the impact of changes is critical since this precisely identifies "cause and effect," streamlining movement to an optimal operating point.

From Figure 6, it is possible to calculate the time constants of the process:

$$\tau_P = 63\%\Delta PV_{ss\text{-}ss}$$

Where τ_P is the time constant of the process, and $\Delta PV_{ss\text{-}ss}$ is the Process Variable transition from one steady state to another. In other words, time constant, τ_P equals 63% of Process Step Response.

This value is an important one for the development of automated process control, but in this case, since the value of the time constant is around 25 seconds, it also serves to emphasize the importance of installing analytical systems with a relevant response time. Here measurement frequency needs to be very high because the process can change extremely rapidly.

One further interesting point from this study is the increased fluctuation and variability observed when milling coarser particles at lower mill pressures - *Figure 6.* This variability is a clear sign of instability in the process or more specifically in the vortex. With the same operational set-up, further investigations were conducted to gain greater insight into the process and rationalize this behavior.

In this work, span, a figure calculated from Dv10 (the particle size below which 10% of the particle population lies), Dv50, and Dv90 is used as a measure of particle size distribution. In general, higher milling pressures are used to mill and produce finer materials. The blue line MP1 (milling pressure

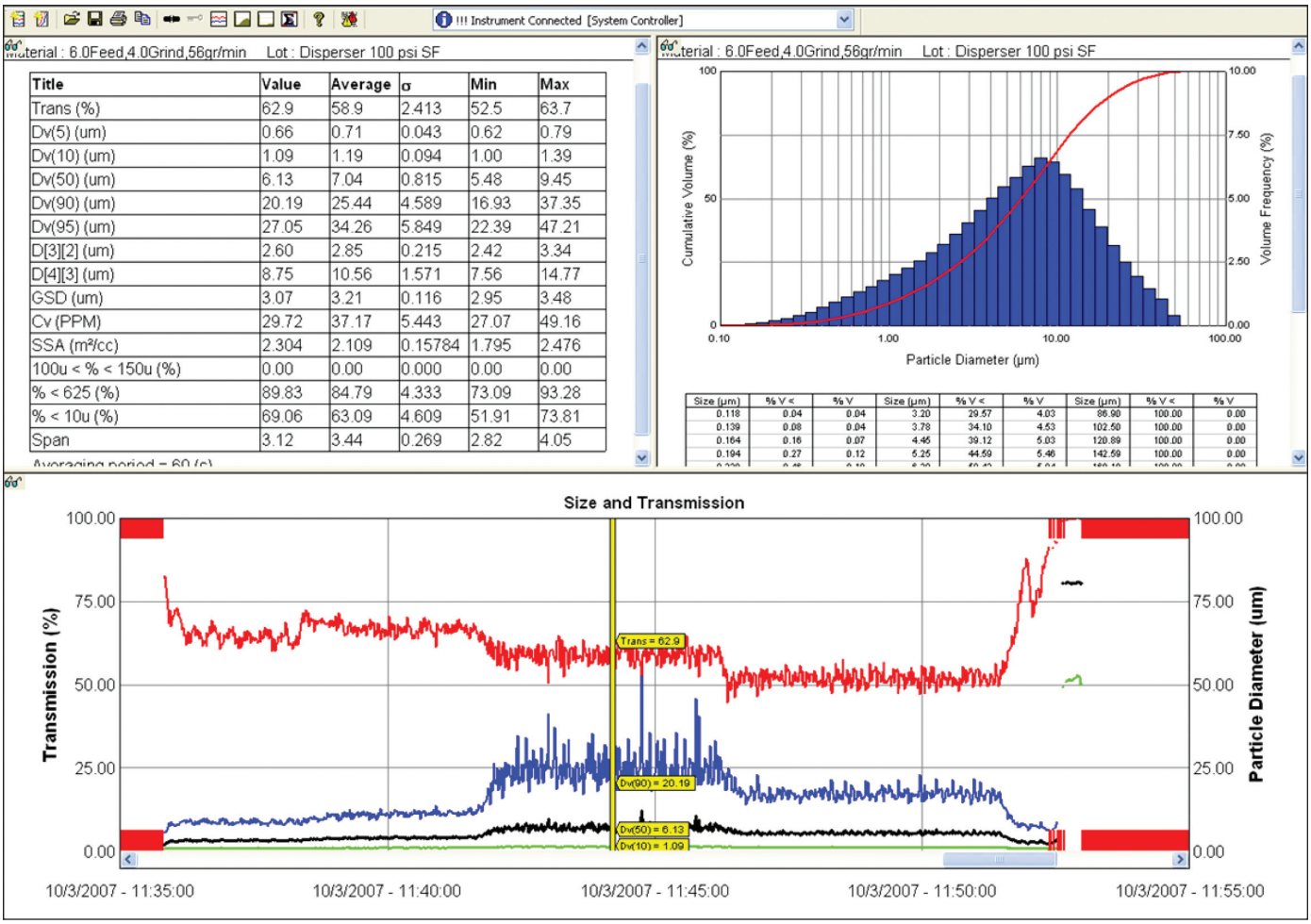


Figure 6. Screen shot showing real-time particle size measurement during an spiral jet milling optimization trial, where variables are being manipulated to target a defined exit particle size distribution.

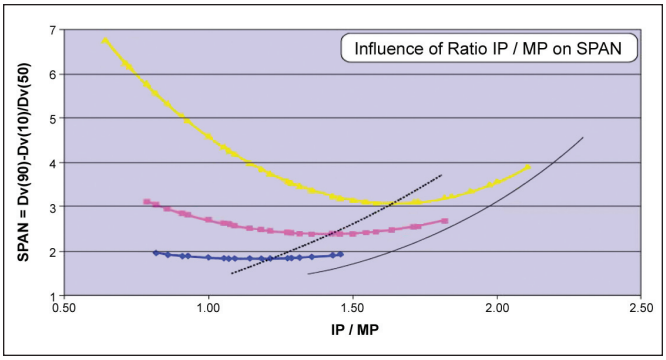


Figure 7. Investigating the influence of ration of Injector Pressure (IP) to Milling Pressure (MP) on the particle size distribution or span of material exiting a spiral jet mill. (Blue line – highest milling pressure, magenta line – intermediate milling pressure, yellow line – lowest milling pressure.)

1) records data measured at the highest milling pressure (i.e., for production of the finest particles), the yellow, MP3, corresponding to the lowest milling pressure and the most coarse feed. Throughout this trial, Injector Pressure (IP) was kept constant to vary the IP/MP ratio.

The results indicate that when milling pressure is high, the IP/MP ratio has little influence on span. This is in line with published literature which suggests that increasing milling pressure produces a steeper particle size profile. However, at lower milling pressures, in the production of coarser powders, span narrows with increasing injector pressure, up to a critical value, beyond which it broadens again.

Under the high throughput, low milling pressure conditions typically used for coarser materials, a large percentage of the energy introduced through the grinding nozzles is used to accelerate the material. This reduces the amount of kinetic energy available for grinding and results in a relatively low circulation velocity, leading to an unstable vortex, and secondary flows that allow even big particles to leave the mill. Consequently, span becomes very broad.

In this scenario, increasing milling pressure is not really a suitable solution since this will bring down the Dv50, taking the material out of specification. Figure 7 suggests a better alternative which is to increase the injector pressure. As the particle-gas-mixture is fed tangentially into the mill with a velocity component in the direction of the circulating vortex, increasing the injector pressure increases the circumferential speed and the magnitude of centrifugal forces stabilizing the vortex. This prevents large particles leaving the mill bringing down the span.

Unfortunately, the additional air from the injector, introduced by the increase in pressure, also increases drag forces on the particles drawing them toward the vortex finder; a counterproductive effect. This explains why there is an identifiable minimum in span value – the point at which the stabilizing effect on the vortex is most beneficial relative to the negative impact of increased drag forces in the classification area. It is important to recognize that for all milling pressures the span minima lie on a single line making interpolation to other conditions straight forward.

Implementing Real Time Particle Size Analysis

Selecting an appropriate system for real-time particle size measurement is essential for the realization of its full potential. Laser diffraction can be an appropriate choice for jet milling,[5] and many other applications because it is:

- rapid
- non-destructive
- suitable for particles in the size range 0.1 to 2000 microns
- sufficiently robust for in-process use.

Laser diffraction systems are commercially available for off-, at-, in, and online measurement and are well-established within the pharmaceutical industry. For real-time measurement and the automated control of processes with fast response times, in- and online solutions are optimal, providing a data stream that maximizes process insight. The best in- and online analyzers incorporate data analysis software and control functionality facilitating effective process monitoring and multivariate automated control.

Real-time laser diffraction particle size measurement is a commercially available, proven solution so the technical risks associated with its adoption are low. With a well-planned and executed project, installation is generally complete in just a few days, commissioning is brief, and operational reliability high. Continuous automated analysis essentially eliminates the risk of operator exposure to potentially hazardous process material and is a vital element of assured real-time release, a long term goal in the industry. These arguments alone may provide a sound basis for justifying expenditure in a suitable system, but there is frequently a strong economic case, as highlighted earlier, that derives from the improvement and automation of process control.

Automated Control

The examples above clearly demonstrate how real-time analysis delivers value by extending the knowledge base. Information gathered forms the basis of a process model, a detailed understanding of the correlations between processing parameters and product quality, and ultimately a mathematical representation of the plant. This is a valuable tool for optimization and control, measurement within a process-relevant time frame providing a data stream that is ideal for automation. At the pilot scale, the tighter control automation delivers and improves the quality of the decision-making processes associated with development. During full-scale manufacture, it enhances product quality and minimizes manufacturing cost.

For spiral jet mills, real-time particle size analysis allows the development of closed loop control solutions that automatically manipulate variables, such as feed rate and injector pressure, to maintain the output particle size specification. Figure 8 graphically illustrates the associated benefits.

With closed loop control, the plant is significantly steadier, operating consistently at the specified set point with little manual input. Product properties are extremely stable.

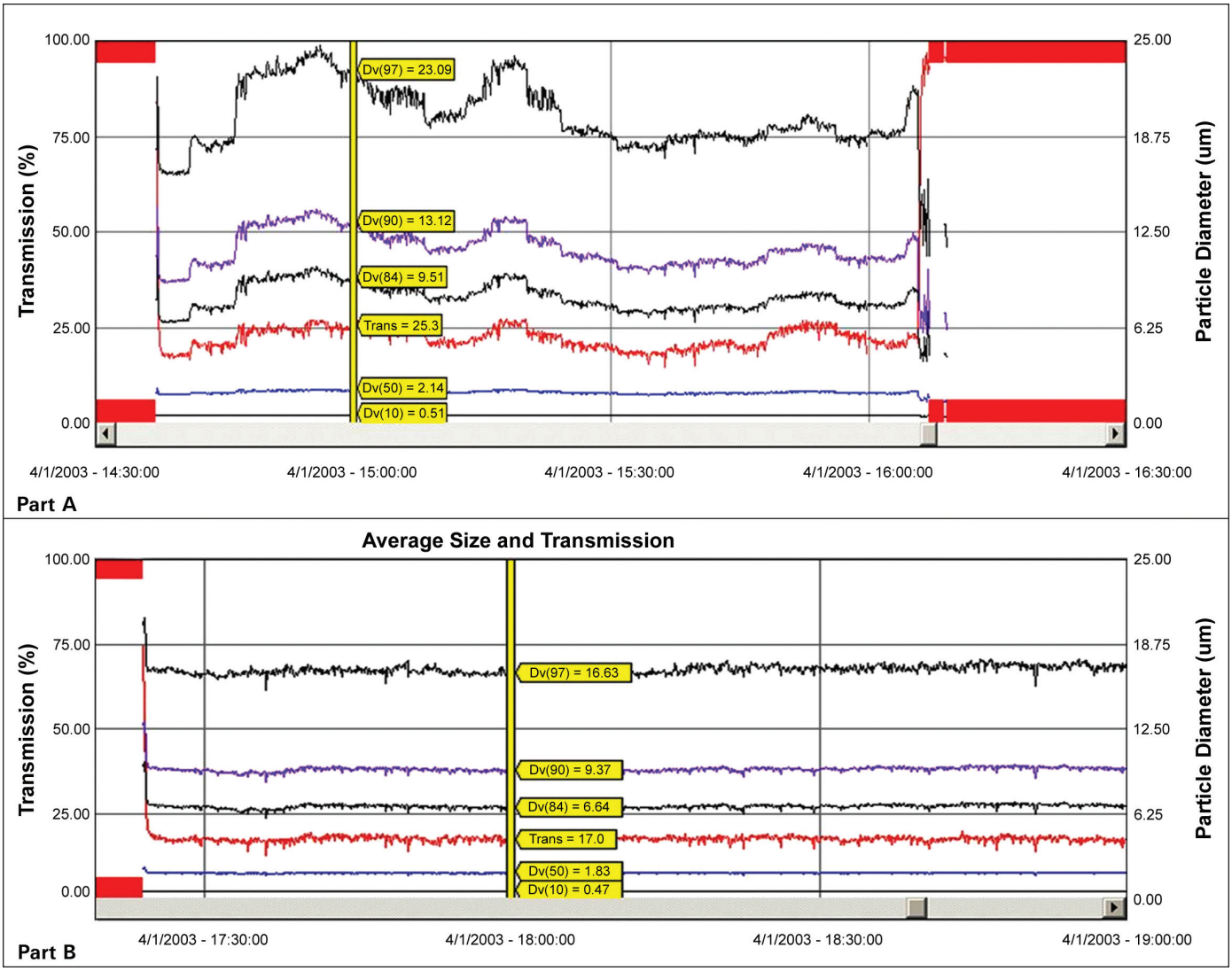


Figure 8. Screen shots contrasting real time particle size data for a jet milling process under (A) manual control and (B) closed loop control.

Conclusion

While spiral jet mills are an attractive solution for many micronization applications, their operating mechanism, which combines comminution and classification in a single unit, is complex. For these units, real-time particle size analysis is a key PAT tool. Continuous timely size measurement simplifies the identification of Critical Quality Attributes (CQAs), those properties that define product performance, and Critical Process Parameters (CPPs), the operational variables that control CQAs.

Within the pharmaceutical industry, there is significant interest in relevant PAT systems because of the role they have to play in supporting the implementation of QbD and the move to a transformed, more flexible manufacturing model incorporating automated control and real-time release. Here, online analysis is shown to be an important tool for extending the process knowledge base. With real-time measurement in place, it becomes possible to develop a responsive automated control strategy. Moving away from the rigidity of a fixed process to one that responds to variations in the feed, resulting from, for example, upstream crystallization processes, to consistently produce material with a well-defined particle size distribution is a big step forward.

It is crucial to recognize that although real-time analysis delivers important information, it cannot in isolation control the process. Conversely, process control will be far from optimal if CPPs are "guessed" from models and soft sensors rather than directly monitored. The full potential of real-time analysis is realized when it is applied to all CPPs and the data, instead of being viewed in discrete sets, are combined in the implementation of multivariate process control. Effective and dynamic data management is a critical element in the effective implementation of PAT, an important goal for many manufacturers.

References

1. Methfessel, J. and J-R Roy, "A Practical Approach to PAT Implementation," http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=310780.
2. ICH Q6A Guideline – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New

Drug Products: Chemical Substances (including Decision Trees), www.ich.org.
3. Sturtevant Web site: www.sturtevantinc.com/micronizer.php.
4. Vaisman, Alon and Yanhui Hu, "A PAT Solution for Automated Mill Control," *Pharmaceutical Technology,* Volume 34, Issue 1, 2 Jan 2010, http://pharmtech.findpharma.com.
5. Gomeren, H.J.C., et al. "Dynamic Modeling of a Closed Loop Jet Mill," *International Journal of Mineral Processing,* Volume 44 - 45, March 1996, pp. 497 – 506, www.elsevier.com.

About the Author

Alon Vaisman is an Application Development Manager Pharmaceuticals for Malvern Instruments. Based at the company's offices in Westborough MA, USA, he supports pharmaceutical manufacturers world-wide in developing and improving their process operations through the use of in-process particle characterization systems. Vaisman's background is in mechanical engineering and he has more than 15 years of applications and support experience. He can be contacted by telephone: +1-508-768-6400 or by email: alon.vaisman@malvern.com.

Malvern Instruments, Inc., 117 Flanders Rd., Westborough, Massachusetts 01581-1042, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I

This article reviews the history of Cleaning Validation Acceptance Limits for Active Pharmaceutical Ingredients (APIs) and identifies where the currently used industry limits came from.

by Andrew Walsh

Introduction

Part I of this article reviews the history of Cleaning Validation Acceptance Limits for Active Pharmaceutical Ingredients (APIs) and identifies the origins of currently used industry limits. The current approaches to setting acceptance limits will be analyzed and some of the problems and weaknesses of these approaches will be discussed.

Early Ideas on Cleaning Validation Acceptance Limits

In the early 1980s, most companies were just beginning to grapple with the FDA's shift to validation. This activity was of course more focused on Process Validation, but some companies took a wider view and began looking at cleaning processes as well. In 1984, Samuel Harder published an article, "The Validation of Cleaning Procedures," and discussed many aspects of what he saw would be required to validate a cleaning process.[1] Most, if not all, of the ideas he expressed can still be seen in practice in cleaning validation today. Concerning the setting of Acceptance Limits, Harder wrote that limits

> "...must be *practical* and *achievable* by a reasonable cleaning procedure... ...must be *verifiable* by analytical methodology existing in the company... ...and must be safe and acceptable and in line with residual limits set for various substances in foods."

(Note: The phrase "Practical, Achievable, and Verifiable" began to appear in many guidelines and literature subsequently.)

Harder goes on to reference 21 CFR 193 "Tolerances for Pesticides in Food Administered by the Environmental Protection Agency" and showed a table of limits for a variety of hazardous pesticides and herbicides. These limits ranged from a low of 0.5 ppm for Diquat to a high of 200 ppm for hydrogen cyanide. Harder pointed out that the amount of drug products ingested by an individual is much lower than the amount of food ingested. Therefore, he suggested that Acceptance Limits for drug substances comparable to those used for pesticides would be reasonable.

In 1988, the FDA had its first major experience with cross contamination traceable to inadequate cleaning and cleaning validation.[2] A supplier of the API Cholestyramine Resin USP had to recall the product, due to contamination with low levels of intermediates and degradants from the production of agricultural pesticides. This cross-contamination was believed to have occurred from the use of drums in the manufacture of the API that had been used to recover solvents from the manufacture of agricultural pesticides at another location. The drums were not properly cleaned leading to agricultural pesticides entering the API manufacturing process. This incident raised the FDA's awareness to the potential for cross contamination from unvalidated cleaning processes and heightened the concern in the industry that validation would become required for cleaning as well as for process.

In 1989, Doug Mendenhall of Abbott Labora-

tories published a chapter "Cleaning Validation" in Drug Development and Industrial Pharmacy.[3] Mendenhall expanded upon the ideas presented by Harder adding ideas, such as using a matrix approach, testing for cleaning agents, placebo batches, and most interestingly, pointed out the potential use of visual inspection. In addition, for Acceptance Limits, he suggested to "...establish in collaboration with tox and medical authorities an effect threshold" or alternatively, to "... superimpose an appropriate safety factor, e.g., 10X, or 100X." Although not cited as such, this suggestion was probably connected to a much older article by Lehmann and Fitzhugh on the use of a 100-fold safety factor.[4] The 100-fold safety factor consists of two 10-fold factors to allow for human variability and interspecies differences. Mendenhall proposed that limits for surface residue levels be calculated based on a smallest batch size/maximum dose combination. Mendenhall goes on to state that based on these calculated surface limits, visual inspection should be adequate in many cases. Mendenhall writes:

> "Alternatively, one could use a very pragmatic approach: visual cleanliness. While the latter may sound far too unsophisticated and non-quantitative, in our experience quantitative calculations have almost universally yielded tolerable levels of residues which were readily apparent visually, i.e., the visual cleanliness criteria was (sic) more rigid and clearly adequate. Clearly, however, for extremely potent or toxic substances, calculated tolerable residuals may be well below visual detectability. Hence, common sense and judicious use of quantitative methods when appropriate are called for depending on the nature of the possible residues involved."

(It is interesting to note that the use of visual inspection is now being seriously investigated, as of this writing, more than 20 years later.)

These two industry articles laid the foundations from which most cleaning validation acceptance criteria were derived and are the origins of many cleaning validation activities practiced up until today (2011). Shortly after these publications, a major event began to unfold that shaped the direction of cleaning validation and many other industry practices. This event was...

The U.S. vs. Barr Laboratories and the Wolin Decision

From 1989 through 1992, the US FDA inspected several Barr Laboratories, Inc. facilities and became engaged in a struggle with the company over many issues concerning the FDA's interpretation of the GMPs. This struggle resulted in the issuance of multiple FDA Form 483s with increasing numbers of observations. The FDA finally sued Barr Labs in June of 1992 with District Judge Alfred M. Wolin presiding over the trial.[5] The trial ended in February of 1993 with the decision by Judge Wolin that resulted in a major loss for, and an injunction against, Barr Laboratories. The significance of this trial to the pharmaceutical industry cannot be overstated. Up until this time, the industry had been in an ongoing debate with the FDA's interpretation that compliance with the GMPs required process validation. Now, the FDA's process validation requirement was upheld in a court of law. In addition, among several other things, *cleaning validation was now required*.

Dose-based Limits	"Default" Limits
1/10th of a therapeutic dose	Not more than 1 ppm
1/50th of the maximum therapeutic dose	3 ppm (based on Arsenic Limit)
1/1,000th of the lowest dose	10 ppm
Less than the smallest therapeutic dose	22 ppm
	30 ppm for cleaning agents
Some Other Limits	
Detection Limit of Method	< 5 mg/swab

Table A. 1992 Pharmaceutical Manufacturers Association survey on acceptance limits.

The action in the Barr Laboratories case was closely followed by the pharmaceutical industry, and one trade organization, Pharmaceutical Manufacturers Association (PMA now PhRMA), sent out a survey to all of its members asking many questions on what they were doing in regard to cleaning validation. In particular to this discussion, they asked how companies were setting acceptance limits. In the survey results, PMA listed 44 unique acceptance criteria from the responses. A representative sampling of these limits is shown in Table A.

As can be seen in Table A, the acceptance limits in use at that time were inconsistent from company to company, and in many cases, arbitrarily selected. There were two patterns that appeared; the use of limits based in some way on the therapeutic dose and limits set arbitrarily (or as some workers call them today, "default" limits). At least one company tied their default limit to the USP Arsenic limit reasoning that if Arsenic could be present at 3 ppm, then residues of their compounds at lower levels should be considered safe. Note that both types of limits are of the kinds suggested by Harder or Mendenhall.

Concurrent with the Barr Laboratories trial and the PMA Industry Survey, the foundations for acceptance limits were further expanded by another publication known in the industry as...

The Fourman and Mullen Article

At the time of the Barr Labs trial, another company, Eli Lilly, was also involved in a number of issues with the FDA over cleaning validation. In particular was the setting of acceptance limits. In 1993, Gary Fourman and Dr. Mike Mullen of Eli Lilly published an article where they proposed the use of a combination of limits.[6] These authors suggested that "any carryover of product residue meet the following criteria:"

- No more than 0.001 dose of any product will appear in the maximum daily dose of another product.
- No more than 10 ppm of a product will appear in another product.

- No quantity of residue will be visible on the equipment after cleaning procedures are performed.

In the article, the authors explain that these 0.001 and 10ppm criteria were selected in the following manner.

For the 0.001 dose criterion, the three factors of 10 were based on: "The first is that pharmaceuticals are often considered to be non-active at 0.1 of their normal prescribed dosage; the second is a safety factor; and the third is that the cleaning validation program must be robust, i.e., be vigorous enough that it would be considered acceptable for quite some time in a world with ever tightening standards."

For the 10 ppm criterion, the article states that it has its roots in the regulations that apply to food products: "In those regulations, certain levels of hazardous substances are considered acceptable in animal tissues and poultry products that enter the human food chain." Unfortunately, no regulatory reference was cited for this criterion nor was it explained how the value of 10 was selected. However, the origin of this criterion is very likely related to the article by Sam Harder.

For the visible residue criterion, the authors point out that some products meet the first two criteria, but there could still be residue visible and "...it does not seem appropriate that residues could be visible on GMP equipment even though it is labeled *clean*." It seems appropriate to note here that 21 CFR 211.67(b) always required cleaned equipment to be inspected for cleanliness immediately before use. Theoretically, such inspection should already be in place and would not allow equipment with visual residues to be used making this criterion redundant.

At the time, this was a landmark article in the world of cleaning validation as it was the first publication to lay out specific criteria for determining cleaning validation acceptance limits. Underscoring its importance, this article was cited in almost every subsequent article on cleaning validation for years afterward. Pharmaceutical companies now had something to point to in how they had derived acceptance limits for their cleaning validation program.

After Effects of Barr Laboratories Decision

There was significant fallout from the Barr Laboratories case for the industry. Judge Wolin described the Barr case as a "confrontation between a humorless warden and its uncooperative prisoner" and a product of "an industry mired in uncertainty and conflict, guided by vague regulations which produce tugs-of-war of varying intensity."[7] During the course of the trial, Judge Wolin observed that the GMP regulations were vague and not very detailed – certainly not detailed enough to expect companies to easily understand what the FDA's interpretations and expectations were. Judge Wolin criticized the GMPs for their lack of detail and clarity. The FDA responded to these criticisms in a number of important ways. One by initiating a rewrite of the GMPs, which added much more detail. In this rewrite, they called for validation of cleaning (Proposed §211.220(a)) and the dedication of manufacturing facilities from just Penicillin to potentially many more compounds, such as cytotoxic agents, steroids, etc. And two, they also responded in the MidAtlantic region by issuing in 1992 the following...

Guide to Inspections: Validation of Cleaning Processes

As the case was proceeding against Barr Laboratories, a number of inspectors in the MidAtlantic region put together a guide clarifying what their expectations were for Cleaning Validation. This was a Guide for FDA MidAtlantic region inspectors on what to look for in a cleaning validation program, including what is and what is not acceptable. The effort was led by a well known inspector at the time, Henry (Hank) Avallone. This Guide was very detailed and specific and included many of the elements that are typically found today in company cleaning validation programs. One year later, the Guide developed by the MidAtlantic region inspectors was adopted by the national center for use by all FDA inspectors.

The Guide also contained content that can be traced back to the publications we have already discussed; the Harder, Mendenhall, and Fourman and Mullin articles. For the establishment of limits, the Guide states that:

> "The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be ***practical, achievable,*** and ***verifiable***. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels, such as ***10 PPM***, biological activity levels such as ***1/1000 of the normal therapeutic dose***, and organoleptic levels such as ***no visible residue***."

Type of Limits Used (APIs)						
Dose-based only	**Dose-based/ default**	**Dose-based/ default/Visual**	**Default Value**	**Process Capability**	**Limits of Detection**	**Other Criteria**
49%	22%	45%	4%	10%	6%	16%
Range of Dose-based Limits Used (APIs)						
1/1,000th		1/100th		1/2,000th		1/10,000th
85%		13%		2%		6%
Range of Default Limits Used (APIs)						
10 ppm		1 ppm		< 15 ppm		< 1 ppm
89%		6%		6%		3%

Table B. 2006 Parenteral Drug Association survey on acceptance limits.

While at the start of the section on establishment of limits, the Guide makes a point of stating that they do not intend to set acceptance specifications, the fact that they mention limits, such as 10 ppm and 1/100 of the normal therapeutic dosage as examples has been understood by many in the industry as tacit approval of these limits. However, it is worth highlighting that in concluding the discussion of the establishment of limits, the FDA sets a very clear criterion for inspection:

> "The objective of the inspection is to ensure that the basis for any limits is ***scientifically justifiable***." So despite the mention of these limits and regardless of any industry adoption of them, the FDA still clearly expects that companies will put some thought and analysis into the selection of their cleaning validation acceptance limits. Simple adoption of the three Fourman and Mullin criteria is not satisfactory without a scientific justification for using these limits.

As mentioned earlier, the Fourman and Mullin article turned into a landmark publication for cleaning validation and the impact of this article on the industry also can be understood by considering how many regulatory guidelines subsequently adopted the three criteria they presented. Examples of the use of the Fourman and Mullin approach can be found in:

- PIC/S 2001 Guideline (European)
- CEFIC/APIC* 2000 Guideline
- TPP 2000 CV Guidelines (Health Canada)
- ICH (Q7A)
- Pan American Health Organization
- WHO Guide to GMPs

*European Chemical Industry Council/Active Pharmaceutical Ingredients Committee

Finally, in August of 1998, The Parenteral Drug Association (PDA) released their PDA Technical Report No. 29 "Points to Consider for Cleaning Validation," which summarized the current thinking and outlined the elements considered fundamental to a compliant cleaning validation program, including the setting of acceptance limits, at that time. Concerning the selection of limits the Report states: "It is very important that cleaning limits not be selected arbitrarily, but rather, that there be a logical and scientific basis for the numerical limit selected."

More recently, in 2006, PDA conducted a survey on acceptance limits. The results can be seen in Table B. The types of limits reported look nearly the same as the ones listed in Table A. Unlike the 1992 PMA survey, the percentages of companies using the same limit are shown; however, the percentages in each case do not add up to 100 (Type of Limit = 152%; Range of Dose-based Limits = 106% and Range of Default Limits = 104%) so it is impossible to clearly interpret these data. But what can be taken away is that the industry is not following the limits stated in the regulatory guidelines mentioned above, they are still inconsistent in the application of limits, and they are still apparently using arbitrarily set limits. One important change is that approximately 10% (true % not known) report using Process Capability to set their acceptance limits. This is an important development that will be discussed in Part II of this article.

Analysis of Current Approaches to Setting Acceptance Limits

The author of this article started working in cleaning validation in 1994 just as all these events were unfolding. All of the previously mentioned articles were eagerly read and incorporated in the new cleaning program being created as part of the author's responsibilities. However, after implementing these limits, a number of issues began to surface.

For one thing, when calculating limits using these approaches, it seemed that the limits were everywhere since they will vary based on the value of the lowest doses, the batch size, and equipment surface area, etc. In some cases, the calculated limits seemed to leave large amounts of residues and in other cases, the calculated limits could be below analytical capabilities and impossible to meet; this situation has already been reported in the literature.[8] Table C demonstrates this issue through a simulation of the calculation.

In Table C, two drug products with widely different minimum doses are shown; a high of 500 mg and a low of 1 µg. Limits are calculated based using high/low combinations for Batch Size, Maximum Daily Dose, and Total Equipment Surface Area. Every possible combination of these factors was calculated (basically using a 2^4 Full Factorial Design) and the data then sorted by their Maximum Allowable Carryover (MAC) values from lowest to highest. Although some of these combinations may not actually occur in every manufacturing operation, this simulation is meant to demonstrate how widely varying the limits can be. These data clearly show that acceptance limits can vary by many orders of magnitude for the same drug compound depending on the Batch Sizes and Maximum Daily Doses of the next drug product and the Total Surface Area of the equipment used. It should be evident that different drugs manufactured in the same equipment will have different limits; the same drug manufactured in different equipment will have a different limit; and different drugs manufactured in the different equipment will have greatly different limits. For example, a drug with a higher minimum dose manufactured in a Granulator/Wet Mill/Fluid Bed Dryer Train (larger surface area) may have much lower limits than a drug with a lower minimum dose manufactured in a Single Pot Processor (smaller surface area). Or if the tablets are sent to a Contract Packaging Organization, the limits for a Thermoformer, which has much smaller product contact areas by comparison, will be much higher. This is inconsistent; why does a Granulator/Wet Mill/Fluid Bed Dryer Train need to be "cleaner" (have much lower limits) than a Single Pot Processor or even lower for a Thermoformer line for the exact same product?

Another difficulty with this calculation (Batch Size/Maximum Daily Dose) is that it is primarily applicable to tablets and capsules where dose sizes are fixed and known. Some workers have pointed out the problem of employing the calculations with Topical Formulations.[9] For example,

Calculation for a Swab Sample:

1. $\frac{\text{Lowest Dose (Product A)}}{\text{Safety Factor}} \times \frac{\text{Batch Size}}{\text{Max Daily Dose (Product B)}} = \text{Maximum Allowable Carryover (MAC)}$

   (Product A is the product being cleaned/Product B is the subsequent Product)

2. MAC/Total Surface Area = Surface Residue $\mu g/cm^2$
3. Surface Residue/cm^2 × Area Swabbed = Residue on Swab (μg)
4. Residue on Swab(μg)/Dilution Volume (mL) = Residue level in swab sample (ppm)

The table below shows the MAC values , Surface Residues, and PPM values in an Analytical Sample for all combinations of Lowest Dose (0.001 mg and 500 mg), Batch Size (15 kg and 50 kg), Maximum Daily Dose (0.05 gm and 5 gm), and total Surface Areas (1,000 cm2 and 100,000 cm2). A swab area of 100 cm2 and a swab recovery of 100% are assumed.

Lowest Dose (mg)	Batch Size (kg)	Max Daily Dose (gm)	MAC (mg)	Total Surface Area (cm^2)	Surface Residue ($\mu g/cm^2$)	ppm in 20 mL
0.001	15	5	**0.003**	100000	0.00003	0.0002
0.001	15	5	**0.003**	1000	0.003	0.02
0.001	1200	5	**0.24**	100000	0.0024	0.01
0.001	1200	5	**0.24**	1000	0.24	1
0.001	15	0.05	**0.3**	100000	0.003	0.02
0.001	15	0.05	**0.3**	1000	0.3	2
0.001	1200	0.05	**24**	100000	0.24	1
0.001	1200	0.05	**24**	1000	24	120
500	15	5	**1,500**	100000	15	75
500	15	5	**1,500**	1000	1,500	7,500
500	1200	5	**120,000**	100000	1,200	6,000
500	1200	5	**120,000**	1000	120,000	600,000
500	15	0.05	**150,000**	100000	1,500	7,500
500	15	0.05	**150,000**	1000	150,000	750,000
500	1200	0.05	**12,000,000**	100000	120,000	600,000
500	1200	0.05	**12,000,000**	1000	12,000,000	60,000,000

Table C. Calculation for a swab sample limit and simulated results.

what are the Minimum Dose and Maximum Daily Dose of a topical such as a sun screen? In the case of a sunscreen, the Maximum Daily Dose may be based on the total body surface not covered by the swimwear. Conversely, what is the Minimum Dose of a sunscreen or any Topical product for that matter? The use of a Finger Tip Application (FTA) as a standard minimum dose has been proposed by Ovais, et. al.[9] Since Topicals are typically manufactured as a percentage of the formulation calculating the limits as a fraction of the percentage is a simpler approach. For example, the allowable level of the API of a 1% Topical would be 0.001% in another Topical. This approach avoids this issue and greatly simplifies the calculations. Clinical and Development batches face similar issues with minimum dose. The minimum and maximum doses may not be known or established yet.

The author has had many discussions with coworkers involved in Cleaning Validation on how the calculations of these limits can be confusing and are time consuming. A great deal of time is spent on calculations and in some cases, the calculated limits can not always be met; either the residues after cleaning are higher than the calculated limit or the swab analysis is not capable of detecting the levels dictated by the calculations. In practice, it has been found necessary to rework and/or rethink the calculations, sometimes in very creative ways, to arrive at limits that could be passed. In so doing, these calculations raised some questions: for example, why should a Topical product have to meet limits as low as those for an Injectable product?

PDA's Technical Report No. 29 in Section 8.5 "The Basis for Quantitative Limits" contains a table showing ranges of safety factors to be used based on the type of product - *Table D*. There is no reference to this table anywhere in the text and no rationale was given for the choices. An example calculation for an oral product only shows 1/1,000th as the safety factor to use. Regardless, it is clear that the intent was to provide lower safety factors for products with apparently lower risks. For example, why should a topical ointment for treating athlete's foot have the same limits for an injectable solution for treating cancer? While superficially these ranges seem to make sense when they are looked at in detail, this approach only raises more questions.

Approach	Approach Typically Applicable To
1/10th to 1/100th of a normal daily dose	topical products
1/100th to 1/1,000th of a normal daily dose	oral products
1/1,000th to 1/10,000th of a normal daily dose	injections, ophthalmic products
1/10,000th to 1/100,000th of a normal daily dose	research, investigational products

Table D. PDA's Technical Report No. 29 in Section 8.5 "The Basis for Quantitative Limits."

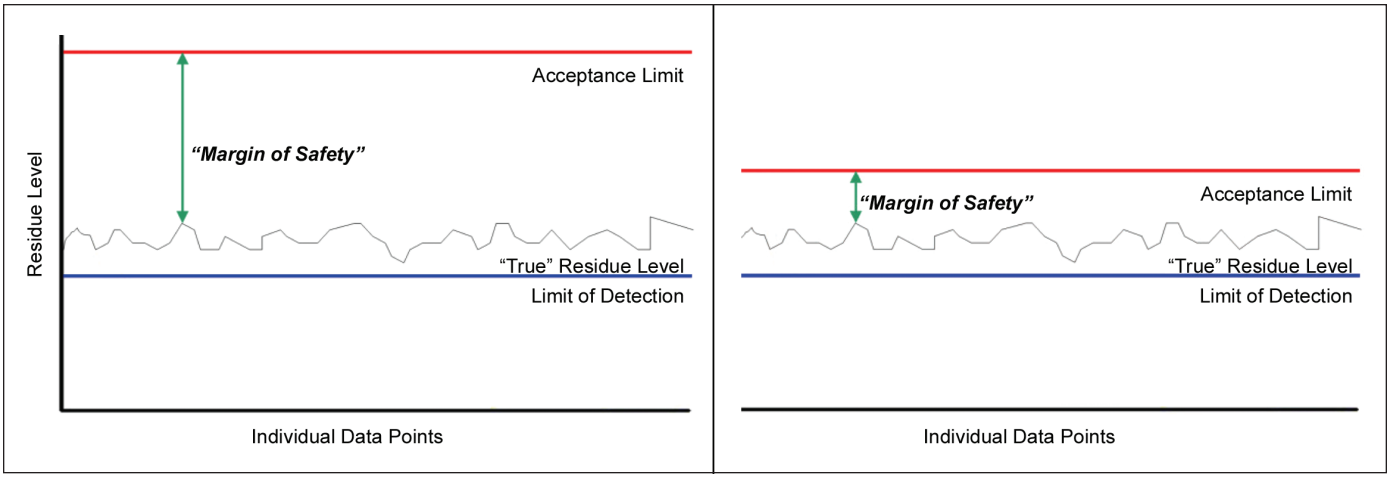


Figure 1. Effect of adding safety factors on margin of safety.

Let's say we are manufacturing a Topical product that is a low risk so we choose 1/10th as our "safety factor" to calculate a MAC value. So, if we are manufacturing a 400 kg batch of this Topical product and we are following it with another 400 kg batch of another product, by definition we can leave 39.99 kg of product behind and pass this limit. This is clearly a substantial amount of material that should easily be visible so clearly not what we could consider GMP; notwithstanding the implied yield loss. So is this limit really of any use?

At the other end of the spectrum, let's consider a Clinical Manufacturing scenario where we are manufacturing clinical batches of a Topical product and we choose to use 1/100,000th to calculate our MAC value. In this scenario, the calculated limits may very well not be passable. I am aware of several situations where equipment was used once and then relegated to a corner since the analytical method was not capable of detecting to the level calculated while a debate raged on what to do. Repeated washings, exhaustive rinsing, and even re-passivation could not release this equipment from its prison. The use of such "safety factors" has even driven a perceived need for disposable equipment. Simple hand scoops for weighing raw materials are now disposable since they cannot be demonstrated to be "clean enough." Taking this scenario even further, our new Topical product would use the 1/100,000th "safety factor" when in Clinical Manufacture, requiring disposable equipment, but when we move our product to launch in Commercial Manufacture the 1/10th "safety factor" would now be applied? All these situations prompted this author to ask the question:

Does Adding Safety Factors Actually Increase Safety?

My answer to this question, at the present state of setting cleaning validation limits, is no. So why is adding safety factors a problem? Let's look at the actual effect of adding safety factors. Figure 1 shows the relationships between a drug's "safe" limits, the drug's residue levels after cleaning, and the Limit of Detection (LOD) of the method. On the left, there is a clear separation between the residue data and the acceptance limit. This is shown by the green arrow labeled "Margin of Safety." It should be axiomatic that the greater the separation between the residue data and the acceptance limit, the greater the "Margin of Safety" is and the lower the risk to the patient.

The result of the application of additional "safety factors" to acceptance limits can be seen in the graph on the right. Here the acceptance limit (red line) is now lower. This has significantly decreased the apparent "Margin of Safety," but with no improvement in the residue data. In both cases, the patient is exposed to the same level of residue. If the original acceptance limit was already safe, the addition of more safety factors did not provide any additional safety to the patient; but it may certainly cause the manufacturer to fail the cleaning validation and may result in restrictive and unnecessarily costly measures in operations. In many cases, we are being ***overly restrictive*** with cleaning validation limits and ***causing many operational difficulties***.

As shown in Figure 1, improvement in patient safety is not achieved through adding extra safety factors to acceptance limits. If patient safety is the goal, a more appropriate approach is to focus on reducing the residue data rather than adding safety factors to acceptance limits. In Figure 2, we see the same graph on the left as in Figure 1, but the graph on the right shows the effect of providing a better developed cleaning process. The "true" residue levels are much lower (shown below the Limits of Detection) and the "Margin of Safety" is much higher since the acceptance limit was not arbitrarily lowered. This clearly improves patient safety and is a superior situation. Note also that in this example, the LOD of the method also was improved to provide a greater measure of how large the "Margin of Safety" actually is.

A firm should always start by designing quality into its cleaning procedures. The focus should be on developing robust cleaning processes; ***not*** on simply adding safety factors. On top of the issues concerning the calculation of acceptance limits and the use of safety factors there are...

Other Limitations to Using Dose-Based Limits

In addition to the difficulties with the MAC calculations

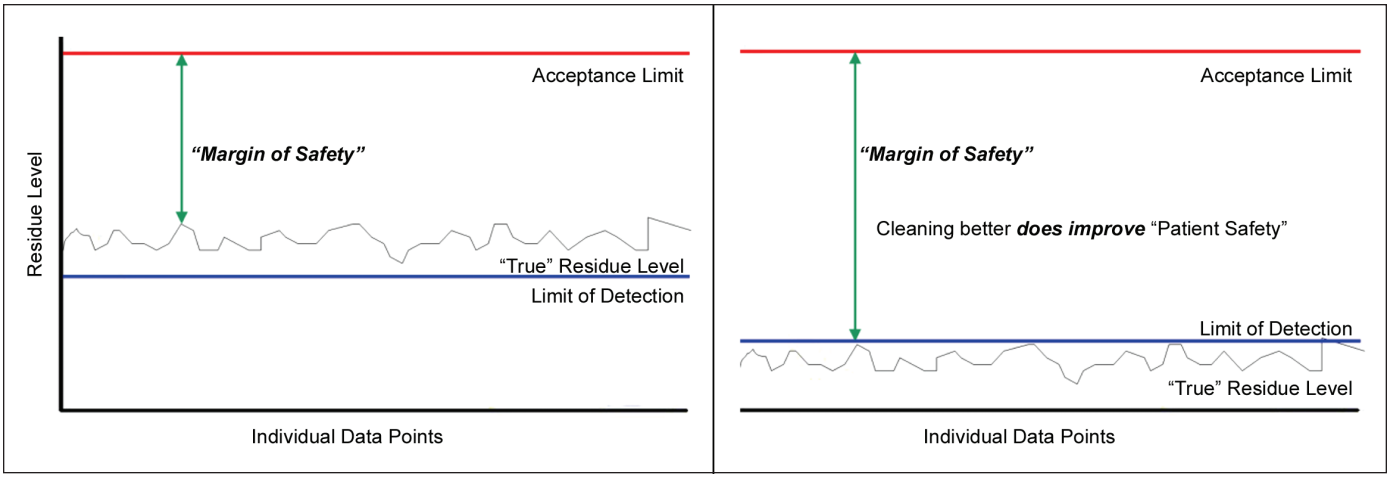


Figure 2. Effect of cleaning better on margin of safety.

and the application of safety factors discussed above, there are other fundamental difficulties with the concept of calculating acceptance limits based simply on the compound's therapeutic dose. Remembering that according to Harder the goal of setting Acceptance Limits is that they "...must be safe" and that FDA also expects limits to be safe and "...to be scientifically justified" we need to look critically at whether these simple fractions of the therapeutic dose actually can achieve these criteria. There are many instances where the simple application of a fraction of the therapeutic dose may not be considered safe.

Teratogens

One aspect of a drug's safety profile is whether the drug has teratogenic effects, that is, it can cause birth defects. The degree of teratogenicity is dependent on the dose, but it is not at all associated with the therapeutic dose. Let's look at a few examples. In Table E, there are three drugs with the same lowest therapeutic dose; Difenoxin HCL, Coumadin, and Diethylstilbestrol. Consequently, their acceptance limits based on 1/1,000th of the lowest therapeutic dose are all the same (0.001 mg). Although, in the fourth column, the doses shown to cause teratogenic effects for these compounds are vastly different. Difenoxin HCL is not teratogenic even at doses more than 60 times higher than its normal dose. Coumadin is teratogenic at 4 mg/kg, while Diethylstilbestrol is teratogenic at a dose as low as 0.006 mg/kg. Clearly, these compounds present greatly different risks to patients, yet their cleaning validation acceptance limits are the same. So once again products that have the same dosage will have the same acceptance limits although the products may have greatly different safety profiles. Below these three, the drug Ribavirin has a lowest therapeutic dose 600 times higher and its corresponding acceptance limit also 600 times higher than the other three compounds, including Difenoxin HCL which demonstrates no teratogenicity. Clearly, this important aspect of drug safety is not factored into the calculation of limits considered when simply using the therapeutic dose.

Therapeutic Index

All drugs are evaluated for their Therapeutic Index, that is, the ratio of their toxic dose to their effective dose (LD_{50}/ED_{50}). This ratio is the lethal dose of a drug for 50% of the population divided by the minimum effective dose for 50% of the population. This ratio shows the relative safety of the drug; the higher the value the safer the drug is. Figure 3 compares two drug compounds that have the same therapeutic dose (1.0 mg), but have very different Therapeutic Indices.

So for calculating limits, if the products have the same dosage they will have the same acceptance limits although the products may have greatly different safety profiles. Drugs with very low ratios are known as "Narrow Therapeutic Index." For example, warfarin, a drug with a notoriously Narrow Therapeutic Index is metabolized by cytochrome P450 2C9. Up to 35% of the population suffers from a deficiency in this enzyme.[10] Since members of this population do not metabolize Warfarin as quickly as the normal population, they can be harmed if their blood levels are too high. While this is normally seen as a clinician's problem for dosing, what about the effect on this population if Warfarin residues are

Drug Compound	Lowest Therapeutic Dose	1/1,000th of Therapeutic Dose	Lowest Reported Teratogenic Dose (mg/kg)	Limit (ADE) based on Teratogenicity
Difenoxin HCL	1 mg	0.001 mg	*No teratogenic effects* at up to 61X therapeutic dose	N/A*
Coumadin	1 mg	0.001 mg	4	1.9
Diethylstilbestrol	1 mg	0.001 mg	0.006	0.003
Ribavirin	600 mg	0.6 mg	0.12 – 0.14	0.06
Acceptable Daily Exposure values supplied by Dr. Bruce Naumann of Merck, Inc.			*(ADE must be set using other safety data)	

Table E. Comparison of 1/1,000th limits to ADE limits for teratogens.

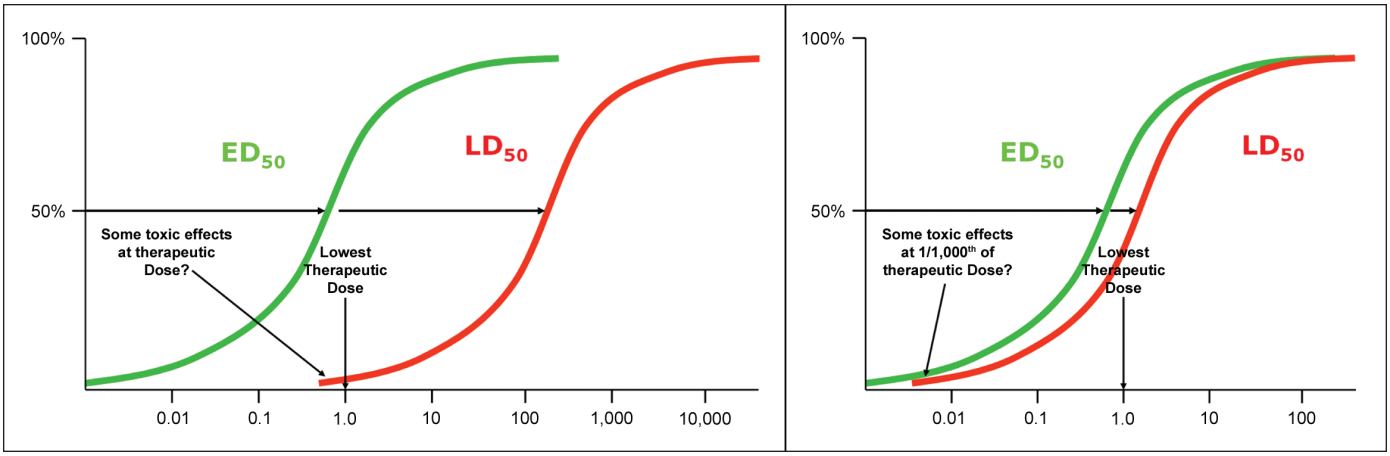


Figure 3. Effect of therapeutic index on acceptance limits.

carried over into another product manufactured on the same equipment? What is a safe level for them? Is 1/1,000th of a dose sufficiently safe?

Sensitizers

There are many drugs that are sensitizers; that is, they induce a specific immune response if introduced to a susceptible patient. Drugs with a molecular weight greater than 1000 Daltons can be immunogenic or allergenic on their own, but some drugs act as haptens, binding to host carrier proteins, and can then induce an immunogenic or allergenic response. The reaction to these drugs in a patient can be severe leading to anaphylaxis and death. The best known example of this is Penicillin which has been shown to elicit hypersensitivity at extremely low doses. So how does pharmacologic dose take sensitization into consideration?

Other Safety Characteristics

The drug characteristics discussed above are not the only categories that play a role in a drug's safety profile and its risk to a patient. Drugs may be cytotoxic or genotoxic and may have damaging effects on a patient's tissues; they may be steroidal and may have profound effects on a patient's hormone system; they may be radioactive posing a potential cancer threat to the patient; they may be immunomodulating agents possibly affecting the patient's immune system – the list goes on of drug characteristics that may play a role in the safety of a drug. It may be obvious to the reader by now that simply applying a fraction of the therapeutic dose does not consider many safety criteria and may not result in a limit that is truly safe. Even for relatively safe drugs, such as aspirin whose pharmacological effect is to relieve a headache, why would a "safe" cleaning limit be 1/1,000th of the lowest dose that relieves a headache? Let's compare aspirin to some other more "risky" drugs - *Table F*.

Drug Compound	Drug Type/ Adverse Effects	Lowest Therapeutic Dose	1/1,000th of Therapeutic Dose
Low dose Aspirin	NSAID/low side effects	81 mg	0.081 mg
Ribavirin	Anti-viral/teratogen	600 mg	0.6 mg
Capecitabine	Chemotherapy/numerous side effects	1150 mg	1.15 mg

Table F. Comparison of 1/1,000th limits for low and high risk compounds.

Using the 1/1,000th approach, a low risk drug such as Aspirin can have much lower limits than some drugs that are much riskier. This doesn't seem science-based and certainly not logical at all. How then should a drug company go about determining what is safe?

As it turns out, all drug companies have ready answers at their disposal. The pharmaceutical industry is unique in that it has the most extensive safety data on their products than any other industry, and in particular, data in humans. Extensive pharmacological and toxicological testing is performed on all drugs prior to marketing. All drug companies have already established comprehensive safety profiles of their products. All it takes is consulting the individuals in their companies who developed this information and have knowledge of the drugs' safety data. Indeed, Hank Avallone wrote as early as 1989 that "It is also recommended that a medically qualified responsible person, such as a physician, have input in the establishment of a limit."[11] Ironically, drug companies have always had everything they need for establishing science-based limits.

Part II of this article will discuss how to establish science-based limits for APIs using data from clinical and toxicological studies, a risk-based approach to evaluating cleaning validation data, and guidance on setting statistical process control limits from that data.

References

1. Harder, S., "The Validation of Cleaning Procedures" *Pharmaceutical Technology,* May 1984, www.pharmtech.com.
2. FDA Guide To Inspections: Validation Of Cleaning Processes.
3. Mendenhall, D., "Cleaning Validation," *Drug Development and Industrial Pharmacy,* 15(13), pp. 2105-2114, 1989.
4. Lehman, A.J., and Fitzhugh, O.G., "*100-fold margin of safety*" Assoc. Food Drug Off. U.S.Q. Bull. 18, 33–35, 1954.

5. United States vs. Barr Laboratories, Inc. Civil Action No. 92-1744, US District Court for the District of New Jersey: 812 F. Supp. 458. 1993 US Dist. Lexis 1932; 4 February 1993, as amended 30 March 1993.

6. Fourman, G., and Mullin, M., "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," *Pharmaceutical Technology,* April 1993, www.pharmtech.com.

7. Jimenez, F.J., "*Enforcement of the Current Good Manufacturing Practices for Solid Oral Dosage Forms After United States v. Barr Laboratories*" 52 Food Drug L.J. 67, 1997.

8. Sharnez, R., "Setting Rational MAC-Based Limits Part I—Reassessing the Carryover Criterion," *Journal of Validation Technology*, Winter 2010, www.gxpandjvt.com.

9. Ovais, M., and Lian, Lai Yeo, "Setting Cleaning Validation Acceptance Limits for Topical Formulations," *Phamaceutical Technology*, January 2008, www.pharmtech.com.

10. Redman, AR, "Implications of Cytochrome P450 2C9 Polymorphism on Warfarin Metabolism and Dosing," *Pharmacotherapy*, (2001) 21 pp. 235-242, http://pharmacotherapyjournal.org.

11. Avallone, H.L., "Drug Substance Manufacture and Control," *Pharmaceutical Engineering*, 1989, 9 (2), 37-40, 57, www.ispe.org/pe.

Acknowledgements

The author wishes to thank Dr. Richard Berkof, Nick Haycocks, Robert Kowal, Dr. Bruce Naumann, Mohammed Ovais, and Joel Young for reviewing this article and for their insightful comments and helpful suggestions.

About the Author

Andrew Walsh is an Industry Professor at Stevens Institute of Technology in their Pharmaceutical Manufacturing Program where he teaches courses on Validation and Lean Six Sigma. In 2009, Walsh founded the Stevens Pharmaceutical Research Center (SPRC), a research lab focusing Pharmaceutical Manufacturing topics, such as cleaning process development, Total Organic Carbon analysis and method development, visual inspection method development and automation of GMP systems. A current chair of an international task team to write a cleaning Guide for ISPE and ASTM, he was one of the contributors to the ISPE Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) Baseline® Guide. He has more than 20 years of diverse validation experience in pharmaceutical and biotech companies, including Johnson & Johnson, Schering-Plough, and Hoffmann-La Roche. Walsh has given numerous presentations over the past 15 years with IIR, Barnett, WorldPharm, IPA, IVT and ISPE. He can be contacted by telephone: +1-201-216-5533 or email: andrew.walsh@stevens.edu.

Stevens Institute of Technology, Castle Point on Hudson, Hoboken, New Jersey 07030, USA.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Practical Application of Quality Risk Management to the Filling Process of Betamethasone Injections

This article presents risk analysis performed on the Betamethasone Injections filling process and the conclusions obtained from the analysis.

by Rodolfo Díaz, Germán Fernández Otero, and Cristian Muzzio

Introduction

In the last years, the pharmaceutical industry has begun to incorporate the new paradigm promoted by the US FDA through the risk management/Quality by Design (QbD) approach:[1-3] "Quality cannot be tested into products; it should be built-in or should be by design." To ensure that quality is built into pharmaceutical products, the most up-to-date technologies and concepts of risk management should be incorporated into the manufacturing process. As part of this new approach, work was performed to evaluate the filling process of Betamethasone Injection in order to reduce its associated risks, where *risk* is understood as "the combination of the probability of occurrence of harm and the severity of that harm."[2] In addition, is the aim of the present work to illustrate the application of different Risk Management tools and the permeability of the local pharmaceutical industry to these ideas.

Betamethasone (BTM) is a powerful glucocorticoid used in the treatment of diverse allergic and inflammatory pathologies. It is available in different pharmaceutical forms like tablets, drops, ointments, creams, and injections. In this last case, soluble or insoluble derivatives of BTM or the combination of both can be used according to the desired therapeutic effect. Soluble derivatives of BTM (i.e., betamethasone sodium phosphate) are used when a fast effect is required whereas insoluble derivatives (betamethasone acetate or betamethasone dipropionate) are used when a depot effect is needed. Several works[4-6] have been devoted to this drug due to its properties and applications. BTM dipropioniate and acetate are practically insoluble in water, thus forming in this medium a white suspension that settles fast. The Stokes' law drives the speed of the settlement. This means that the viscosity of the medium, the density of both medium and particle and the particle size, have strong influence on the settlement rate. Due to formulation requirements, medium should be aqueous so density and viscosity could not be significantly changed. Particle density is a fixed attribute of the drug. Particle size is defined considering therapeutic requirements: particle should not be too fine since this could reduce the extent of the depot effect and should not be too coarse since irritation in the application area may occur. Normally, an average Particle Size Distribution (PSD) between 5 to 10 microns is suitable.

During the filling process of BTM suspension into vials, the suspension is contained in an agitated tank. Due to the fast sedimentation of the water-insoluble BTM, an inappropriate medium agitation leads to an inhomogeneous distribution of BTM in the vials that can adversely affect the quality of the final product. While a too low agitation speed would result in an accumulation of BTM in the bottom of the tank because of sedimentation, a too high agitation speed would produce an increment in the concentration of BTM near the walls of the tank. Furthermore, if the tank stirrer stops for a short period of time, the concentration of BTM in a few vials might reach unacceptable values, and these values could not be detected in a classic quality control because of the statistical nature of the sampling process.

Due to the aforementioned difficulties related to the filling process of BTM and the high risk of producing a poor quality product, a risk-based analysis was performed to improve the understanding of the filling process and reduce its associated risks. As a consequence of the risk

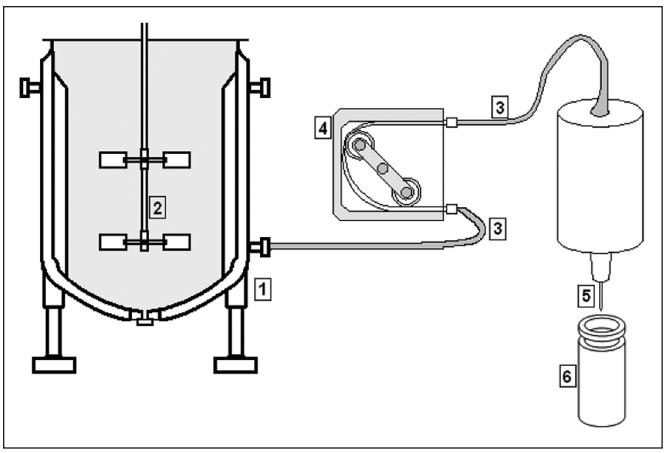


Figure 1. Schematic illustration of system setup: 1. tank 2. tank stirrer 3. silicone tube 4. peristaltic pump 5. filler nozzle 6. vial.

analysis application, a new device for in-line monitoring of the process was developed. The description and features of this device would exceed the scope of the present study so they will be described in a future work.

Betamethasone Filling Process

The filling system mainly comprises a tank, a peristaltic pump, a filler nozzle, a silicone tube, and a tank stirrer - *Figure 1.* A recirculation circuit is also present, but not shown in Figure 1. At present, the stirrer speed is manually controlled by an operator. After the suspension has been homogenized in the tank, it is impelled through the silicone tube toward the filler nozzle, where a pre-calibrated volume of suspension will fill the vials. The vials are filled every time they are under the filler nozzle. The release of suspension from the valve is automatically controlled by a mechanical switch. It is clear that speed of agitation and height of the suspension in the tank are critical factors that could adversely affect the final quality of the product. Since the process is not fully monitored and automated, several sources of risk arises (human failure or lack of training are among the sources to consider). The risks include the modification of product attributes (like uniformity of dose) up to unacceptable values. A large part of these modifications might not be detected in the final quality control of the product performed in the laboratory, due to the statistical nature of the assays and the short-term variability that can take place in the process conditions (e.g., short variations in the stirrer electrical power supply), which could affect few vials in the batch. Therefore, an analysis of the filling process through the Failure Mode, Effects, and Criticality Anaylsis (FMECA) tool was carried out to increase the understanding of the process and reduce its variability and possible risks.

What is FMECA?

Failure Mode, Effects And Criticality Analysis (FMECA[7,8]), an extension of FMEA, is a methodology developed to detect and analyze potential failure sources for products or process, which includes the identification of the potential failure mode and its causes, the evaluation of the associated risks (criticality or severity), and the definition of mitigation strategies. Originally designed in the late '40s for military purposes,[7] this technique has been widely spread among different industries including aeronautics and space, military, and commercial. Although FMECA is one of the most used reliability analysis methodology in the initial stages of the process or product development, it also can be employed to introduce modifications in preexisting processes or products and to analyze the future potential impact of such modifications. FMECA comprises a series of steps that can be summarized as follows:

- Define the system boundaries and the critical aspects to consider.
- Conform a multidisciplinary group.
- Collect data and information related to the critical aspects to consider (e.g., charts, manuals, reports, functional descriptions).
- Define the criteria associated with the different levels related to rate, detectability and severity of failure.
- Generate a FMECA worksheet, which includes the following columns: failure mode (hazards), failure causes, failure consequences, failure detectability, failure severity, failure rate, and mitigation strategies.
- Complete the FMECA worksheet by making use of analyst process comprehension and previous knowledge.
- Consider applying the FMECA again to analyze risks added from the application of mitigation strategies.

The development of these steps is depicted in the following section.

Process Analysis and Risk Control

The analysis of the BTM filling process was performed by a multidisciplinary team comprised of qualified personnel from different sectors of Química Montpellier S.A. (i.e., Galenical Development, Analytical Development, Quality Assurance, Maintenance, and Technical Direction), along with R&D personnel from Hitec S.R.L. The diversity of approaches proved very valuable, as can be seen from the conclusions extracted. The risk-based analysis of the BTM filling process considered the following:

- Objective: risk reduction of the BTM filling process.
- Scope: filling process including tank stirrer, filler nozzle, and in-line monitoring equipments.
- Risks: limited to the quality risks related with the patients' health.
- Data Collection: manufacturing records, volume control records (registered during the filling process), equipment qualification reports, equipment manuals, calibration reports of pump and tank stirrer, reports on product composition, analysis methods, stability studies, deviations, complaints.

The risk assessment of the filling process was divided in to "Risk Identification," "Risk Analysis," and "Risk Evaluation."

Unit Operation: Filling		
Critical Quality Attributes	**Description**	**Commentaries with respect to the influence during the filling process**
Aspect	NA	This parameter is visually evaluated in the primary container. It does not allow to distinguish slight modifications in the insoluble API concentration.
Identity	NA	This parameter is not modified by changes in the insoluble API concentration.
Filling Volume	A	This parameter is modified by inappropriate dosification or air addition in the suspension.
Potency (due to difference in the insoluble API titre)	A	This parameter is modified by sedimentation of the insoluble API.
Potency (due to stability)	NA	Stability studies demonstrated stability at normal atmosphere and light. Therefore, Nitrogen inertization or light protection is not required.
Impurity (incorporated during the process)	AEC	Available cleaning validation, routine verifications. Process which does not generate stress on the product.
Content Uniformity	A	This parameter is modified by sedimentation of the insoluble API.
Osmolarity	NA	This parameter is not modified by changes in the insoluble API concentration.
Density	NA	This parameter is not affected by slight changes in the insoluble API concentration.
pH	NA	This parameter is not affected by slight changes in the insoluble API concentration.
Related Substances (due to stability)	NA	Stability studies demonstrated stability at normal atmosphere and light. Therefore, Nitrogen inertization or light protection is not required.
Sterility/Microbiology	AEC	The aseptic filling process is performed in a class 100 classified area, qualified and with a routine of ambient, personnel, and surfaces monitoring. Validation of aseptic process and qualification of sterilized equipment is available.
Pyrogens	AEC	The aseptic filling process is performed in a class 100 classified area, qualified and with a routine of ambient, personnel and surfaces monitoring. Validation of aseptic process and qualification of sterilized equipment is available.
References	NA	Attribute not affected by the filling process, based on process comprehension and previous knowledge.
	AEC	Attribute affected by the filling process. Effects reduced by means of an existing control strategy.
	A	Attribute affected by the filling process. High potential risk.

Table A. Critical Quality Attributes and the influence on the filling process.

		Criterion	Examples and Related Notes
Severity			
Low	L	Therapeutic action or product safety is not affected.	Appearance differences (slight difference in color)
Medium	M	Product quality defects that do not compromise product safety. Efficacy might be affected.	Appearance is affected. Product does not meet organoleptic specifications.
High	H	Defects that compromise product safety and therapeutic action. Serious and permanent secondary effects on patient's health may be related. Product recall is mandatory. Container integrity is compromised.	Product contaminated. Stability affected. Dose higher or lower than required.
Probability			
Low	L	Less than once every twenty batches	N/A
Medium	M	Once or twice every twenty batches	N/A
High	H	3 or more times every twenty batches	N/A
Detectability			
Low	L	Defect needs a specific laboratory assay to be detected.	There is no associated alarm, there is no continuous monitoring. The deviation might not be detected by Quality Control.
Medium	M	Defect does not need a specific laboratory assay to be detected, but cannot be detected by visual inspection on the product.	There is an alarm indirectly associated to the deviation. The deviation can be observed in a record. There is an indicator that can be seen by an operator. The deviation might be recognized in the process documentation.
High	H	Defect can be detected by visual inspection on the product.	There is an alarm directly associated to the deviation. There is continuous monitoring.

Table B. Definitions of severity, detectability, and probability of occurrence levels.

Risk Identification

Focused on the identification of hazards, and its possible causes and consequences,the risk identification step did not consider probability of occurrence nor severity. Table A shows the Critical Quality Attributes (CQAs) of the product and the grade in which each CQA is affected by the process. A short commentary that relates the attribute and process conditions is also included. As a conclusion, three CQAs were identified as potentially affected during the filling process, i.e., the CQA that should be analyzed according to the scope of the present work: filling volume, potency (due to difference in the insoluble API titre), and content uniformity. In the present risk assessment, both content uniformity and potency are considered, owing to the greater difficulty in reducing their Risk Priority Number (RPN). Conversely, RPN related to filling volume can be readily reduced by improving detectability in a non-invasive way. Hence, filling volume is not further considered in this study.

Risk Analysis

In the present work, risk analysis was considered as defined in ICH Q9,[2] i.e., "the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk." The criteria for high, medium, and low levels related to severity, detectability, and probability of occurrence have been defined and listed in Table B. These estimations are utilized in risk evaluation in order to decide the appropriate mitigation strategy and the residual risk acceptance. It is worth noting that assessment of severity is limited to potential harm to patient's health, according to the constraints imposed in the definitions. In Table C, RPN is defined and listed.

Risk Evaluation

Risk evaluation is the last step in risk assessment. Different causes can lead to undesirable CQA values. This work only considered the CQA potentially affected by deviations in the filling process (CQA qualified with "A" in Table A). These causes, their consequences on product quality, and the potential risks on patient's health are summarized in Table D. As can be readily seen, most of the items reach unacceptable RPN values according to the levels and criteria defined in the preceding section. Thus,

Risk	Frequency of Ocurrence		
Severity of the Consequences	L	M	H
L	3	3	2
M	3	2	1
H	2	1	1

Priority (RPN)	Risk		
Detectability	1	2	3
L	I	I	II
M	I	II	III
H	II	III	III

Table C. Definitions of risk and RPN levels.

"The use of ICH Q9 and a formal risk management tool (FMECA) applied to the BTM filling process yields the risk reduction of the BTM filling process by focusing on the critical points and establishing the more appropriate mitigation strategies."

a mitigation strategy was necessary to reduce the risk to an acceptable level. The cost-effectiveness of different mitigation were considered, always prioritizing the patient's safety.

Risk Reduction

Different mitigation strategies have been proposed to reduce the RPN, mainly focused on the detectability improvement. For example, the following strategies can be enumerated: addition of a low and high speed alarm, directly associated to the stirrer axis; addition of a low and high recirculation pump speed alarm, directly associated to the speed into the recirculating tubes (flow meter); installation of a tank level alarm. However, further analysis leads to a better solution for hazards number 1 to 5 in Table D: the development of an in-line device that could continuously monitor the suspension concentration close to the filler nozzle. Unlike the previous mentioned strategies, this type of equipment would measure the suspension concentration directly and continuously, ensuring the product potency and uniformity. In addition, the equipment would not only provide a continuous real time quality assurance, but also be a tool to improve the process knowledge by performing in-line measurements, which could be correlated with variations in process conditions. However, the required equipment had to be developed in compliance with process requirements: it should be non-invasive, sterilizable, and perform fast measurements.

After two months of development, the prototype device and its insertion housing were finished and the in-line measurements obtained were compared to a reference off-line method, which demonstrated the good agreement between both methods. The measurement systems comprises a Trb 8300 turbidity transmitter along with an InPro 8100 single optical fiber turbidity sensor (Measuring range: 10 to 4000 FTU – 0 to 250 g/l), and a housing specially designed and developed for this project. Further details of the new in-line method, including the results from a comparison with the reference method, will be published soon.

As a consequence of the potential implementation of the new device, detectability of most of the items in Table D were improved, leading to the decrease in RPN as listed in Table E. Since the strategies implemented are non-invasive and do not include changes in the process, it was concluded that they do not introduce new risks into the system under study, nor increase existing risks. As a result, no further risk evaluation is required.

Conclusion

The use of ICH Q9 and a formal risk management tool (FMECA) applied to the BTM filling process yields the risk reduction of the BTM filling process by focusing on the criti-

N°	Identification of Hazards and Scenarios		Causes of the Hazard	Consequences of the Hazards	Harm (limited to patients)	Freq	Sev	Risk	Det	RPN
1	During the filling process, the tank stirrer speed is very low, or the stirrer is even stopped. The operator does not detect the failure.	A	Stirrer stops due to failure in the electrical supply.	The product settles in the tank. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose (depending on the filling step).	M	H	1	H	II
		B	Stirrer stops or its speed decreases due to failure in stirrer.			L	H	2	L	I
		C	Low stirrer speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
2	During the filling process, the tank stirrer speed is very high. The operator does not detect the failure.	A	Stirrer speed increases due to failure in stirrer.	The foreseen dose is modified due to addition of air in the suspension and adsorption of solids by surface tension to the air bubbles (it leads to solid separation). In addition, concentration of floccules near the side walls of the tank may increase due to centrifugal force.	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I
		B	High stirrer speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
3	During the filling process, the speed of recirculation is very low, or the recirculation is even stopped. The operator does not detect the failure.	A	The peristaltic pump stops due to failure in the electrical supply.	The product settles in the tube. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose.	M	H	1	H	II
		B	The peristaltic pump stops or its speed decreases due to failure in the peristaltic pump.			L	H	2	L	I
		C	Low recirculation speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
		D	The recirculation tube is obstructed.			L	H	2	L	I
4	During the filling process, the speed of recirculation is very high. The operator does not detect the failure.	A	High recirculation speed due to failure in the frequency inverter.	The foreseen dose is modified due to addition of air in the suspension and adsorption of solids by surface tension to the air bubbles (it leads to solid separation).	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I
		B	High recirculation speed due to value incorrectly set, because of human failure or lack of training.			L	H	2	L	I
5	During the filling process, the stirrer speed is not appropriate to the height of the suspension in the tank. The operator does not detect the failure.	A	Level indicator or filled units was not verified due to human failure or lack of training.	The foreseen dose is modified because of addition of air in the suspension due to the fact that the stirrer speed is higher than the one indicated in the manufacturing records.	Lack of therapeutic effectiveness or overdose.	L	H	2	M	II
6	After a stop of 5 minutes, the operator does not discard units in a number equivalent to a volume of 100 mL.	A	The instructions depicted in the product manufacturing records are not followed due to human failure or lack of training.	The product settles in the "tank-filler machine" circuit. As a consequence, the concentration uniformity of the insoluble API is modified.	Lack of therapeutic effectiveness or overdose.	L	H	2	L	I

Table D. RPN associated to different hazards, before applying mitigation strategies.

cal points and establishing the more appropriate mitigation strategies. Among the mitigation strategies considered, the in-line continuous monitoring would substantially reduce the probability of releasing out-of-specification units in comparison to conventional quality control assays, which are usually limited by its statistical and destructive nature. It is reasonable to estimate that it will not take a long time until the BTM filling process can be controlled and optimized by making use of in-line technologies, thus reducing significantly both the risks and the costs of production (as a consequence of decreasing the scrap and reprocessed units). However, the introduction of new and evolved technologies in existing pharmaceutical processes will require the previous application of a risk management tool along with the accumulated knowledge of experts from different sectors of the company in order to enhance the process efficiency and avoid the undesirable appearance of unexpected risks. In this regard, the present study is expected to serve as base of future works in the field of risk analysis and technology application within the Process Analytical Technology (PAT[9]) framework.

References

1. ICH Q8(R2) – *Pharmaceutical Development,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf, 2009.

2. ICH Q9 – *Quality Risk Management,* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128053.pdf, 2006.

3. ICH Q10 – *Pharmaceutical Quality System,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf , 2009.

4. Frears J., Hodgson S., Friedman M.,"Effect of Placebo Substitution During Long-Term Betamethasone Valerate Aerosol Treatment in Asthmatic Children," *Arch. Dis. Childhood,* (1975), Vol. 50, Issue 5, pp. 387-392.

5. Pershing, L.K., Silver B.S., Krueger. G.G., Shah V.P, Skelley, J.P. "Feasibility of Measuring Bioavailability of Topical Betamethasone Dipropionate in Commercial Formulations Using Drug Content in Skin and a Skin Blanching Bioassay," *Pharmaceutical Research,* (1992), Vol. 9 , No. 1, pp. 45-51.

6. Schwab, M., Antonow-Schlorke, I., Kühn, B., Müller, T., Schubert, H., Walter, B., Sliwka, U., Nathanielsz, P.W., "Effect of Antenatal Betamethasone Treatment on Microtubule-associated Proteins MAP1B and MAP2 in Fetal Sheep." *J. Physiol.,* (2001), February, Vol. 530 (Pt.3), pp. 497-506.

7. U.S. Department of Defense, Procedures for performing a Failure Mode, Effects and Criticality Analysis (FMECA), http://www.fmea-fmeca.com/milstd1629.pdf,1949.

8. Borgovini, R., Pemberton S., Rossi, M. "Failure Mode, Effects and Criticality Analysis (FMECA)," *Reliability Analysis Center,* 1993.

N°	Identification of Hazards and Scenarios		Causes of the Hazard	Mitigation Strategy	Freq	Sev	Risk	Det	RPN
1	During the filling process, the tank stirrer speed is very low, or the stirrer is even stopped. The operator does not detect the failure.	A	Stirrer stops due to failure in the electrical supply.	Detectability may be increased by installing an in-line device in order to measure the suspension concentration. The device should be installed as close to the filler nozzle as possible, and it should include an alarm system to indicate deviation from the parameters.	M	H	1	H	II
		B	Stirrer stops or its speed decreases due to failure in stirrer.		L	H	2	H	III
		C	Low stirrer speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
2	During the filling process, the tank stirrer speed is very high. The operator does not detect the failure.	A	Stirrer speed increases due to failure in stirrer.		L	H	2	H	III
		B	High stirrer speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
3	During the filling process, the speed of recirculation is very low, or the recirculation is even stopped. The operator does not detect the failure.	A	The peristaltic pump stops due to failure in the electrical supply.		M	H	1	H	II
		B	The peristaltic pump stops or its speed decreases due to failure in the peristaltic pump.		L	H	2	H	III
		C	Low recirculation speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
		D	The recirculation tube is obstructed.		L	H	2	H	III
4	During the filling process, the speed of recirculation is very high. The operator does not detect the failure.	A	High recirculation speed due to failure in the frequency inverter.		L	H	2	H	III
		B	High recirculation speed due to value incorrectly set, because of human failure or lack of training.		L	H	2	H	III
5	During the filling process, the stirrer speed is not appropriate to the height of the suspension in the tank. The operator does not detect the failure.	A	Level indicator or filled units was not verified due to human failure or lack of training.		L	H	2	H	III
6	After a stop of 5 minutes, the operator does not discard units in a number equivalent to a volume of 100 mL.	A	The instructions depicted in the product manufacturing records are not followed due to human failure or lack of training.	Detectability may be increased by installing a timer with alarm for operation interruption, and a system for automatic discard, which allows to eliminate the units related to the process restart.	L	H	2	H	III

Table E. RPN associated to different hazards, after applying mitigation strategies.

9. FDA, *Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf, 2004.

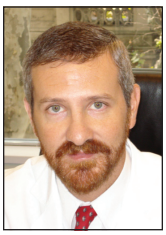
Acknowledgements

The authors would like to thank HITEC and Química Montpellier S.A. for funding this research and authorizing the publication of this work.

About the Authors

Rodolfo Díaz is the founder and CEO of Hitec S.R.L. He has been working for more than 15 years in automation and process optimization in the pharmaceutical industry and has dictated numerous courses in different countries. Díaz graduated as an electronic engineer from the Buenos Aires University, where he worked as Professor at the Faculty of Engineering, and specialized in optoelectronics in Paris Nord University. He can be contacted by email: rdiaz@hitec.com.ar.

Departamento de Investigación y Desarrollo, Hitec S.R.L., San Blas 2655 (C1416EFU), Buenos Aires, Argentina.



Germán Fernández Otero is the Technical Director of Química Montpellier S.A. He is a pharmacist from the Buenos Aires University. He has been working for more than 24 years in areas such as quality control, research and development, and quality assurance. He also worked for 10 years at the Department of Analytical Chemistry at Buenos Aires University, Pharmacy and Biochemistry College, where he published many papers and articles related to analytical technology. He can be contacted by email: gfotero@montpellier.com.ar.

Química Montpellier, Virrey Liniers 673, Buenos Aires, Argentina.

Cristian Muzzio is responsible for the R&D Department at Hitec S.R.L., where his responsibilities span from developing new technologies to creating innovative solutions for optimization of pharmaceutical processes within the PAT approach. His research activity has been mainly focused on mathematical modeling and application of non-invasive technologies to pharmaceutical processes, such as turbidimetry or NIR spectroscopy. Muzzio graduated with a chemical engineering degree from the Buenos Aires University in 2006, where he is currently a Teaching Fellow in process simulation and applied thermodynamics. He can be contacted by email: cmuzzio@fi.uba.ar.

Departamento de Investigación y Desarrollo, Hitec S.R.L., San Blas 2655 (C1416EFU), Buenos Aires, Argentina.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

The ISPE GAMP Community of Practice (COP) provides its interpretation of the revised EU GMP Annex 11 *Computerised Systems* and consequential amendment of EU GMP Chapter 4 Documentation.

ISPE GAMP COP Annex 11 Interpretation

by Winnie Cappucci, Chris Clark, Tim Goossens, and Sion Wyn

Introduction

This interpretation of the revised Annex 11 requirements has been produced by a core GAMP COP Task Team, and reviewed by the GAMP COP Council and members of GAMP Regional Steering Committees.

The GAMP COP believes that there is nothing in the revised Annex 11 – if interpreted in a pragmatic and reasonable way – that should cause major concern or problems to any regulated company that was complying with the previous Annex 11, and generally following good practice as defined in GAMP 5 and associated key Good Practice Guides. The revised Annex 11 adopts a risk based approach, and is aligned with current industry good practice.

There is a risk of regulated companies and their suppliers over-analysing detailed wording (either new or changed) in extreme detail, looking for nuances and distinctions not intended by the authors of the regulation.

The GAMP COP advocates a sense of perspective and balance, and avoiding any unnecessary over-reaction to a sensible and reasonable piece of regulation.

Overview

The European Commission (EC) has announced a new revision of EU GMP Annex 11 *Computerised Systems*, and consequential amendment of EU GMP Chapter 4 *Documentation*. These will come into operation by 30th June 2011.

Annex 11 has been revised in response to the increased use of computerised systems and the increased complexity of these systems. The Annex defines EU requirements for computerised systems, and applies to all forms of computerised systems used as part of GMP regulated activities.

EU GMP Chapter 4 requirements on generation, control, and retention of documents have been revised in the light of the increasing use of electronic documents within the GMP environment, and in the light of the Annex 11 revision.

Initial draft revisions had been released for public consultation in April 2008. There was significant industry feedback, including substantive and detailed comments from the ISPE GAMP Community of Practice. Most of the issues raised by the GAMP COP have been addressed in the final revisions. The most significant aspects of the revisions are:

- Risk based approach to validation and operational controls
- Harmonization with current industry good practice
- Clarification of the acceptability of electronic records and signatures

Quality Risk Management

A significant addition to the revised Annex is a new clause on quality risk management, which states:

> *Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.*

This risk management based thinking, focused on patient safety and product quality, and based on good product and process understanding, is the key to a correct interpretation and understanding of the requirements in this regulation,

and how appropriate controls to meet the requirements should be applied by the regulated companies.The revised Annex also states that regulated companies should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

The risk management approach adopted is very much in line with ICH Q9 *Quality Risk Management* and the ISPE GAMP 5 Guide: *A Risk Based Approach to Compliant GxP Computerized Systems*.

Current Good Practice

The revised requirements are closely aligned with current industry good practice.The Annex is harmonised with GAMP 5 life cycle terminology such as the use of Project Phase and Operational Phase, and uses GAMP 5 terminology for roles and responsibilities such as System Owner and Process Owner. There is also good match between the operational requirements and the topics covered in the GAMP Good Practice Guide: *A Risk Based Approach to Operation of GxP Computerized Systems*.

Enhanced and clarified requirements covering suppliers and service providers have been included, reflecting the increasing role of IT service providers, and the increased dependence on supplier activities and documentation.

One aspect requiring clear interpretation is the requirement that quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request. Other interesting aspects include the need for:

- An up-to-date inventory of GMP systems and their functionality
- Documented adequacy assessments for automated testing tools and test environments
- Periodic evaluation of systems to confirm that they remain in a validated state and are compliant with GMP.

These are, however, already established industry good practice.

Electronic Records and Signatures

Annex 11 and Chapter 4 revisions together clarify the acceptability of the use of electronic records and signatures for GMP purposes. Some definitions, terms, and requirements for electronic records have been moved to Chapter 4.

Chapter 4 states that documentation may exist in a variety of forms, including paper-based, electronic or photographic media. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based.

Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.The requirements of Chapter 4 include:

- Complex systems need to be understood, well documented, validated, and adequate controls should be in place
- Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented.
- Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

The requirements covering electronic records and signatures are broadly in line with current US FDA expectations and interpretation of 21 CFR Part 11, but are less detailed and prescriptive.

Detailed Interpretation

Disclaimer: ISPE cannot ensure and does not warrant that computerized systems managed in accordance with this interpretation will be acceptable to regulatory authorities.

This interpretation is subject to update and change without notice.

Limitation of Liability: In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

Section	Interpretation
Principle	
This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfil certain functionalities.	This is similar in intent but not identical to the *PIC/S Good Practices for Computerised Systems in Regulated "GXP" Environments' (PI 011)*, which also includes controlled functions and associated documentation in the definition of computerised system. The definition is interpreted as being consistent with GAMP 5 terminology and usage, where the computerised system consists of the hardware, software, and network components, together with the controlled functions and associated documentation.

Section	Interpretation
Principle (continued)	
The application should be validated; IT infrastructure should be qualified.	This is consistent with the GAMP 5 approach to validate GxP regulated applications and to ensure control and compliance of the infrastructure (following GAMP 5 guidance regarding Category 1 components, and the *GAMP Good Practice Guide: IT Infrastructure Control and Compliance*). GAMP 5 defines Computerized System Validation as: *Achieving and maintaining compliance with applicable GxP regulations and fitness for intended use by:* • *the adoption of principles, approaches, and life cycle activities within the framework of validation plans and reports* • *the application of appropriate operational controls throughout the life of the system* The compliant and validated status of GxP applications are dependent upon an underlying IT Infrastructure being in a demonstrable state of control and regulatory compliance. The infrastructure should be brought into initial conformance with the regulated company's established standards through a planned verification process building upon acknowledged good IT practices. Once in conformance, this state should be maintained by established processes and quality assurance activities, the effectiveness of which should be periodically verified.
Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.	This is largely equivalent to a similar clause in the previous version. It underlines the focus on risk. This is consistent with the overall risk-based approach taken in GAMP 5 and ICH Q9.
General	
1. ***Risk Management*** Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.	This is a significant, and welcome, new clause. This is consistent with the overall risk-based approach taken in GAMP 5 and ICH Q9.
2. ***Personnel*** There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.	This is largely equivalent to similar clauses in the previous version. The GAMP 5 terms Process Owner and System Owner are used. Training should ensure that persons who develop, maintain, or use computerized systems have the education, training, and experience to perform their assigned tasks.
3. ***Suppliers and Service Providers*** 3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.	The revision has expanded the requirements to clarify what is required, but has not introduced new concepts beyond current good practice. ICH Q10 Pharmaceutical Quality System, specifically the guidance on Management of Outsourced Activities and Purchased Materials is relevant and should be considered. This clause reflects the trend to centralize or outsource computerized system related services throughout the system lifecycle. Where this introduces additional GxP risk, such risk should be controlled by clear definition of delegated responsibilities and quality standards, supported by an assessment and periodic evaluation process. For internal providers such as IT departments, an established QMS including formal policies, procedures and supporting audits, are an effective way of meeting this requirements, and in such cases formal contracts – such as would be typical with external service providers –would not be required. For internal service providers agreements such as Service Level Agreements (SLA) and Operational Level Agreements (OLA) as described in Information Technology Infrastructure Library (ITIL) may be useful good practice, but are not mandatory.
3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.	This is largely equivalent to similar clauses in the previous version, and consistent with GAMP 5 and ICH Q10 approach to supplier assessment. The regulated company should verify, prior to contract placement, that the supplier has adequate expertise and resources to support user requirements and expectations. The most common mechanism for this is the supplier assessment, which may include an audit depending on risk, complexity, and novelty.
3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.	This is largely equivalent to similar clauses in the previous version, and consistent with GAMP 5 approach to supplier assessment, traceability, and design review. Commercial off-the-shelf products should be assessed and verified as being able to meet user and GxP requirements. This requires clearly defined requirements based on product and process understanding, and appropriately traced to verification.

Section	Interpretation
General (continued)	
3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.	This is a significant new clause. This, like Clause 3.2 above, is related to the regulated company's responsibility to verify that supplier has adequate expertise and resources to support user requirements and expectations. Evidence of an appropriate assessment process and subsequent judgement of supplier suitability, including significant GMP related findings and outcomes should be made available to regulators on request. Some detailed aspects of assessment finding, especially those related to supplier intellectual property and technology may be covered by confidentiality agreements between the regulated company and the supplier. If a regulator requests supplier information, a request may be passed on to the supplier – and when necessary further confidentiality agreements discussed. For service suppliers of high risk processes, contracts should notify them of the possibility for direct inspection and request timely access to their QMS if needed during regulatory inspection. Note also that general life cycle and validation documentation – including validation plans, validation reports, and verification documents – will also demonstrate that the system is fit for intended use. For IT service suppliers, the regulated company is responsible for assessing the supplier's QMS as fit for purpose and monitoring its effectiveness.
Project Phase	
4. ***Validation*** 4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.	This is consistent with the overall risk-based approach taken in GAMP 5 and ICH Q9. It emphasises the risk based approach and the need for documented justification of the life cycle approach.
4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.	This is current good practice, and consistent with GAMP 5. Project change control and configuration management should be applied. A computerized system validation report should be produced summarizing the activities performed, any deviations from the plan, any outstanding and corrective actions, and providing a statement of fitness for intended use of the system. See GAMP 5 Appendix M7 for further details.
4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available. For critical systems an up to date system description detailing the arrangements, data flows and interfaces with other systems or processes, software pre-requisites, and security measures should be available.	A system list or inventory is current good practice, and is consistent with Annex 15, Clause 4c. See also GAMP 5 Section 6.1.5 Maintaining the System Inventory The need for system descriptions is largely equivalent to similar clauses in the previous version. Current industry good practice is to have a system description (or equivalent – see below) for all GxP regulated systems. This may be covered by the User Requirements specification (URS) or Functional Specification (FS), or a separate document may be produced. A detailed system description may not be necessary for systems with a low risk to product quality or patient safety. The level of detail should be commensurate with risk and complexity of the system. See GAMP 5, Appendix D6 System Descriptions.
4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.	This is largely equivalent to similar clauses in the previous version, but with increased emphasis on the documented assessment of risk and GMP impact. It also underlines the interrelationship of requirements definition and risk assessment activities. Requirements should be based on product and process understanding, and relevant regulatory requirements. Specification of requirements should be focused on aspects with highest risk to product quality and patient safety. Traceability is a process for ensuring that: • requirements are addressed and traceable to the appropriate functional and design elements in the specifications • requirements can be traced to the appropriate verification Traceability should be focused on requirements with highest risk to product quality and patient safety. See GAMP 5 Appendix M5 for further guidance on traceability.
4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.	This is largely equivalent to similar clauses in the previous version. See also comments on other supplier assessment and management requirements above.
4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.	This reflects the added life cycle activities required for a bespoke or customized application, and the use of a controlled life cycle with clearly defined phases or stages. Such life cycle activities should be scaled based on risk, complexity, and novelty. At the conclusion of the project, a computerized system validation report should be produced summarizing the activities performed, any deviations from the plan, any outstanding and corrective actions, and providing a statement of fitness for intended use of the system.

Section	Interpretation
Project Phase (continued)	
4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered.	This shows a welcome increased focus on careful choice of test strategy, including negative or challenge testing, intended to identify defects. Verification confirms that specifications have been met. This may involve multiple stages of reviews and testing depending on the type of system, the development method applied, and its use. Testing computerized systems is a fundamental verification activity. Regulated companies should be prepared to justify the adequacy of their verification approach. Testing is concerned with identifying defects so that they can be corrected, as well as demonstrating that the system meets requirements.
Automated testing tools and test environments should have documented assessments for their adequacy.	Testing often is performed at several levels depending on the risk, complexity, and novelty. One level of testing may be appropriate for simple and low risk systems This clause reflects the increased use of, and acceptability of automated testing methods. The use of the phrase documented assessment for adequacy is consistent with a GAMP Category 1 approach. The type and level of assessment should be commensurate with potential risk. Testing tools and test environments do not typically need to be validated. Specific controls and verification may be appropriate, based on risk, if such tools are used to maintain regulated records.
4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.	This is a new clause aimed primarily at data migration and archiving. It is consistent with statements in US FDA Part 11 SCOPe and Application Guidance on the preservation of content and meaning of GxP records during COPying or migration. It is also consistent with the approach described in the GAMP Good Practice Guide: *A Risk-Based Approach to Compliant Electronic Records and Signatures*. Data migration may be required when an existing system is replaced by a new system, when an operational system experiences a significant change, or when the sCOPe of use of a system changes. The migration process should be accurate, complete, and verified. Appropriate guidance is given in GAMP 5 Appendix D7 Data Migration, and the GAMP Good Practice Guide on *Electronic Data Archiving*.
Operational Phase	
5. ***Data*** Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.	This is a new clause aimed at system interface design, reflecting the increasing inter-connectedness of systems and increasing number of system-interfaces, and the corresponding need to focus on appropriate risk control during system specification, design, and verification.
6. ***Accuracy Checks*** For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.	This is largely equivalent to similar clauses in the previous version. The term "critical data" in this context is interpreted as meaning data with high risk to product quality or patient safety.
7. ***Data Storage*** 7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.	This is largely equivalent to similar clauses in the previous version. It is consistent with statements in US FDA Part 11 SCOPe and Application Guidance on record retention requirements. GAMP 5 gives guidance on data security, specifically in Appendix O11 Security Management.
7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.	This is largely equivalent to similar clauses in the previous version, but with added emphasis on the verification of the backup and restore process, and periodic monitoring of that process (e.g. to cover media aging) Backup is the process of COPying records, data and software to protect against loss of integrity or availability of the original. Restore is the subsequent restoration of records, data or software when required. Applicable GAMP 5 guidance on the topic includes Appendix O9 on Backup and Restore. In many cases backup and restore capability will be provided by elements of the IT infrastructure, which as discussed above (See discussion of "Principle") should be in a state of control and compliance. In such cases the individual system backup and restore needs should be specified, configured, and verified.
8. ***Printouts*** 8.1 It should be possible to obtain clear printed COPies of electronically stored data.	This is largely equivalent to similar clauses in the previous version. Regulated companies must provide reasonable and useful access to GMP records to regulators. This is consistent with statements in US FDA Part 11 SCOPe and Application Guidance regarding the availability of human readable COPies in order to provide such reasonable and useful access to records during an inspection. See also GAMP Good Practice Guide: *A Risk Based Approach to Compliant Electronic Records and Signatures*.

Section	Interpretation
Operational Phase (continued)	
8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.	This is similar to clauses in the previous version, but with significant additions. Additions indicate the importance of a high level of control over, and transparency of changes to, records supporting batch release. Suitable methods should be selected based on a justified and documented risk assessment, and an analysis of the process. The term printout is interpreted as indicating a suitable human-readable form.
9. ***Audit Trails*** Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.	This is largely equivalent to similar clauses in the previous version. The need for, and the type and extent of, any audit trail should be based on a documented and justified risk assessment. This is consistent with statements on audit trails in US FDA Part 11 SCOPe and Application Guidance. See also GAMP Good Practice Guide: *A Risk Based Approach to Compliant Electronic Records and Signatures*. The need for audit trail review should be based on a documented and justified risk assessment, taking into account: • Initial verification of audit trail functionality, and subsequent verification (as appropriate) during change management • Effective segregation of duties and related role-based security • Established and effective procedures for system use, administration, and change management Any review of audit trails deemed necessary should focus on checking that they are enabled and effective. Suitable records security controls should be in place for high risk records, and appropriate segregation of duties enforced (e.g. such that nobody with a conflict of interest has privileges that would allow alteration of data or audit trail configuration). Audit trails should be regarded as only one element in a wider framework of controls, processes, and procedures aimed at an acceptable level of record and data integrity. Audit trails should be regarded primarily as a tool to be used for investigation, as and when required, rather than for continuous routine review. Routine review of all audit trail content is not required, and is not consistent with a risk-based approach. The cost and effort is not justified by any likely benefit.
10. ***Change and Configuration Management*** Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.	This is largely equivalent to similar clauses in the previous version. Change management is the process of controlling the life cycle of changes, enabling beneficial changes to be made without compromising regulated processes or records. Configuration management comprises those activities necessary to be able to precisely define a computerized system at any point during its life cycle, from the initial steps of development through to retirement. All changes should be reviewed, risk assessed, authorized, documented, tested, and approved before implementation. These activities should be documented. See GAMP 5 Appendix O6 Operational Change and Configuration Management for more details.
11. ***Periodic Evaluation*** Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.	This is a new clause, but consistent with current industry good practice as described in GAMP 5. (See Appendix O8 Periodic Review). It is consistent with Annex 15 clauses 23 and 45. Periodic reviews are used throughout the operational life of a computerized system to verify that it remains compliant with regulatory requirements, fit for intended use, and satisfies company policies and procedures. The review should confirm that, for all components of a system, the required support and maintenance processes are established and that the expected regulatory controls (plans, procedures and records) are established and in use.
12. ***Security*** 12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.	This is largely equivalent to similar clauses in the previous version. Measures should be implemented to ensure that GxP regulated computerized systems and data are adequately and securely protected against wilful or accidental loss, damage, or unauthorized change. Such measures should ensure the continuous control, integrity, availability, and (where appropriate) the confidentiality of regulated data. This process should include: • Establishing and maintaining security roles and responsibilities, policies, standards, and procedures • Performing security monitoring and periodic testing, e.g., manual check of system access log, automated notification of lockouts, testing of tokens • Implementing corrective actions for identified security weaknesses or incidents.

Section	Interpretation
Operational Phase (continued)	
12. ***Security (continued)*** 12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas. ***(continued)***	• Ensuring a list of those authorized to access the system is established and maintained The design of the system's physical and technical security mechanisms should be assessed and (if necessary) tested. GAMP 5 gives guidance on security, specifically in Appendix O11 Security Management.
12.2 The extent of security controls depends on the criticality of the computerised system.	See above. This is consistent with GAMP 5 risk-based approach to operational controls.
12.3 Creation, change, and cancellation of access authorisations should be recorded.	See above. This is consistent with current industry good practice.
12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.	This is a new clause, but the intent is already covered in Clause 9 and Clause 12.1. The approach should be commensurate with the risk associated with the data in question.
13. ***Incident Management*** All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.	This is largely equivalent to similar clauses in the previous version. This is current industry good practice. Further guidance is available in GAMP 5 Appendix O4 Incident Management The primary objective of Incident Management is to ensure that any unplanned issues that could impact patient safety, product quality, and data integrity are addressed before any harm occurs. The incident management process should ensure that operational events which are not part of the standard operation (i.e., issues, problems, and errors) are identified, evaluated, resolved, and closed in a timely manner.
14. ***Electronic Signature*** Electronic records may be signed electronically. Electronic signatures are expected to: a. have the same impact as hand-written signatures within the boundaries of the company, b. be permanently linked to their respective record, c. include the time and date that they were applied.	This clarifies that electronic signatures are allowed, but are not mandatory. It reflects current industry good practice. The phrase "within the boundaries of the company" clarifies that such signatures applied to records maintained by the regulated company are not subject to Directive 1999/93/EC on a Community framework for electronic signatures, nor the 2000/31/EC Directive on electronic commerce, nor any associated national regulations of EU member states on such topics. The approach is consistent to that described in in the US FDA Part 11 SCOPe and Application Guidance See also GAMP Good Practice Guide: *A Risk Based Approach to Compliant Electronic Records and Signatures*, which describes an approach that is consistent with the revised Annex 11 and Chapter 4, as well as the current FDA interpretation of Part 11.
15. ***Batch Release*** When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.	This is largely equivalent to a similar clause in the previous version, with additional discussion of electronic signatures This additional discussion is interpreted not as making the use of electronic signatures mandatory for batch release, but rather requiring that if the release is performed electronically that the requirements of Clause 14 above are met. The possibility of repudiation or lack of integrity of such high risk signatures should be managed by suitable controls, based on a justified and documented risk assessment.
16. ***Business Continuity*** For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.	This is largely equivalent to similar clauses in the previous version. This is current industry good practice, and consistent with GAMP 5, e.g. Appendix O10 Business Continuity Management. Patient safety, product quality, and data integrity should not be compromised by system failure or breakdown. The regulated company should perform business continuity planning to actively protect its ability to continue to supply the public, and to comply with the regulatory requirements. Business continuity processes should be documented, communicated, and verified as effective.
17. ***Archiving*** Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.	This is largely equivalent to similar clauses in the previous version, and is consistent with Section 7 and 10 above. It underlines that checks and controls are required to ensure the preservation of data and record content and meaning throughout the required retention period. Computerised systems change management should take into account potential risks to data and record retention capability.

Reprinted from PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4
www.ISPE.org

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 44447777. See our ad in this issue.

Sartorius Stedim North America Inc., 5 Orville Dr., Suite 200, Bohemia, NY, 11716. (800) 368-7178. See our ad in the issue.

BioProcess Manufacturing

Alfa Laval Inc., 5400 International trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

Cleanroom Products/Services

Perfex Corp., 32 Case St., Poland, NY, 13431. (800) 848-8483. See our ad in the issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Consulting

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 4444 7777. See our ad in this issue

Dust Collectors

Camfil Farr Air Pollution, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filling & Packaging Equipment

Robert Bosch Packaging Technology, 8700 Wyoming Ave. N. Brooklyn Park, MN 55445. (763) 424-4700. See our ad in the issue.

Measuring Instruments

GE Analytical Instruments, 6060 Spine Rd., Boulder, CO, 80301. (800) 255-6964. See our ad in the issue.

Particle Measuring Systems, 5475 Airport Blvd Boulder, CO, 80301. (800) 238-1801. See our ad in the issue.

Micro Leak Detection Machines

Bonfiglioli Pharma Machinery, Via Rondona, 31, 44018 Vigarano Pieve (Fe), Italy. Tel: +39 0532715631 Fax: +39 0532715625 WEB: www.bonfigliolipharma.com Email:h.carbone@bonfiglioliengineering.com. Manufactures of Laboratory or High Speed Leak Testing Machines for ampoules, vials, blister packs, BFS, HDPE containers and any other type of pharmaceutical packaging.

Passivation and Contract Cleaning Services

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Processing Systems

Pharmaceutical Online, 5340 Fryling Rd., Suite 101, Erie, PA 16510. (814) 897-7700. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Emerson, 8000 W. Florissant Ave., St Louis, MO 63136. (314) 553-2000. See our ad in this issue.

ProPharma Group, 10975 Benson Dr., Suite 330, Corporate Woods Bldg 12, Overland Park, KS, 66210. (888) 242-0559. See our ad in the issue.

Vaisala Inc., 100 - 13775 Commerce Parkway, Richmond, BC Canada V6V 2V4. (800) 683-8374. See our ad in the issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.

Online Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4

International

PIC/S' 40th Anniversary[1]

This year, PIC/S is celebrating its 40th Anniversary. A special symposium,"40 Years of Cooperation and Mutual Confidence: Challenges and Future Perspectives," was held in Geneva on 31 May 2011. Many Heads of Agencies attended the event, including Dr. Margaret Hamburg, US FDA Commissioner, who delivered a keynote address on "The Importance of PIC/S in our Globalized World."

The objectives of the symposium were to celebrate 40 years of PIC/S as well as promote and highlight PIC/S contributions to international issues. The symposium was divided into three sessions: 1. key considerations for becoming a PIC/S participating authority, 2. management of risk, and 3. challenges ahead and the future of PIC/S (attendance by invitation only).

Chinese Delegation Visits the Danish Medicines Agency[2]

The Danish Medicines Agency was visited by representatives from the SFDA, the Agency's counterpart in China. The representatives were welcomed by Chief Executive Officer, Jytte Lyngvig, who spoke on joint inspections and later, the Chinese delegation met with Head of Department of Medical Devices, Ellen Jespersen. Cooperation with the SFDA was formalized in 2009 through the signing of a so-called Memorandum of Understanding, and the Chinese visit to Copenhagen builds on this Memorandum of Understanding.

US and Chinese Standards Setters for Drug Quality Become Mutual Advisors[3]

In an agreement that promises to further advance and harmonize standards for drug quality, leaders of the United States Pharmacopeial Convention (USP) and the Chinese Pharmacopoeia Commission (ChP) exchanged appointments to serve as Special Councilors on International Affairs to each other's organization. The unprecedented step builds upon strong relationships that the organizations have built over the past several years and promises benefits to manufacturers, regulators, patients, and consumers who rely on quality standards for medicines.

Asia/Pacific

Australia

Australian TGA Publishes Guidance on the GMP Clearance of Overseas Medicine Manufacturers[4]

The Therapeutic Goods Act of 1989 requires that the standard of manufacture and quality control of therapeutic goods manufactured outside Australia be taken into consideration for the registration or listing of those therapeutic goods on the Australian Register of Therapeutic Goods (ARTG), unless the goods are exempt from this requirement by the Act.

A sponsor applying to the Therapeutic Goods Administration (TGA) for registration or listing of a therapeutic good manufactured outside Australia must provide an acceptable form of evidence to show that the manufacture of the goods is of an acceptable standard. This is referred to as Good Manufacturing Practice (GMP) clearance of overseas manufacturers.

The purpose of this guidance document is twofold. It is intended to provide information to sponsors and manufacturers on the acceptable form of evidence of GMP compliance for overseas manufacturers and, outline how to submit such evidence to the TGA for assessment. It is not intended to provide a definitive list of the forms of evidence that are considered acceptable or unacceptable.

The Australian Regulatory Guidelines Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers (17th edition) will be phased in over the next three months. At the conclusion of the phase-in period (15 August 2011), the preceding 16th edition of the guidelines will be retired. Subsequent applications after this date will be required to meet the requirements of the 17th edition of the guidance.

Australia Publishes Regulatory Framework for Complementary Medicines[5]

Australia has a two-tiered system for the regulation of medicines, including complementary medicines: higher risk medicines must be Registered on the ARTG, which involves individually evaluating the quality, safety, and effectiveness of the product; and lower risk medicines containing pre-approved, low-risk ingredients and that make limited claims can be listed on the ARTG. The majority of complementary medicines, but not all, are listed on the ARTG because of their low risk. Unlike many other countries in the world Australia ensures that complementary medicines are manufactured safely and only contain approved, safe ingredients.

Australian TGA Web site Changes Launched 4 May 2011[6]

For help navigating the new Web site, please visit http://www.tga.gov.au/newsroom/media-2011-website-110406.htm.

India

India Publishes Clarification with Respect to the Manufacturing and Marketing of New Drugs[7]

This document provides clarification in the following six areas: 1. scale of trial batches, 2. pilot scale batch, 3. significant change criteria, 4. mentioning of address on Form 44, 5. co-packaging products, and 6. submission of stability data. For more information, see http://www.cdsco.nic.in/clarification_new_drugs_10_3_2010.pdf .

Europe

European Union

European Medicines Agency Responds to Criticism Over Transparency in British Medical Journal[8]

The European Medicines Agency has responded to an article published in the British Medical Journal (BMJ) that called for more transparency by medicines regulatory authorities. The letter, which was published on the BMJ's Web site on 13 May, outlines the steps that the Agency has taken to increase its transparency since its establishment in 1995. These steps include the new access to documents policy, which came into effect in November 2010 and the

launch of the European Union Clinical Trials Register. The Agency also has launched public consultations on the draft policy concerning the release of safety data held in the EudraVigilance database and on the draft transparency policy.

The letter, signed by the Agency's acting Executive Director, responded to the article "Opening up data at the European Medicines Agency" by Peter Gøtzsche and Anders Jørgensen. The BMJ published this article online on 10 May.

EU Law: Commission Acts to Ensure that European Legislation is Fully and Properly Implemented[9]

In its monthly package of infringement decisions, the European Commission is pursuing legal action against 27 Member States for failing to comply properly with their obligations under EU law. These decisions cover many sectors. They aim at ensuring proper application of EU law for the benefit of citizens and businesses. The Commission has taken today 320 decisions, including six complaints taking Member States before the European Union's Court of Justice. In this package, one decision relates to failure to respect a previous Court ruling and might imply financial penalties.

Publication of the Revised Annex 14 of the GMP Guide in Regard to the Manufacture of Medicinal Products Derived from Human Blood or Plasma[10]

The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the EU/EEA. The Annex applies also to the starting material (e.g., human plasma) for these products. In line with the conditions set out in Directive 2003/63/EC, the requirements apply also for stable derivatives of human blood or human plasma (e.g., Albumin) incorporated into medical devices.

This Annex defines specific Good Manufacturing Practices (GMP) requirements for processing, storage, and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma. The Annex addresses specific provisions for when starting material is imported from third countries and for contract fractionation programs for third countries. The Annex does not apply to blood components intended for transfusion.

Traditional Herbal Medicines: More Safety for Products put on EU Market[11]

The expiry of the seven year transition period set out in the 2004 Herbal Directive (2004/24/EC) means that only medicinal products which have been registered or authorized can remain on the EU market after 1 May 2011. The Herbal Directive introduces a simpler registration procedure than for other medicinal products, in respect of the long history of use of traditional herbal medicinal products. At the same time, the Directive provides the necessary guarantees of their quality, safety, and efficacy.

European Medicines Agency Holds First Stakeholder Forum on the Implementation of the New Pharmacovigilance Legislation[12]

On 15 April 2011, the European Medicines Agency held a stakeholder forum on the implementation of the new pharmacovigilance legislation with a broad cross-section of participants including industry, patient and healthcare professional representatives and national medicines regulatory authorities.

This was the first in a series of stakeholder meetings taking place during 2011 and 2012, when the Agency aims to raise awareness of the requirements of the new legislation and promote the exchange of ideas, concerns, and opinions.

During this first meeting, immediate feedback from stakeholders was received mainly in relation to the Agency's and Member States' technical contribution to draft European Commission implementing measures. Close coordination and cooperation with stakeholders will maximize the opportunities for a successful and efficient adoption of new requirements, which come into legal force in July 2012.

European Medicines Agency Announces Increased Fees[13]

Fees payable to the European Medicines Agency by applicants and marketing-authorization holders increased by 2.1% on 1 April 2011.

European Medicines Agency Publishes News Bulletin for Small and Medium-Sized Enterprises – Issue 15[14]

This edition provides information on CMC guidance, clinical guidance, advanced therapies, veterinary guidance, regulatory guidance, meetings, SME companies registered with the EMA, and contact information.

Denmark

Danish Medicines Agency Announces New Requirements for Qualified Persons in Pharmaceutical Companies[15]

The Danish Medicines Agency has updated the guidelines on requirements and expectations for the Qualified Person in a pharmaceutical company, stating that a person cannot be approved as a Qualified Person on the authorization if on leave, because they expect a Qualified Person to be present at the company regularly. Therefore, it is required that, e.g., during maternity leave, the company must apply to replace the Qualified Person concerned on the authorization. When the Qualified Person concerned returns from leave, the company must reapply to have this person approved as Qualified Person on the authorization.

Danish Medicines Agency Publishes "Perspectives and Challenges 2011-2016"[16]

In this strategy, the Danish Medicines Agency describes how it works for effective and safe healthcare products, and how it cooperates in various areas with both the European Medicines Agency (EMA) and the World Health Organization (WHO). It also describes the objective of taking responsibility for the climate by reducing our energy consumption and CO_2 emission. The strategy also addresses the future perspectives of digitizing workflow processes.

Finland

Finnish Medicines Agency Sets out Agenda for the Future in New Strategy Document[17]

During the current strategy period until 2020, Fimea's operational remit will widen and the agency's existing responsibilities will continue to evolve. A key change is the inclusion of pharmaceutical services under the wider social and health service system. It means that the Finnish healthcare sector will now be a key Fimea client alongside the pharmaceutical sector and license holders, healthcare professionals, and patients. Fimea's operations are now focused on networking, underpinned by its motivated and expert personnel. Fimea's statutory purpose is to supervise and develop the pharmaceutical sector to promote the health of the population.

United Kingdom

Earlier Access to Medicines Scheme Update[18]

At the present time, ministers have decided not to progress the proposed Earlier Access to Medicines Scheme, given the many other ongoing initiatives in the NHS. Other existing mechanisms for earlier access to unlicensed medicines, such as via clinical trials and named patient use, are unaffected by this.

North/South America

Canada

Health Canada Publishes Guidance Document Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines – Veterinary Drugs (GUI-0012)[19]

The revisions to this Annex include addition of a Section 2 for non-sterile, non-prescription veterinary drugs that require no withdrawal period at the highest dosage in each species for which they are approved.

Health Canada Amends Food and Drug Regulations (1319 – New Drugs For Extraordinary Use)[20]

The current practice of using the Special Access Programme (SAP) to authorize the sale of EUNDs for broad distribution was deemed inappropriate by the Office of the Auditor General of Canada (OAG). The proposed regulatory amendment creates a new type of drug submission for an EUND within the Food and Drug Regulations (the Regulations). The regulatory amendments detail the inclusion criteria for EUNDs and outline the requirements for EUND submissions, labeling, plans for post-market safety and efficacy studies and annual reporting. Existing regulations that apply to other drugs including, but not limited to, those regarding adverse drug reaction reporting, establishment licensing, good manufacturing practices and data and patent protection also apply to EUNDs. Because of the nature and intended purpose of these drugs, manufacturers are only able to sell EUNDs to different levels of Canadian governments (i.e., federal, provincial, territorial, municipal).

United States

New Sources of FDA Enforcement Information Posted[21]

The FDA is implementing the first in a series of proposals to increase public understanding of the public health impact of FDA's enforcement efforts, help inform companies' efforts to comply with FDA requirements, increase company accountability to consumers and business partners, and help consumers make more informed decisions about the products they buy.

This action stems directly from the FDA Transparency Initiative, which Commissioner Margaret A. Hamburg, M.D. launched in 2009. The initiative is designed to examine all agency activities and consider ways to make them more transparent. After holding public meetings and inviting written comments, the FDA issued its first report, proposing 21 actions to increase disclosures about agency activities. Today, the agency is taking several steps to increase transparency related to its enforcement activities:

- Posting a summary of the most common inspectional observations of objectionable conditions or practices that are made during inspections.
- Providing a searchable database that includes the name and address of inspected facilities, the date(s) of inspection, type of FDA-regulated products involved, and final inspectional classification.
- Alerting the public in a consistent manner about enforcement actions, by issuing press at the beginning and the end of the process, unless confidentiality is necessary.

The FDA is also providing a new web page to house all of the agency's key transparency activities related to enforcement so that these resources will be easier to find and use. In the coming months, three additional enforcement-related transparency actions will be implemented. The FDA will begin to disclose additional information about FDA evaluations of importers, expand disclosure of Untitled Letters, and in appropriate situations, support industry efforts during a food recall to inform consumers of products that are not subject to the recall. The FDA also will move forward on other proposals in the report.

US FDA Publishes a Presentation Entitled "Process Validation – A Lifecycle Approach"[22]

This presentation, which can be found at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM255585.pdf, addresses three topics: 1. cGMPs and Process Validation (PV) for Drug Manufacturing; 2. Lifecycle Approach: Stage 1 (Process Design), Stage 2 (Process Qualification), and Stage 3 (Continued Process Verification); and 3. Comments to the 2008 Draft. It was authored by Grace E. McNally, Senior Policy Advisor US Food and Drug Administration, CDER, Office of Compliance Division of Manufacturing and Product Quality.

US FDA Requests Input on Development of User Fee Program for Biosimilar and Interchangeable Biological Products[23]

The Biologics Price Competition and Innovation Act of 2009, a provision of the Affordable Care Act, creates an abbreviated approval pathway for bio-

logical products that are demonstrated to be highly similar (biosimilar) to or interchangeable with an FDA-licensed biological product. It directs the FDA to develop recommendations for a 351(k) user fee program for fiscal years 2013 through 2017. The recommendations must be presented to Congress by 15 January 2012.

In addition to accepting written comments, the agency will consult with a range of groups, including scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and regulated industry. The FDA will take this input into account in developing proposed recommendations that will be published in the Federal Register for public comment, presented to Congressional committee staff, and presented at a public meeting.

Medicines Quality Strengthened in Ongoing FDA-USP Collaboration - Expanded Joint Testing Between FDA and USP Laboratories[24]

Continuing and expanding a prior pact, the US Pharmacopeial Convention (USP) and the US Food and Drug Administration (FDA) have signed a three-year Cooperative Research and Development agreement that supports development of USP written and physical reference standards for the quality, identity, purity, and strength of medicines.

The new agreement furthers annual collaborative testing between USP and FDA laboratories of roughly 40 chemical reference standards, primarily for controlled substances. It also promotes joint work to modernize tests and assays in USP's written or documentary standards, and to further develop test methods for hand-held instruments that law enforcement inspectors can use to screen drugs in the field for adulteration, contamination and authenticity.

US FDA Solicits Comments Regarding Online Direct-to-Consumer Prescription Drug Promotion[25]

This notice solicits comments on a series of studies, Examination of Online Direct-to-Consumer Prescription Drug Promotion. These studies are designed to test different ways of presenting benefit and risk information in online Direct-To-Cosumer (DTC) prescription drug Web sites.

US FDA Announces Periodic Review of Existing Regulations; Retrospective Review of the Food and Drug Administration[26]

The FDA is conducting a review of its existing regulations to determine, in part, whether they can be made more effective in light of current public health needs and to take advantage of and support advances in innovation. The goal of this review of existing regulations, as with other reviews, is to help ensure that FDA's regulatory program is more effective and less burdensome in achieving its regulatory objectives. FDA is requesting comment and supporting data on which, if any, of its existing rules are outmoded, ineffective, insufficient, or excessively burdensome and thus may be good candidates to be modified, streamlined, expanded, or repealed. As part of this review, the FDA also invites comment to help review its framework for periodically analyzing existing rules.

US FDA "Strategic Priorities 2011 – 2015" Now Available[27]

This 50-page document provides a vision of the FDA that includes:

- a modernized field of regulatory science that draws on innovations in science and technology to help ensure the safety and effectiveness of medical products throughout their life cycles
- an integrated global food safety system focused on prevention and improved nutrition
- expanded efforts to meet the needs of special populations

References

1. PIC/S, http://www.picscheme.org/news.php#n14.
2. Danish Medicines Agency, http://laegemiddelstyrelsen.dk/en/service-menu/about-us/news/chinese-delegation-visits-the-danish-med--nes-agency.
3. United States Pharmacopeia, http://us.vocuspr.com/ViewAttachment.aspx?EID=p5FrtVW6x8BzeShHYv0joRDqQEAxpoOu3W%2fzQ1nx48k%3d.
4. Australian Therapeutic Goods Administration, http://www.tga.gov.au/industry/manuf-overseas-medicines-gmp-clearance.htm.
5. Australian Therapeutic Goods Administration, http://www.tga.gov.au/newsroom/btn-cm-framework.htm.
6. Australian Therapeutic Goods Administration, http://www.tga.gov.au/newsroom/media-2011-website-110406.htm .
7. Indian Central Drug Standard Control Organization, http://www.cdsco.nic.in/clarification_new_drugs_10_3_2010.pdf.
8. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/05/news_detail_001257.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true.
9. European Medicines Agency, http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/11/220&format=HTML&aged=0&language=EN&guiLanguage=en.
10. European Medicines Agency, http://ec.europa.eu/health/files/eudralex/vol-4/annex14_rev30-03_2011_en.pdf.
11. European Medicines Agency, http://europa.eu/rapid/pressReleasesAction.do?reference=IP/11/510&format=HTML&language=en.
12. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/04/news_detail_001247.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true.
13. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001232.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenable

d=true.
14. European Medicines Agency, http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2011/03/WC500103920.pdf.
15. Danish Medicines Agency, http://laegemiddelstyrelsen.dk/en/topics/authorisation-and-supervision/company-authorisations/news/new-requirements-for-qualified-persons-i---companies.
16. Danish Medicines Agency, http://laegemiddelstyrelsen.dk/en/service-menu/about-us/news/perspectives-and-challenges-2011-2016.
17. Finnish Medicines Agency, http://www.fimea.fi/whats_new/1/0/pharmaceutical_sector_facing_future_challenges_2.
18. British Medicines and Healthcare Products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/CON117317.
19. Health Canada, http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0012_annex_4-eng.php.
20. Health Canada, http://canadagazette.gc.ca/rp-pr/p2/2011/2011-04-13/html/sor-dors88-eng.html.
21. US Food and Drug Administration, http://www.fda.gov/AboutFDA/Transparency/PublicDisclosure/default.htm.
22. US Food and Drug Administration, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM255585.pdf.
23. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm254572.htm.
24. United States Pharmacopeia, http://us.vocuspr.com/Newsroom/ViewAttachment.

Online Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
July/August 2011, Vol. 31 No. 4

Influence on Drug Manufacturers and Drug Distributors with Promulgation of the Tort Liability Law of the People's Republic of China (PRC)

This article presents the drug quality tort liability of drug manufacturers and drug distributors in China and reviews the related provisions of the Tort Liability Law.

by Ling Su

In China, the drug quality tort had been following the Product Quality Law of the People's Republic of China, which became effective on 1 September 2000. In order to protect the legitimate rights and interests of parties in civil law relationships, clarify the tort liability, prevent and punish tortious conduct, and promote social harmony and stability, the Tort Liability Law of the People's Republic of China, adopted at the 12th session of the Standing Committee of the Eleventh National People's Congress of the People's Republic of China on 26 December 2009, promulgated as Decree of the President of the People's Republic of China (No. 21), and on 1 July 2010. Since then, the drug quality tort liability of drug manufacturers and drug distributors has been clarified by the Tort Liability Law of the People's Republic of China instead of the Product Quality Law of the People's Republic of China. This article presents the definition and types of the drug quality liability in China, compares the difference of drug quality tort liability between the Product Quality Law of PRC and the Tort Liability Law of PRC, and attempts to illustrate the new provisions and amendments of drug quality tort liability for drug manufacturers and drug distributors, which have manufactured or distributed drugs in China since 1 July 2010.

Contents of Drug Quality Liability

In China, drug quality liability refers to the legal liability caused by any drug with potential safety risks, which are unreasonable risks to human health and life safety. Drug quality liability can be caused by a counterfeit drug, a substandard drug, or a qualified drug with potential safety risks found post-market.

Drug quality liability is divided into administrative liability, criminal liability, and tort liability. A drug manufacturer or a drug distributor which is at fault for infringement upon a civil right or interest of any drug customer should be subject to the tort liability. If a drug manufacturer or distributor should assume administrative liability or criminal liability for the same conduct, it also should legally assume the tort liability. If the assets of a drug manufacturer or distributor are not adequate for payments for the tort liability and administrative liability or criminal liability for the same conduct, the drug manufacturer or distributor shall first assume the tort liability.

In China, administrative liability is stipulated by the Drug Administration Law of the People's Republic of China and the Administration Measure on Drug Recall; criminal liability is stipulated by the Criminal Law of the People's Republic of China; and tort liability is stipulated by the Tort Liability Law of the People's Republic of China.

Assumption of Drug Quality Tort Liability

Tort Liability was clarified for the first time by the Tort Liability Law of the People's Republic of China. Tort Liability Law entitles the victim of a tort to require the tortfeasor to assume the tort liability. Whoever infringes upon civil rights and interests shall be subject to the tort liability according to the Tort Liability Law. The manufacturer or distributor shall be subject to the tort liability where a defective product

causes any harm to another person. For drug manufacturers or distributors, a defective product refers to a drug with potential safety risks; harm to another person refers to harm to human health and life safety.[1]

It is not stipulated in the Tort Liability Law, but is stipulated in the Product Quality Law and is still valid that the drug manufacturer shall not be liable for compensation if it can prove the existence of any of the following circumstances: 1. the drug has not been put in circulation; 2. the defect causing the damage does not exist at the time when the drug is put in circulation; or 3. the science and technology at the time the drug is put in circulation is at a level incapable of detecting the defect.[2]

If any drug with potential safety risks causes harm to human health and life safety, the drug manufacturer and distributor shall assume the tort liability. If the drug with ADR indicated in package insert or the drug mentioned on 1., 2., or 3. of the previous paragraph, causes harm to human health and life safety, the drug manufacturer and distributor shall not assume any tort liability.

In China, with regard to Traditional Chinese Medicine, the available techniques cannot fully explain the effective and harmful ingredients, and also cannot purify them. Based on the Tort Liability Law, if any drug manufacturer in China produced Traditional Chinese Medicine injection which results in new ADR or ADR already indicated in package insert, it need not assume any tort liability. For example, "Shuang Huang Lian Injection," "Acanthopanacis Senticosi Injection," "Heartleaf Houttuymia Herb Injection," and "Puerarin Injection" have caused ADR frequently for the past few years, but the drug manufacturers do not assume any tort liability.

Joint and Several Liabilities of Drug Quality Tort

Based on the Tort Liability Law, the drug manufacturer shall assume the tort liability where a drug with potential safety risks causes any harm to human health and life safety, and the drug distributor shall assume the tort liability where a drug with potential safety risks caused by the fault of the drug distributor causes any harm to human health and life safety. Where the drug distributor can neither specify the manufacturer nor the supplier of the drug with potential safety risks, the drug distributor shall assume the tort liability.[1]

Based on the Product Quality Law, where physical injury is caused to a person by a drug with potential safety risks resulting from the drug distributor's fault, the drug distributor shall be liable for compensation; where the drug distributor can neither identify the manufacturer of the drug with potential safety risks nor the supplier thereof, the drug distributor shall be liable for compensation. From the provisions mentioned above, the Tort Liability Law is based on the Product Quality Law in the joint and several liabilities of drug quality tort and are similar.[2]

The drug manufacturer and distributor have joint and several liabilities for drug quality tort, which is a special tort liability and is applicable to the principle of no-fault liability. For internal tort liability between the drug manufacturer and distributor, the drug manufacturer is applicable to the principle of no-fault liability, but the drug distributor is applicable to the principle of fault liability. In other words, the drug manufacturer shall assume the tort liability where a drug with potential safety risks causes any harm to human health and life safety. Whether the drug manufacturer has the fault or not; the drug distributor shall assume the tort liability only where a drug with potential safety risks caused by the fault of the drug distributor or the drug distributor can neither specify the drug manufacturer of the drug with potential safety risks nor specify the supplier of the drug with potential safety risks, then the drug distributor is concluded to have the fault and shall assume the tort liability.

For example, if any drug store sells counterfeit drugs or substandard drugs, the drug manufacturer shall assume the joint and several tort liabilities whether it has the fault or not. If any drugstore sells purposely counterfeit drugs, substandard drugs, or drugs without purchasing proof, according to the Tort Liability Law, the drugstore shall assume the tort liability.

Reimbursement of Drug Quality Tort Liability

According to the Tort Liability Law, where any harm is caused by a drug with potential safety risks, the victim may require compensation to be made by the drug manufacturer or distributor of the drug with potential safety risks. If the drug with potential safety risks is caused by the drug manufacturer and the drug distributor has made the compensation for the defect, the drug distributor shall be entitled to be reimbursed by the manufacturer. If the drug with potential safety risks is caused by the fault of the drug distributor and the drug manufacturer has made the compensation for the defect, the drug manufacturer shall be entitled to be reimbursed by the drug distributor.[1]

According to the Product Quality Law, where a drug with potential safety risks causes physical injury to a person, the victim may claim compensation from the drug manufacturer or the drug distributor of such drug. Where the drug distributor has made the compensation when it is the drug manufacturer that should bear the liability, the drug distributor shall have the right to recover the loss from the drug manufacturer. Where the drug manufacturer has made the compensation when it is the drug distributor that should bear the liability, the drug manufacturer shall have the right to recover the loss from the drug distributor. It is evident from the provisions mentioned above, the Tort Liability Law is based on the Product Quality Law in requirement and reimbursement of drug quality tort liability and are similar.[2]

It is stipulated definitely for the first time by the Tort Liability Law, where any harm to a patient is caused by the defect of any drug, medical disinfectant, or medical instrument, the patient may require a compensation from the manufacturer or require compensation from the medical institution. If the patient requires compensation from the medical institution, the medical institution that has paid the compensation shall be entitled to be reimbursed by the liable manufacturer.

The drug manufacturer, drug distributor, and medical institution have the parallel tort liability for the drug with potential safety risks; the victim may require entire compensation to be made by either the manufacturer, distributor, or medical institution, and do not consider the primary and secondary.

The medical institution shall assume the tort liability whether the medical institution had known the drugs could have potential safety risks. First, if the medical institution has not any fault, in the case of joint and several liabilities, only the medical institution shall be entitled to be reimbursed by the drug manufacturer, but the drug manufacturer shall not be entitled to be reimbursed by the medical institution. Second, if the medical institution has fault during the medical process simultaneously, the medical institution and drug manufacturer constitute a joint tort and shall assume joint and several liability; the compensation amounts shall be determined according to the fault degree of the medical institution or drug manufacturer; and if the fault degree of the medical institution or drug manufacturer can not be determined, the medical institution and drug manufacturer shall evenly assume the compensatory liability. The medical institution which has paid an amount of compensation exceeding its contribution shall be entitled to be reimbursed by the drug manufacturer, but the drug manufacturer which has paid an amount of compensation exceeding its contribution shall not be entitled to be reimbursed by the medical institution unless the medical institution has fault during the medical process.

For example, in April 2006, a medical institution in China found 64 patients who had used the "Armillarisin Injection," which was manufactured by the second Qiqihar Pharmaceutical Co., Ltd., suffered renal failure and 13 of whom eventually died. Guangdong Institute for Drug Control identified the "Armillarisin Injection" immediately, and determined that it used "diethylene glycol for industrial use" instead of "propylene glycol for medical use." Between July 2006 to June 2007, 11 victims (nine of whom died) and their families sued the medical institution, the drug distributors, the second Qiqihar Pharmaceutical Co., Ltd. and claimed up to a total of 2 million yuan ($309,023 USD[4]). On 26 June 2008, the First Instance Verdict demanded the second Qiqihar Pharmaceutical Co., Ltd. compensate 11 victims a total of more than 350 thousand yuan ($54,079 USD[4]), while the medical institution and the drug distributors should assume joint liability. The medical institution appealed that it is the first ADE report of "Armillarisin Injection," so the court should not equate the medical institution with the manufacturer and the drug distributors. The drug distributors appealed that the defendants should assume shared liabilitiy instead of joint liability, the victims' death was caused by three things, including their own disease, the counterfeit drugs involved, and improper treatment; therefore, claiming that the drug distributors should only assume the shared liability in accordance with the corresponding profit ratio for the injury consequences caused by the counterfeit drugs involved. On 10 December 2008, the Court of Second Instance upheld the first instance verdict. The Court of Second Instance considered that it is legal obligation for the medical institution to report in a timely manner to the relevant administrative departments after finding the serious adverse reaction of counterfeit drugs, and it is not the reason to be exempted from product quality tort liability. The Court of Second Instance also would not adopt the shared several liabilities, for the victims' death is caused by the counterfeit drugs involved, and there is no evidence that the victims' death is caused by the patients' own disease and the hospital's medical practice. On 9 January 2009, the victims applied for enforcement compensation from the medical institution. If based on the Tort Liability Law today, the court's decision is also correct. The victims may require compensation from any tortfeasor with compensation ability. If the medical institution has paid the compensation, it shall have the right to recover the loss from the second Qiqihar Pharmaceutical Co., Ltd.

Drug Quality Tort Liability of the Third Party

It is stipulated definitely for the first time by the Tort Liability Law that the drug manufacturer or drug distributor shall be entitled to be reimbursed by the third party. Where any harm is caused by a third party, the third party shall assume the tort liability. So where any harm is caused to a drug consumer by a drug with potential safety risks and the defect is caused by the fault of a third party such as carrier and so on, the manufacturer or distributor of the drug that has paid the compensation shall be entitled to be reimbursed by the third party.[1]

The drug manufacturer or drug distributor can not be exempt from the tort liability even though the defect is caused by the fault of a third party. The drug manufacturer or drug distributor pay the compensation first and are not entitled to be reimbursed by the third party unless the defect is caused by the fault of a third party. So in reality, the third party does not pay the compensation to the drug consumer directly and can not be indicted as the defendant.

For example, if any drug is contaminated during the logistics and distribution, basing on the Tort Liability Law, the drug manufacturer should pay the compensation first and then shall have the right to recover the loss from Logistics Company.

Tort Liability of Not Warning and Recalling

Based on the Administration Measure on Drug Recall, where a post-marketing drug with the potential safety risks is detected, a drug manufacturer should recall the drug with potential safety risks, and inform drug distributors or medical institutions to stop selling and using the drug with potential safety risks. Where a drug manufacturer does not recall the drugs with potential safety risks, no matter what is decided initially or ordered passively by drug regulation department, it shall be ordered to recall the drugs. Three times the value of the drugs also shall be imposed. If the circumstances are serious, the drug approval documents shall be withdrawn by the original certification department. Even the Drug Manufacturing Certificate shall be revoked. Where a drug manufacturer does not inform the drug distributors or medical

institutions to stop selling and using the drugs with potential safety risks after it makes a decision to recall the said drugs, the drug manufacturer shall be given a disciplinary warning and shall be instructed to rectify within a time limit. If it fails to do so, the drug manufacturer shall be fined 30,000 yuan[3] ($4,635 USD[4]).

According to the Administration Measure on Drug Recall, where a post-marketing drug with the potential safety risks is detected by a drug distributor or medical institution, it should stop selling and using the drug with the potential safety risks, inform the drug manufacturer or supplier, and report to the drug regulation department. If it fails to do that, it shall be ordered to stop selling and using the drugs; a fine not less than 1,000 yuan ($154 USD[4]), but not more than 50,000 yuan ($7,725 USD[4]) shall be imposed.[3]

It is stipulated definitely for the first time by the Tort Liability Law, that the drug manufacturer or drug distributor shall assume the tort liability for not timely warning and recalling the drug with potential safety risks. Where any drug with potential safety risks is detected after the drug is put into circulation, the drug manufacturer or drug distributor shall take remedial measures as warning and recall in a timely manner. The manufacturer or distributor which fails to take remedial measures in a timely manner or take sufficient and effective measures and has caused any harm shall assume the tort liability.[1]

According to the Product Quality Law, the drug manufacturer shall not be liable for compensation if it can prove the existence of the science and technology at the time the drug is put in circulation is at a level incapable of detecting the defect. This provision is unfair for the victims, and the drug manufacturer can take advantage of it and be exempt from the tort liability easily. The Tort Liability Law limits the exception clause stipulated on the Product Quality Law.[2]

The drug manufacturer or drug distributor shall not assume the tort liability if it takes necessary, timely, reasonable, and effective remedial measures, for in such a case, the damage can be considered an accident instead of the fault of the manufacturer or distributor.

For example, in 2000, a drug manufacturer found that "Manchurian Dutchmanspipe Stem" has serious renal toxicity which is the ingredient of "Long Dan Xie Gan Pill," and reported to the drug regulatory authorities that "Aristolochic Acid" can cause renal injury. On 1 April 2003, the State Food and Drug Administration of China issued "Notice on cancellation of the Manchurian Dutchmanspipe Stem pharmaceutical standard." The "Notice" cancels the "Manchurian Dutchmanspipe Stem" pharmaceutical standards; and demands the drug manufacturers of "Long Dan Xie Gan Pill" series product replace "Manchurian Dutchmanspipe Stem" with "Akebia Stem (without Aristolochic Acid)" before 30 April 2003; and other drug manufacturers which use "Manchurian Dutchmanspipe Stem" do that before 30 June 2003. The Pharmacopoeia of People's Republic of China 2005 deleted the Manchurian Dutchmanspipe Stem. So the drug manufacturer was not required to assume any tort liability for their "Long Dan Xie Gan Pill" manufactured before 30 April 2003, but if according to the Tort Liability Law and Administration Measure on Drug Recall now, the drug manufacturer must suspend manufacturing and selling and recall the "Long Dan Xie Gan Pill" after finding the drugs with renal toxicity, otherwise it shall assume Tort Liability.

Tort Liability of Punitive Compensation

It is stipulated definitely for the first time by the Tort Liability Law that the drug manufacturer or drug distributor shall assume a punitive compensation. Where a drug manufacturer or drug distributor knowing any drug with the potential safety risks continues to manufacture or distribute the drug and the defect causes a death or any serious damage to the human health, the victim shall be entitled to require the corresponding punitive compensation.[1]

Punitive compensation is applicable under the following conditions: 1. the manufacturer or distributor has subject intent; 2. serious damage to the human health or life safety; and 3. causality between defect and serious damage. But answers to the following questions: "What is punitive compensation?" and "How much shall be the punitive compensation?" are not stipulated on Tort Liability Law. It is important to pay close attention to relevant judicial interpretations enacted subsequently.

Now China still has no case of tort liability of punitive compensation. According to the Tort Liability Law now, if the drug manufacturer mentioned above knows the "Long Dan Xie Gan Pill" with renal toxicity, but does not suspend manufacturing and selling and recall the drugs, it also shall assume a punitive compensation.

Mitigation and Exemption of Drug Quality Tort Liability

It is stipulated definitely for the first time by the Tort Liability Law that the tort liability of the drug manufacturer or drug distributor shall be mitigated or exonerated. Where the victim of a tort is also at fault as to the occurrence of harm, the liability of the drug manufacturer or drug distributor may be mitigated. The drug manufacturer or drug distributor shall not be liable for any harm that is caused intentionally by the victim.[1]

The drug manufacturer or drug distributor has the burden of proof. In other words, the liability of the drug manufacturer or drug distributor shall not be mitigated or exonerated, unless it can prove that the victim is also at fault as to the occurrence of harm or the harm is caused intentionally by the victim.

For example, if the drug manufacturer can prove that the injury is caused by not following the dispensatory purposely, such as overdose, incompatibility, or precautions, the tort liability of the drug manufacturer shall be mitigated or exonerated.

Compensation Contents of Drug Quality Tort Liability

According to the Tort Liability Law, where a tort causes any personal injury, the drug manufacturer or drug distributor

shall compensate the victim for the reasonable costs and expenses for treatment and rehabilitation, such as medical treatment expenses, nursing fees and travel expenses, as well as lost wages. If the victim suffers any disability, the drug manufacturer or drug distributor also shall pay the costs of disability assistance equipment for the living of the victim and the disability indemnity. If it causes the death of the victim, the drug manufacturer or drug distributor also shall pay the funeral service fees and the death compensation.[1]

According to the Product Quality Law, where physical injury is caused by defects in a product, the person liable shall compensate the victim for the expenses of medical treatment, expenses of nursing care during treatment, and the decreased earnings due to the loss of his working time; where the victim is disabled, the person liable shall, in addition, pay for the self-care equipment, subsistence allowances, disability compensation to the victim, living expenses necessary for any other person(s) supported by the victim, etc. Where such defects cause death to the victim, the person liable also shall pay for the funeral expenses, compensation for death, and the living expenses necessary for any other person(s) supported by the deceased before his death, etc.[2]

Tort Liability Law is based on the Product Quality Law in compensation contents of drug quality tort liability, but it is a wonder that the living expenses necessary for any other person(s) supported by victim is not mentioned in the Tort Liability Law. It is important to be aware of relevant judicial interpretations enacted subsequently.

For example, on 27 May 2005, Miss Wang Xiaohua, the victim of "Long Dan Xie Gan Pill," received the first "Long Dan Xie Gan Pill" Compensation verdict in China. The verdict identified that the prosecutor, Miss Wang Xiaohua from Inner Mongolia Autonomous Region had purchased and used the "Long Dan Xie Gan Pill" which was distributed by the defendant, and it has clear verity and sufficient evidence to support that prosecutor's renal injury is caused by "Long Dan Xie Gan Pill." The verdict supports all the claims of the prosecutor and demand the drug distributor compensate 39,304 Yuan ($6,072 USD[4]) to the prosecutor. If based on the Tort Liability Law today, if the drug distributor had paid the compensation, it would have had the right to recover the loss from the drug manufacturer, but at that time, this claim was not submitted.

Influence on Global Drug Manufacturers with Promulgation of the Tort Liability Law

After implementation of Tort Liability Law of the PRC, the victims have rights to claim compensation freely from drug manufacturers, medical institutions, or drug stores. In China, the patients tend to choose medical institutions or drug stores from which they bought drugs directly to claim compensation. After paying the compensation, if the medical institution or the drug store has not any fault, it shall be entitled to be reimbursed by the drug distributor or the drug manufacturer which has fault; if the medical institution, the drug store or the drug distributor has fault and the drug manufacturer has not any fault, the drug manufacturer may not pay the compensation. It can reduce the various activities in civil litigation claim for global drug manufacturer in China.

The global drug manufacturers which import and sell drugs to China should consider the following aspects:

First, strengthen drug quality control of distributors in China. Global drug manufacturers should be very careful to select the respected distributors in China. Global drug manufacturers also should reduce the fault made by drug wholesalers and drug retailers as much as possible which may cause ADE or any other drugs quality problems, and thus avoid responsibility for no-fault joint and several liabilities.

Second, strengthen recall management of the drugs with potential safety risks. Global drug manufacturers should develop an efficient drug recall system to ensure drug recall successfully, and thus avoid the tort liability of punitive compensation because of failure on drug recall.

Third, ensure the truthfulness and comprehensive of contents in the package insert. Global drug manufacturers should standardized the written form and content of package insert, especially should pay attention to dosage, precautions, ADR, contraindications, and try to avoid the tort liability for the injury caused by patients' misunderstanding on package insert, and mitigate or exempt the tort liability for the injury caused by patients' intentional and negligent action.

References

1. Tort Liability Law of the People's Republic of China, http://www.gov.cn/flfg/2009-12/26/content_1497435.htm, 1 October 2010.

2. Product Quality Law of the People's Republic of China, http://news.xinhuanet.com/legal/2003-01/21/content_700668.htm, 1 October 2010.

3. Administration Measure on Drug Recall, http://www.sfda.gov.cn/WS01/CL0053/26913.html,1 October 2010.

4. Used USD exchange rate as of 21 June 2011.

About the Author

Ling Su is an instructor in the Pharmacy Administration Department, Pharmacy College of Ji'nan University, China. She holds a Masters degree in pharmacy administration of Xi'an Jiao Tong University of China and is currently studying for a Doctorate degree at the International Pharmaceutical Business School at China Pharmaceutical University. She has published more than 40 papers in Chinese academic journals. She has also writen two books, "Pharmacy Administration" and "Comparison with the Laws and Regulations of China and the United States," which were both published in China, June 2010. She can be contacted by email: 38105596@163.com.

Pharmacy Administration Department, Pharmacy College of Ji'nan University, Guangzhou, China, 510632.