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The Increasing Trend of Adherence Packaging and the Implications to Manufacturing

by John W. Musaus and Mel Bahr

This article presents data that highlights the increasing market trend to use adherence packaging and highlights the design and manufacturing options that should be considered to adopt this strategy.

Overview

The pharmaceutical industry has been facing immense challenges to well-established practices as it concludes the era of block buster products and enters a new era of smaller pipelines focused on specialty disease state therapies. From a commercial perspective, many companies have been forced to seek new avenues to drive growth of top line sales. In this new environment, the investment in both research and patient programs to increase the rate of patient adherence to medication has been significantly growing. One commercial tactic that has seen rapid growth over the last few years is to leverage packaging as a tool to increase patient adherence. This article reviews the concept of patient adherence and why it is important to the industry, highlights how packaging is being used to increase adherence, and provides insight on the manufacturing considerations for migrating packaging operations from bottles to adherence packaging.

Adherence or Compliance – *What Is the Difference*?

With any discussion on adherence or compliance packaging, it is important to be grounded on a common definition. The words patient compliance and patient adherence are often used interchangeably by the healthcare value chain. The preference to use one word over the other is often driven by company culture. In the last few years, thought leaders in the field of medication taking behavior research have been moving toward the use of adherence as the preferred term. In similar fashion, the use of compliance is now more often associated with the regulatory and legal aspects of the pharmaceutical industry.

In a recent publication, Vrijens, et al[1] propose a new nomenclature for medication taking behavior that leverages the word adherence. The recommendation is the result of an international collaboration of European research groups in the field of adherence to medications comprising 80 participants from 13 different countries. They define adherence to medications as the process by which patients take their medications as prescribed.

Adherence has three components: initiation, implementation, and discontinuation as seen in Figure 1.

- **Initiation** is when the patient takes the first dose of a prescribed medication.
- **Implementation** of the dosing regimen is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose is taken.
- **Discontinuation** marks the end of therapy when the next dose to be taken is omitted and no more doses are taken thereafter.

One other important term used in this adherence nomenclature is:

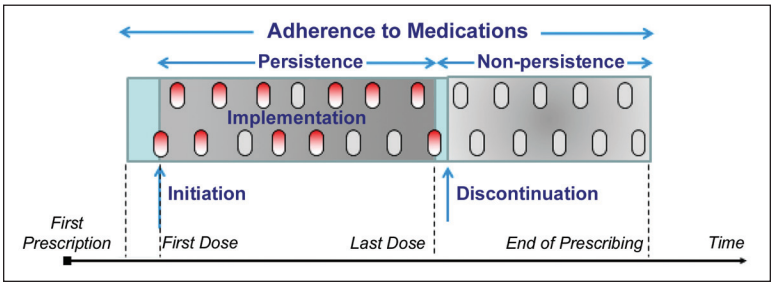

Figure 1. Three components of adherence: initiation, implementation, and discontinuation.

- **Persistence** which is the length of time between initiation and the last dose which immediately precedes discontinuation.

Looking at Figure 1, it is clear that non-adherence to medications can occur in a number of situations or in some cases a combination of situations. Specific situations might be a delayed initiation (patient does not fill their prescription in a timely manner); non-initiation (patient decides to not fill a prescription); sub-optimal implementation (patient misses doses); and early discontinuation (patient ceases taking medication prior the end of the prescribed treatment regimen).

Why Is Adherence Such a Hot Topic?

Alignment of Healthcare Value Chain Partners

The World Health Organization reports that the magnitude of medication non-adherence is so alarming that more worldwide benefits would result from improving adherence to existing treatments than from developing new medical treatments.[2] Because of the widespread effect of non-adherence, there has been unprecedented alignment among healthcare stakeholders including patients, providers, pharmacists, manufacturers, government agencies, and payors to work together to improve adherence. Recently, a diverse group of stakeholders representing consumers, health providers, the academic community, industry, and government, e.g., US Food and Drug Administration (FDA), National Institutes of Health (NIH), Veterans Administration (VA), convened to discuss the state of patient adherence and published a paper in the American Heart Journal entitled *Medication Adherence: A Call to Action*.[3]

Healthcare Systems and Manufacturers are Increasing Investment in Adherence Programs

With the advent of more sophisticated analysis conducted by health economists that measure the impact of non-adherence, payors (both insurance companies and governments) are becoming more aware of the high cost, lost revenues, and system burden that result from poor patient adherence. As a result, they are increasingly willing to fund programs focused on increasing patient adherence.

It Is Harder to Get New Drugs Covered by Payors

Payors are changing the way they evaluate drugs to be included in their formulary coverage by requiring comparative effectiveness research. This is placing new demands on pharmaceutical manufacturers to prove that new products add additional value versus other well accepted and more-often lower cost drugs. Research algorithms used to demonstrate differentiation include a number of variables: One of the most significant and hard to control variables is patient adherence rates.

Governments Are Demanding Better Adherence Rates

The US Government's Centers for Medicare and Medicaid Services recently enacted a five star rating for healthcare insurance plans that are serving patients that qualify for the Medicare Advantage and Prescription Drug Benefit programs (Part C and Part D of the Affordable Care Act). The star rating score is determined by how well they perform in a number of categories and provides a measure of quality and performance. A plan's star rating is publicly listed on the Medicare Plan Finder website which helps patients choose their desired plan. More importantly, quality bonus payments paid by the government are now based on the star rating system – the higher a plan's star rating, the greater the bonus payment percentage. Because patient adherence (or non-adherence) can affect many of the measures that are factored into the star ratings, plans are stepping up their resources to drive higher levels of patient adherence.

Patients and Adherence

Understanding why patients are non-adherent to their prescribed treatment is highly complicated. Hayden Bosworth, Associate Director at the Veterans Affairs' Center for Health Services Research in Primary Care states that, "there are over 100 factors that can be predictive of non-adherence." Research that he has conducted shows that these factors fall into the following five categories:[4-5]

1. Patient Characteristics:
   - Patient knowledge of the disease state
   - Coping skills/ego/strength/motivation
   - Cognition
   - Healthcare literacy level
   - Comorbidities
   - Side Effects
   - Depression/Mental Health
2. Provider/Physician Characteristics:
   - Medication Regimen (frequency, complexity, immediacy of beneficial effects)
   - Medication Intensity
   - Provider Communication (ability to help patients understand the why, how, when of taking their medicine)
3. Medical Environment
4. Social Environment
5. Government Policy

Adherence research focused on patients' medication usage and overall attitudes on taking medication also has been increasing over the last few years. Results from this research is now providing key insights to members of the healthcare value chain in creating programs and systems to increase levels of adherence. One insightful piece of research is an interview based study of 821 patients, conducted by JWM Chang that lists a number of self-reported patient reasons for non-adherence (Figure 2). Chief among them is simple forgetfulness.[6]

In addition to understanding the various factors related to medication adherence, research also has been conducted to expose misconceptions regarding medication adherence. The Outcomes Research Team at Merck recently presented the 10

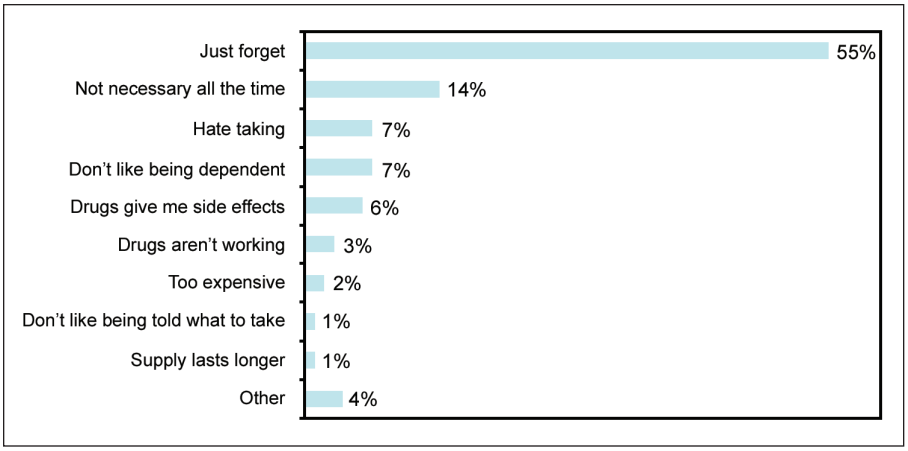

Figure 2. Patient self-reported reasons for non-adherence.

Tenets of Medication Adherence. These provide useful insights about patients' medication decision making and underscore the importance of patient beliefs in determining adherence behaviors. These tenets of medication adherence are:

1. Patients do not communicate their medication adherence intentions to their health care providers.
2. Healthcare providers assume that ***their*** patients are adherent.
3. A non-adherent personality does not exist.
4. Adherence to prescription medications is largely unrelated to adherence to self-care and lifestyle recommendations.
5. Medication adherence is largely unrelated to demographic characteristics.
6. Patients want information about their prescription medications and feel frustrated that not enough information is provided to them.
7. Healthcare providers can be inconsistent communicators about prescription medications.
8. Medication taking is a decision making process and patients actively make decisions about new and existing medications.
9. Non-adherence is rational behavior. It is driven by patients' beliefs about their treatment, disease, and prognosis as well as their objective-experiences with their treatment and disease.
10. Medication adherence involves "shades of gray." Patients can be faithfully adherent to one medication, non-fulfill another, and be non-persistent to another because they hold distinct medications and diseases.

Adherence Packaging Should Be Considered a Marketing Tactic

Within pharmaceutical commercial organizations, focused spending on field sales teams and Direct-to-Consumer (DTC) advertising, usually two of the largest budget items for the commercial team, has been decreasing. Many companies have been reallocating this budget toward programs that are designed to specifically impact adherence. Increasingly, companies are creating dedicated teams to focus solely on adherence. These teams usually have a mix of backgrounds that draw from both the commercial side as well as those with backgrounds in health economics and outcomes research.

These teams spend considerable effort to create, manage, and measure the effectiveness of different adherence programs. Table A lists the most common types of programs found in the market. Depending on the complexity of the disease state, many of these programs can be integrated together. It is not uncommon to see brands fund five to six programs at the same time to get their desired result.

Many of the programs listed in Table A are very expensive and often times cannot scale to include every eligible patient. For example, a program that uses nurses to call patients to check on progress of a highly complex treatment protocol may have a positive ROI and drive desired patient outcomes; however, it may be physically impossible to hire enough nurses to call every patient taking the medicine. Additionally, at a rate $50 to $100 per call, it becomes financially untenable to scale a successful program. The ability to scale and the relatively low cost profile of adherence packaging are the main reasons adherence teams are increasingly focused on incorporating package as a foundational tactic for any company's program.

Based on the definition of adherence used in Figure 1, initiation of the treatment is the pivotal step in building the proper habits to maintain adherence to treatment. Adherence teams know they have little control over the quality of the initiation message delivered by the prescriber or pharmacist (why they are taking the medicine, how to properly take the medicine, how long to take the medicine, etc., to ensure a positive outcome). One thing that they can control is developing preferred messages they want consumers to have. Historically, these messages have been delivered via patient starter kits, physician samples, websites, and physician office brochures.

Patient education	Branded web sites	DTC advertising with adherence message
Call center support	SMS text	Pharmacy intervention programs
Patient assistance programs	Drug discount and loyalty card programs	Patient experience/ sampling programs
Reminder systems and devices	Family involvement programs	Physician training
Patient letters/ direct mail	Email programs	Live calls from a healthcare professional (e.g., nurse)
Automated IVR calls	Public awareness/ celebrity campaigns	Medication counseling
Smart phone applications	Non-branded disease state websites	Packaging

Table A. Common patient adherence programs found in the global market.

Now, brand teams are starting to activate their commercial packaging as a vehicle to deliver important messages that they know impact the initiation phase of adherence. Additionally, packaging is being used as an entry point to other marketing tactics such as Customer Relationship Marketing (CRM) and loyalty card savings programs (i.e., prominent display of website). Marketing teams are becoming more enamored with using packaging as an adherence tool because they know, by default, the package will get into the hand of ***every*** patient that receives a prescription.

Adherence teams also are investigating ways to deliver messages on packaging that overcome health literacy barriers, exploring ways to convey messages through visual illustrations and icons. The Veterans Administration (VA) is conducting a large scale, prospective study utilizing adherence packaging incorporating patient educational information. Figure 3 depicts the graphics that will be used in the test. This package highlights the types of helpful patient information that can be incorporated into package graphics. The graphics on the VA package provide a number of benefits:

- Conveys important information on disease state treatment goals
- Provides a calendar feature that helps patients track medication usage and reduce dosing errors (i.e., missed dosage or over dosage)
- Provides graphics on when and how to take the medicine
- Includes important medical information that provides "reasons to believe" the dosing instructions
- States contraindications to limit safety issues that might not always be addressed by the physician or pharmacist

Data Highlighting the Impact of Adherence Packaging

A major piece of adherence packaging research worth highlighting is a recent study authored by Zedler, et al.[7] This study was the first large-scale pharmacoepidemiologic analysis of the effect of medication packaging alone on adherence. The objective of the study was to evaluate the effect of adherence packaging on long-term prescription refill behavior as compared to traditional amber vials. The retrospective analysis used pharmacy claims data from Wal-Mart retail pharmacies to assess the effect of calendar blister packaging on prescription refill adherence (frequency and timeliness) and duration (persistence). Data from more than three million patients filling prescriptions for the ACE-inhibitors (to treat hypertension) at Wal-Mart was included in the study.

Results from the study reveal some key conclusions of the effectiveness of adherence packaging:

- The use of adherence packaging in both new and ongoing medication users was associated with modest improvement in refill persistence and adherence. Results were measured by Length Of Therapy (LOT), Proportion Of Days Covered (PDC), and Medication Possession Ration (MPR) – all common measures used to analyze adherence.

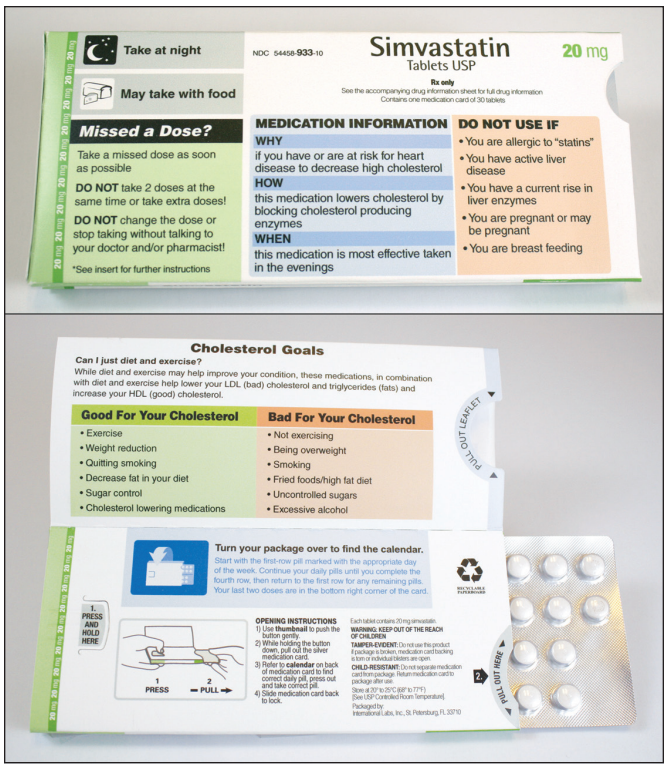

Figure 3. Graphics that will be used in the VA packaging test.

- Packaging alone made a positive impact on adherence – no other adherence programs or interventions such as education were used.
- Patients using adherence packaging were more likely to reach "full refill adherence" in a year than vial users with the greatest effect observed in new medication users.
- An adherence strategy of even small effect size at the patient level, such as found in a packages containing a calendar feature, which is broadly implemented on a population level (scaled to all patients taking a medicine) could significantly leverage therapeutic efficacy and provide substantial cumulative public health.

Sandy Kinsey, VP of Pharmacy Merchandising for Wal-Mart and Sam's Club, was recently quoted saying "Scientific studies have proven that statistically significant patient benefits result from adherence packaging programs and we are working to bring even more medications to our customers in adherence packaging."[8]

The Healthcare Compliance Packaging Council is a trade organization that promotes the greater use of adherence packaging to improve patient adherence rates and patient outcomes. Their website contains two decades of research studies that support the use of adherence packaging and can be found at www.hcpc.org. These studies all draw a similar conclusion that is best expressed by a quote from an Institutes of Medicine article entitled Preventing Medication Errors. "The strategy of using calendar blister packs [adherence packaging] could help large numbers of patients to take their medications more reliably and safely, and enhance their treatment outcomes."[9]

Considerations in the Design and Manufacturing of Adherence Packaging

From a packaging and procurement team's perspective, what's not to like about bottles: they're cheap, they're fast, and they're child resistant. The one thing they are not is a tool to help facilitate patient adherence. In global markets where blisters are preferred, medication is habitually separated from important patient information and labeling, thus reducing the odds for patients to have high levels of adherence. By re-considering older, established packaging paradigms and reward structures, manufacturing organizations can leverage their expertise to help the overall business health of the organization they serve. This can be accomplished in a much more impactful way, not by focusing on efficiencies and reduction in Cost of Goods (COGs), but rather by focusing on tactics that can drive top line sales. Relative to existing packaging, adherence packaging can be more expensive. Relative to the cost of current adherence programs, adherence packaging is extremely cost effective and scalable.

Adherence packaging is certainly not appropriate for every medicine. There are certain disease states and treatment protocols that require measured and dynamic dosing flexibility by both the prescriber and pharmacist. However, there are numerous medicines that can benefit from adherence packaging. These medicines typically treat chronic disease states and have static prescription counts.

Adherence packaging is defined by the adherence attributes that can be included in the design – most notably a dosing calendar feature, detailed dosing instructions, and/or patient information. There are other attributes that are common to adherence packaging:

- Each package is a prescribed or delivered unit.
- The package contains a primary package section (often times a blister) and a secondary outer container made from paperboard or another substrate such as plastic.
- Product stability is often very high due to the blister configuration.
- The package is not opened until the point of use.
- Prescription accuracy is high; product verification and prescription count can be verified by bar code or human readable graphical color schemes.
- Child resistant features are often integrated.
- Printing and verification systems used in manufacturing automation can be used to meet serialization and track and trace requirements.

Producing product in adherence packaging includes additional process steps as compared to operating in bottles. Below is a description of the common processes that are associate with adherence packages and a list of considerations.

Package Design

Since many of the design elements of the package are interlinked with each other, it is important to fully scope requirements into a design brief before development work begins. Adherence packaging typically has two components: the primary packaging (blister packaging) that physically contacts the medicine and the secondary package which secures the primary package.

Blister packaging primarily has two considerations that determine its design: 1) the dosing regimen and 2) the moisture barrier and stability requirements. Dosing regimen is set by how many tablets need to be taken per day and how many tablets need to fit in the blister. The tablet count per package is often set to deliver a specific price point. The moisture barrier and stability requirements have a direct impact on the material selected to form the blister. For drugs that require a complete moisture barrier, a Moisture Vapor Transmission (MTVR) (aluminum-aluminum) or Cold Form Foil (CFF) is used. The majority of product on the market does not require stringent moisture barrier requirements to maintain stability and therefore can leverage materials that are easier and more cost effective to work with. Examples of these are Polyvinyl Chloride (PVC) and Cyclic Olefin Copolymers (COC) materials that use a thermoforming process to shape the blister.

There are a few styles of secondary packaging associated with adherence packaging. The three main categories are 1) wallet cards (either heat sealed or glued), 2) paperboard Sleeve with folded heat sealed inner card containing the blister locked into the sleeve, or 3) paperboard or plastic sleeve that locks the blister. The requirement for a Child Resistance (CR) feature is the primary driver in choosing a style. For example, if no CR is required, a simple fold-over wallet may be optimal. Patient information to be included within the package also can dictate package style. The size and number of messages and graphics, and inclusion of Product Insert (PI) may point to using a packaging with a fifth and sixth panel. Lastly, if an **alu-alu** blister is selected for the primary blister, it typically requires that the secondary package is slightly bigger.

Package Development

Packaging development is sometimes handled in-house, but there is an increasing trend to use external package developers who are experts in CR features and material selection. Substrate selection is an important step to ensure the final package maintains the original intended structural rigidity. Developers will test different calipers of board thickness to meet the optimal cost per rigidity profile.

For packages that are designed for the US market, a major part of the package development process is passing Child Resistance (CR) testing. The US Consumer Product Safety Commission (CSPC) requires prescription medicine and certain oral solid dose medicines, as well as most investigational products used in clinical trials to be packed in child resistant packaging.

The CSPC regulations set specific protocol parameters for testing, and they must be conducted in accredited research facilities. Tests involve a panel of 50 children composed equally of male and female subjects. A package successfully passes the test if 85% of the children are unable to open the package in 5 minutes or 80% are unable to open the package after a demonstration is provided. The CSPC also requires a senior adult test that is similar in protocol to the CR testing. CR requirements are coded based on how many tablets a child would need to access to cause harm. If a child can be poisoned by accessing one tablet, the package requires an F=1 rating; eight tablets requires an F-8 rating and so on.

Figure 4. Paperboard sleeve package.

Package Production (Converting)

Production of the secondary package is typically conducted at an outside resource that specializes in paperboard converting or injection molded applications. The drug manufacturer will want to schedule at least one on-site check to validate the converting process and ensure that the agreed to quality controls are in place to meet specified tolerances of the packaging dimensions and more importantly that the printed graphics align with the approved master graphics file. For paperboard converting, there are three primary operations: printing, cutting, and gluing. The converting of pharmaceutical packages is often done in small batches (as compared to consumer products that have long continual runs). Printing machines that can perform quick changeovers to other print jobs are usually used to run the small batches. For the printing operation, color matching is the primary area of quality assurance focus. For the cutting phase, vision systems are employed to make sure that cutting tolerances are being maintained and to validate that there is no missing copy and that print registrations are within specifications. Gluing is the final phase and the step where product inserts or labels are attached as required. Sampling of product occurs at each step of the process.

Finished Product

This step of the manufacturing process combines the primary and secondary packages together. It can be done in house or at one of the many trusted contract packagers. Many of the manufacturing steps in this stage are similar, but there are subtle differences based on the type of secondary package that is being used that can affect the layout of the manufacturing line. Many of the steps described below can be automated by using modified standard equipment. There are four typical layouts for final assembly packaging lines that produce finished product. These are:

1. Heat sealed wallet
2. Glue sealed wallet
3. Paperboard sleeve with folded heat sealed inner card locked into sleeve
4. Paperboard or plastic sleeve with locked blister

For each layout, the blister former (thermoforming or cold forming) can be run separately or in-line with the rest of the manufacturing process. Table B highlights the line design impact of where the blister forming takes place depending on the package type. Table C highlights the different attributes of each manufacturing layout.

Paperboard sleeves, whether they are used with a locked blister or sealed inner card, can be fed, opened, and closed on a cartoning base with special features. The infeed and loading system of the blister into the sleeve typically uses a specialized piece of equipment. Downstream modules may be used to perform specialized printing, labeling, or attaching (outsert) functions.

Validation Process

Meeting internal QA requirements is a matter of following proven validation processes. Using a risk-based approach, quality critical items can be verified with standard bar code scanning and vision technology. It is always recommended and encouraged to leverage supplier documentation (GAMP® 5 and ASTM E2500) to minimize testing protocols and their execution. Other tips:

- Verification and inspection systems should reject non-complying products without stopping the equipment.

Figure 5. Paperboard wallet card package.

Heat Sealed Wallet and Paperboard Sleeve with folded heat sealed inner card locked into sleeve
• Blister former is operated as a stand-alone system. • Output from the blister former is usually batched in trays. • Automation to stack blisters in trays may be helpful. • As this is a stand-alone unit, it runs/produces at full speed as it is not dependent on downstream equipment. • Speeds as high as 400 blisters per minute are possible.
Glue Sealed Wallet and Paperboard or Plastic Sleeve with locked blister
• The blister former is often operated in-line with the system. • Speed is dependent on downstream equipment.

Table B. Blister former attributes by packaging line type.

Heat Sealed Wallet and Paperboard Sleeve with folded heat sealed inner card locked into sleeve
• Produced in a platen style heat seal machine. • Uses an indexing multiple product machine that feeds a base card, blister, and a secondary card. • The cards/blisters are sealed using heat and pressure at one or two stations. • Cycle rate of this equipment is 15 per minute; total output would be 120 cards per minute total using an eight up platen. • Equipment for heat sealing uses modified standard machines, the folders are custom machines. • Uses multiple magazines for card stocks and blisters which is labor intensive. • Output of the card heat sealer is difficult and expensive to automate if a variety of formats are being produced. • Cards are discharged unfolded requiring an external system of folding. • Cards may be folded in many sequences and formats. • Printing and verification of the lot and date codes as well as closing systems such as a wafer seal is included. • Speeds of 200 cards per minute can be obtained for wallets and 250 cards per minute for sleeves.
Glue Sealed Wallet and Paperboard or Plastic Sleeve with locked blister
• Blister feeder automatically feeds magazine. • Card with multiple panels and blister are simultaneously fed. • Hot melt adhesive is applied in conjunction with the folding sequence. • Final folding and closing are done within a single machine and discharged as a finished product. • Cards may be folded in many sequences and formats. • Printing and verification of the lot and date codes as well as closing systems such as a wafer seal is included. • Speed of this equipment may be as high as 300 to 400 wallets per minute. Paperboard sleeves with locking mechanisms are limited to about 250 to 300 finished products per hour due to the multiple layers of sleeve paperboard and inner card blister. • Equipment is highly customized but available from several manufacturers. • Multipack shippers and dispensers can easily be automated using standard equipment.

Table C. Manufacturing attributes by package line type.

- The secondary packaging equipment will determine the final package aesthetics that patients will see. A verification step should be included to ensure "look and feel" of the package meets specifications.
- Controls should be developed and maintained to meet target CR compliance levels (e.g., F=1).
- Production targets should be scrutinized to minimize capital requirements and investment considerations. Selecting intermittent motion equipment (slow to medium speed) vs. continuous motion equipment (high speed) can reduce capital requirements. Similarly, a phased approach to automation (moving from manual or semi-automatic to full automation) may decrease initial investments.

Conclusion

The trend of leveraging the unique characteristics of packaging to help patients better understand how and why to take their medicines is growing. Scientific data clearly shows that packaging alone can increase patient adherence to taking medicine correctly as prescribed. Never before have packaging and manufacturing engineers been in a better position to help their organizations by driving packaging decisions that drive top-line sales and positive business results – and ultimately helping patients reach better health outcomes.

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Serialization – A Worldwide Challenge

by Dana Buker and David Loy

This article presents operational considerations and related recommended approaches for implementing serialization to address existing and upcoming regulatory requirements in a pharmaceutical environment.

Introduction

Enforcement and global infrastructure discussions aside, it is safe to say that most, if not all, life science product manufacturers and distributors recognize the need for and have been or are in the process of implementing product serialization. This article has been written to provide practical advice for implementing serialization from an operational perspective when attempting to achieve serialization in an automated packaging line environment. This article will focus on the operational aspects of introducing product serialization to meet existing and future regulatory requirements. The article will address process and control considerations requiring a blend of both technical and human capabilities.

Assumptions

1. The article is written as if the reader's company has decided to achieve compliance preparedness with California's ePedigree regulation by 1 July 2015.
2. Compliance with the California Rule will fulfill track and trace requirements for all global, federal, and state regulatory bodies.
3. There will be a period of regulatory stability such that, no major law, rule, or guidance changes in the next decade will result in a need for significant systemic/operational changes once a company has introduced compliance measures for the California Rule.
4. Serialization will allow receiving entities in the supply chain to authenticate received product by scanning a serial number. The scanned value will be submitted to a specific internet-accessible system that will be able to confirm that the product labeled with the scanned serial number has (or has not) been registered and is recognized as a valid number associated with the product that has traveled effectively through the supply chain to that point.
5. The ultimate system(s) design that will deliver full supply chain authentication is yet to be determined. However, the ability for a drug supply chain entity to meet a requirement for serializing saleable packaged units and aggregate the serialization data throughout the packaging process can be met.
6. The Standardized Numerical Identification (SNI) will become the standard.
7. GS1 will be the primary governing body for the standards that will be used for the ePedigree and track and trace.

What Is Serialization as It Relates to Life Sciences Today?

In the context of this article, serialization means the assignment of a unique traceable number to each saleable package unit of product. A serial number must be assigned to each container as a product moves from, for example, primary container (such as a bottle), to a box or carton, and onto a pallet. At each level, every bottle, box, and pallet will be uniquely identified with a serial number.

Serialization is a foundational piece of a track and trace system and is one of the many requirements documented in the "California Rule" (**SB 1307, Ridley-Thomas. Pharmacy: pedigree**).[1]

"The goal is to make investments today that will be flexible enough to accommodate existing laws around the globe *and* whatever ultimately might or might not happen in the U.S., the E.U. and elsewhere. To accomplish that, 'flexibility' is the key word and the key attribute."[2]

So, to this group of interested observers, the question of providing serialization at the smallest saleable unit is more a matter of how, what, and when rather than if.

Overview of the History and Current State of the Regulatory Landscape

Although debate continues as to the specifics associated with the "what to do," "how to do it,"

and "when to do it" concerning global supply chain security, it is evident that life sciences organizations will be required to take measurable steps toward introduction of product serialization. With each recurrence of confirmed counterfeits entering the supply chain, regulatory focus intensifies worldwide.

And as is noted in the US FDA's ***Global Engagement***, "…medical products and their ingredients and components – products that directly and profoundly affect the health and welfare of the U.S. public – are increasingly sourced from abroad."[3]

One indication as to the current thinking at the FDA was presented at the FDA Track and Trace Public Workshop in February 2011. Figure 1 is a slide describing the goals and attributes foreseen for such a system.[4]

Similarly, in the proposed USP <1083> ***Good Distribution Practices – Supply Chain Integrity***, "The global supply chain for pharmaceuticals and medical devices is complex, with many components of a medicine now typically arriving at the point of manufacture from other countries."[5]

With the accelerated pace of regulatory involvement worldwide in serialization and track and trace, a strong working foundation of imminent requirements is necessary. Although not all inclusive, the following is a brief history of some key events resulting in the impetus of serialization:

- April 1987: The Prescription Drug Marketing Act (PDMA) of 1987 was signed into law by President Reagan. As defined by the FDA, "The PDMA was enacted (1) to ensure that drug products purchased by consumers are safe and effective and (2) to avoid the unacceptable risk to American consumers from counterfeit, adulterated, misbranded, sub-potent, or expired drugs. The legislation was necessary to increase safeguards in the drug distribution system to prevent the introduction and retail sale of substandard, ineffective, or counterfeit drugs."[6] The passage resulted in 21 CFR Parts 203 and 205. Many of the specific requirements were not enforced until 2006.
- July 2003: The FDA established its Counterfeit Drug Task Force which established four primary objectives: (1) preventing the introduction of counterfeit drugs, (2) facilitating the identification of counterfeit drugs, (3) minimizing the risk and exposure of consumers to counterfeit drugs, and (4) avoiding the addition of unnecessary costs on the prescription drug distribution system or unnecessary restrictions on lower-cost sources of drugs."[7]
- December 2003: Belgium published a Royal Decree introducing sequential codes for all medicines to uniquely identify each product pack. Starting 1 July 2004 all packages carried a bar code containing a 16-digit sequential code structured as Association of Pharmacists – Belgium (APB) product identification number (seven characters), sequential number (eight characters), and one character check digit (allocated by the manufacturer).
- February 2004: California's initial passage of ***Ridley-Thomas. Pharmacy: pedigree SB 1307*** establishing the mandate to provide a pedigree for each product included on each shipment of prescription drugs.
- January 2009: Brazil passed ***11.903 Track and Trace Mandate*** requiring that drug manufacturers and distributors serialize and comply with track and trace requirements of electronic identification and data capture. The aggressive three-year plan staggered implementation and ultimately required serialization and tracking to the consumer/prescription/doctor level.[8]
- March 2010: the FDA issued recommendations in the ***Standard Numerical Identifier (SNI)*** Guidance explaining the FDA's current thinking on the structure, format, and content of uniquely labeled package-level identifiers.[9]
- July 2010: The European Directorate for the Quality of Medicines (EDQM) started a track-and-trace pilot study for pharmaceuticals to advance previously piloted programs in Europe.
- February 2011: The FDA hosted ***Determination of System Attributes for the Tracking and Tracing of Prescription Drugs*** Public Workshop to specifically outline the following four objectives of serialization requirements associated with track and trace:

1. Preventing the introduction of counterfeit, diverted, sub-potent, substandard, adulterated, misbranded, or expired drugs
2. Facilitating the identification of counterfeit, diverted, sub-potent, substandard, adulterated, misbranded, or expired drugs
3. Providing accountability for the movement of drugs by supply chain participants
4. Improving efficiency and effectiveness of recalls[4]

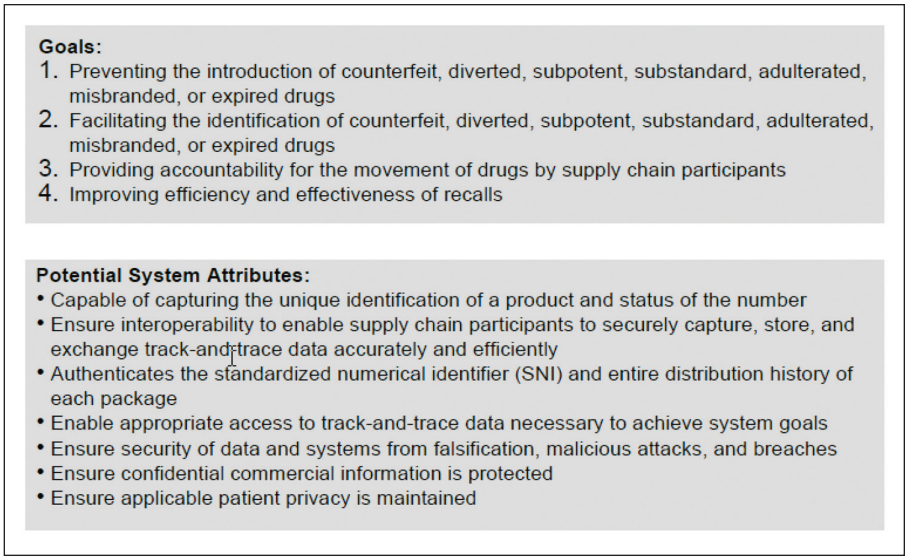

Figure 1. System Goals and Attributes.[4]

- December 2011: The USP publishes proposed <1083> Good Distribution Practices – Supply Chain Integrity presenting recommended practices to secure drug substance and excipient supply chain integrity worldwide. The guidance specifically addresses serialization and SNIs.
- April 2012: The FDA published Global Engagement describing strategies and needs to address globalization, including preventing counterfeit drug products.
- April 2012: The Senate of the United States – 112th Cong., 2d Sess. introduced Title XII – Pharmaceutical Distribution Integrity as an amendment to the Federal Food, Drug, and Cosmetic Act (also known as, Securing Pharmaceutical Distribution Integrity ***to Protect the Public Health Act of 2012 or the Securing Pharmaceutical Integrity Act of 2012)***. Specifically outlined within the proposed legislation are requirements for embedded SNIs applied at the smallest saleable unit level.
- 2012 (planned): Based on Guidance Agenda: New and Revised Draft Guidances, CDER is planning to publish during calendar year 2012, Securing the Drug Supply Chain – Standards for Tracking and Tracing Prescription Drug Packages.[11]

Although several of the US states are in the process of creating legislation for ePedigree, California is by far drawing the most attention for two reasons. First, although they have pushed the initial enforcement date out, there seems to be a common understanding that the current initial enforcement date of 1 January 2015 will stand. Second, of those states actively pursuing similar legislation, California's requirements are the most demanding. For example, Florida's law requires the tracking of product to the lot level, whereas California's goes to the smallest saleable unit level.

Although California's legislation is written such that it will effectively be usurped by Federal legislation, it is not known when the Federal Government may introduce overriding legislation. We do know that the FDA is planning to issue a "Guidance Document" for ePedigree by the end of 2012. What that document may contain is speculative at this moment; however, the key word is "Guidance." Although it will be a good indicator of future regulation(s), it will not override the California rule.

Guided by GAMP® 5

During the project planning and ultimate implementation of a structured track and trace program, *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* considerations must drive decision-making. Immediately upon the formalization of a systematic serialization approach within an organization, it becomes subject to standard GxP quality management system requirements.

"New concepts are being developed and applied, including science-based risk management approaches, a focus on product and process understanding, and the application of quality by design concepts."[12]

...GAMP® guidance must evolve to meet the needs of the changing environment and integrate fully with ISPE initiatives..."[12]

Project Planning – The Critical Success Factor

Many companies will begin a serialization project with a project charter document. A key element of such a document is a scope statement or section. The scope statement will strive to answer some of these questions:

- Is this a plant-level or global project?
- Are elements of a serialization system already in place? And if so, has a gap analysis been performed to identify the differences between the as-is and the to-be processes?
- Have we collaborated with all important stakeholders at – the plant level, among plants, and at corporate headquarters in order to leverage opportunities for standardization and reduce or eliminate the need for duplication?
- If this is a global project, what communication and collaboration mechanisms are or will be in place to support the project?
- Will there be a pilot(s) project to deliver a real-life proof-of-concept?
- If a global project, what is the potential for leverage of corporate standards or guidelines and supplier standardization?
- If a global project, what level of standardization or harmonization is realistic, both at the plant level and the corporate level?

The project plan should consider task ownership so that there are clear expectations of who will deliver what and when. Although this consideration is universally applicable to all elements of the project, the bottom line is that the delivery of the system including all software, hardware, documentation, and on-going support and maintenance must be well understood and agreed upon in writing. For example, when there is a system error who will respond and in what time frame? Keep in mind that when the serialization system becomes unavailable, packaging will stop, at least for a short period of time. Also, given the business-critical nature of the system, business resumption and disaster recovery plans must be developed, tested, and available when the system goes live.

Operational Considerations

Interdependence and Web/Thread of Connectivity

Product serialization and the aggregation of serial numbers converts what might have been thought of as individual steps in the packaging process and binds them together as a continuous process flow. It will no longer be a relatively simple process to remove and replace serialized defective units. The processes of disaggregation and re-aggregation will need to be well understood and adhered to by everyone involved in the packaging process including supervisors, engineers, maintenance technicians, mechanics, line operators, and others.

Education and Training

Because serialization, as part of an ePedigree system, will have greater external utility by systems and personnel directly

and indirectly related to the supply chain, the company and its products will see a higher level of exposure and scrutiny. Accuracy of the ePedigree data is essential. That being the case, the company must be sure that education and training of all personnel who may be involved in the development, testing, operation, and maintenance of these systems are crucial. Everyone involved will require not only the procedural knowledge, but also a "higher level" education to assure that there is a general understanding of the system and its full purpose and importance in protecting the public, the company, and the company's products and its reputation.

Rejects and Rework

Certainly this can be a complex and challenging topic. This is primarily because now we are aggregating serial numbers into containers holding smaller serialized units. When the serial number "chain" is disrupted for whatever reason, the human business processes and automated systems' capabilities to cope with the management of such an issue is key.

Although there are a number of potential scenarios that will inevitably occur, following is an example based on a standard high-speed packaging operation of between 100 to 200 bottles per minute:

Assumptions:

- All labeling within the batch must be uniquely serialized, verified, authenticated, and aggregated during the packaging operation.
- At a minimum, the following automated systems, including mechanized ejection capability, are parts of the packaging train: (1) controlled creation and issuance of a pool of uniquely serialized values for the specific packaging operation; (2) confirmation and verification following application that the barcode is machine readable and is an issued value from the approved pool; (3) aggregation of the serialized product during the final box-out into shipping containers to create the parent – child relationship between the uniquely serialized barcode applied to the shipper case and each uniquely serialized container within the shipper; and (4) reconciliation of used, destroyed, and

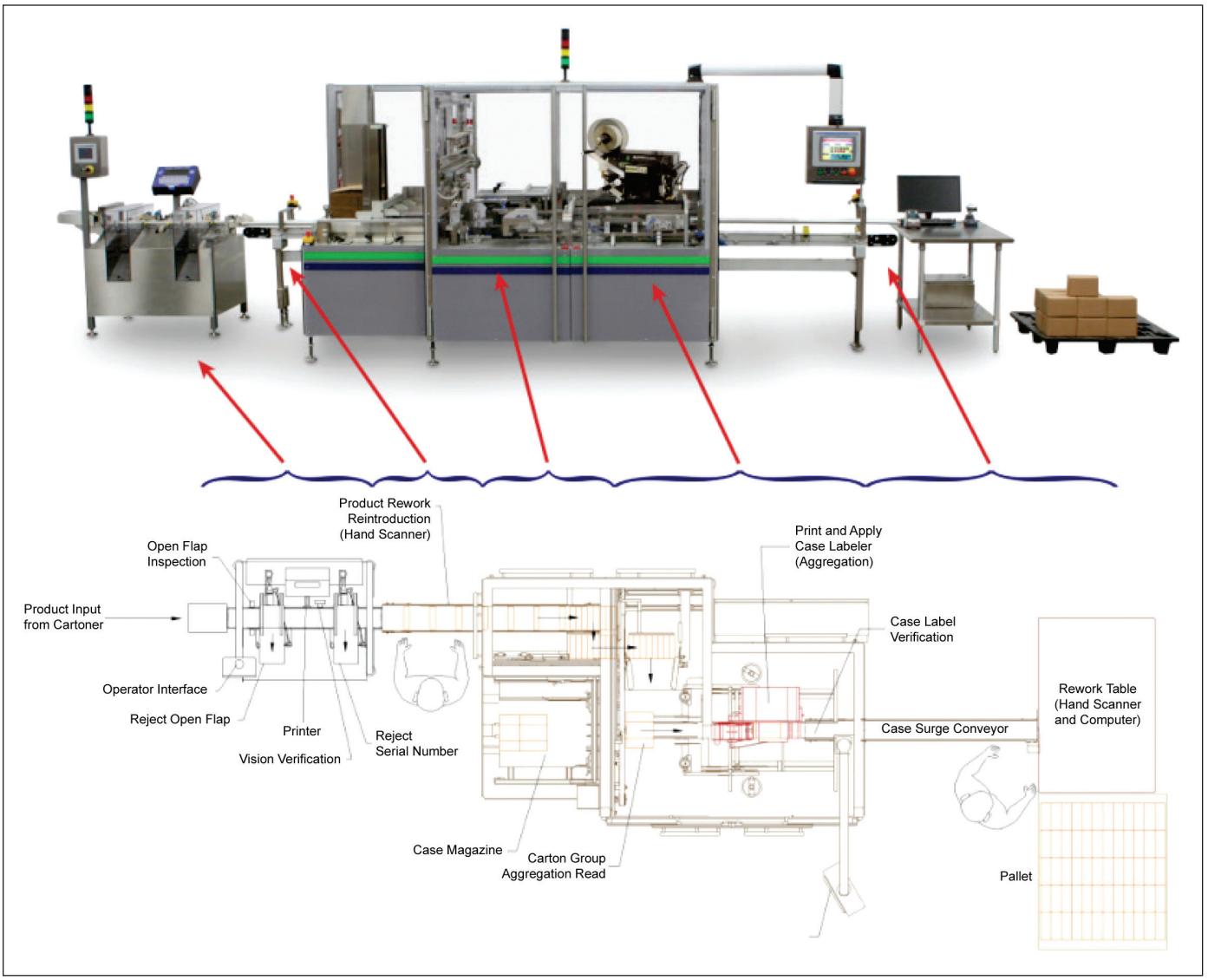

Figure 2. High-speed packaging line with operator/station interface legend.

remaining values against the issuance for the original pool.

1. Product, labeling, and packaging materials (e.g., container, closures, corrugated shippers) are issued to a packaging suite.
2. Inevitably, equipment fails, whether using inkjet, laser, thermal transfer, or some other labeling technology.
3. Upon failure, defective units result causing rejects that are automatically detected and separated from the rest of the batch.
4. Depending on product value, rejects are placed in a secured location and destroyed at the conclusion of the batch or rejects are fully reworked using an approved rework process that specifically addresses the final disposition of the serialized labeled primary container.
5. As the rejects contain controlled serialized values created for the specific batching operation, these units must be closely controlled and reconciled during the batch approval process. Discrepancies will result in delayed batch release, potential quarantines, and investigations.

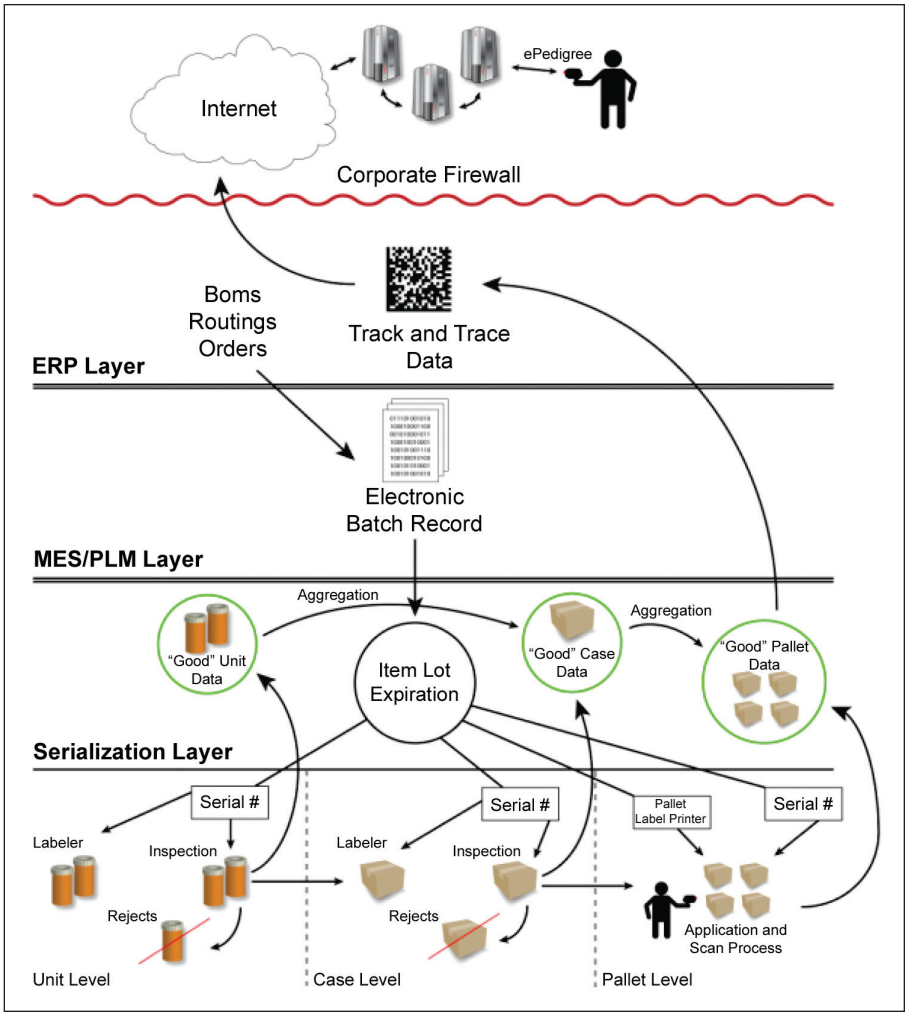

Figure 3. Serialization data and process flow.

It is evident that any fault in the data linkage will result in significant lost production time. Moreover, considering throughput on today's high speed packaging lines, a failure scenario such as the one described above could have significant cost and/or compliance impact.

Systems Integration

In today's world of electronic systems, it seems that nearly all "new" systems require multiple systems to "talk" to one another. So, tight and timely integration is a key to success as well. Think about the system responsible for maintaining the repository of serial numbers and how it must interact with other hardware and software on the packaging line. Data spawned in the system responsible for creating the serial number may need to be merged with other product and lot information at print time. The serial number and its corresponding lot-related data may then need to be sent to another system for aggregation to the next layer of packaging. At the same time, perhaps a vision system must confirm legibility of the values, other data, and images on the label and so on. In addition, it may be (and eventually there will be) a system external to the company that requires serial numbers to satisfy ePedigree track and trace requirements. The database associated with whatever global track and trace system evolves must be updated at time of product shipment.

Figure 3 is an image of how the integration of disparate electronic systems might bring about the delivery of an ePedigree beginning with the assignment of serialization at the lowest saleable unit.

Compliance Considerations

One Approach – A Variety of Global Regulations

Certainly there are numerous additional questions to address before starting a serialization effort. The point here is that although the concept of serialization has been around for decades, we are now looking at a potentially universal approach in large part because of the more recently recognized global interdependencies of the supply chain.

Any and all systems added or maintained to resolve the ePedigree initiative must be compliant with the regulations. So, although the need for attacking the problem of counterfeit medicines in the supply chain is obvious, many of the system design considerations may be derived from an analysis of the regulations the system(s) will address. This is not to say that all of our requirements may be derived from the regulations and of course we will use our internally developed system life cycle procedures throughout the design, build, test, and implementation phases.

So where do we start? We can begin with gathering the

essential requirements of the "to-be" solution. Boil them down into manageable, clearly stated user requirements. In this case, we might begin by parsing out a regulation and converting the system-related verbiage into user requirements terminology familiar to folks in our organization. From there, the evolution to the associated functional requirements is a natural one. This will deliver a system definition that is logical and traceable within our internally approved life cycle documentation package. Also, it will support an audit process leaving little doubt that the company has taken an approach specifically aimed at addressing the regulation(s) in the design of the system.

So, for example, we might read from California's SB1307:

> "*This bill would instead, on and after January 1, 2015, define a pedigree, as specified, and would revise the information required to be contained in a pedigree to, among other things, include a specified unique identification number.*"
>
> and combined with the above…
>
> "*The bill would require the board to promulgate regulations defining the circumstances under which participants in the distribution chain may infer the contents of a case, pallet, or other aggregate of individual units, packages, or containers of dangerous drugs, from a unique identifier associated with the case, pallet, or other aggregate, if certain standard operating procedures are complied with and made available for the board to review*."

Although because of the writing style, these excerpts are difficult to parse (unlike, for example, the point-by-point language seen in the FDA's 21 CFR Part 11), several user requirements may result including ones that may read:

- "The system shall be able to assign a unique serial number to each package unit beginning at the lowest saleable individual package unit level."

  and

- "The system shall be able to assign a serial number to each packaging level in order to 'aggregate' packaging units into containers holding a number of smaller serialized package units."

Of course, not all of the system requirements will be gleaned from a review of the regulations. So, in addition to the user requirements focused specifically on meeting the regulations, additional requirements will need to be gathered and documented clearly describing our internal users' expectations for the delivered system. Examples of requirements for this group may read similar to these:

- "The system shall be able to monitor availability of serial numbers and notify an operator when a 'low level' limit is reached."

  and

- "The system must be able to 'read' all serial numbers applied by scanning with appropriate equipment and immediately reject defective units and notify operator(s) when illegible serial number(s) is/are encountered."

However, the "project" of "serialization" must be considered a part of a much broader project aimed at delivering a full ePedigree solution. Without consideration for how the association of a unique serial number for each saleable package unit fits into the broader goal of ePedigree, we may not provide for a fully effective and compliant system as we attempt to provide for fast and accurate track and trace capabilities.

Once the requirements have been gathered and reviewed, we will use standard internal procedures to complete the system design. The design and build processes will follow internal Computer System Life Cycle (CSLC) defined in local procedures.

Supplier Selection

From Section 7 of *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, "Although the responsibility for compliance with GxP regulations lies with the regulated company, the supplier may have considerable involvement in the process."[12]

It makes sense that serialization project leaders take advantage of the fact that there may well be suppliers capable of providing a significant amount of documented testing and evidence of a system's fitness for use in the industry from a compliance as well as from a functional perspective. It is strongly recommended that external partners considered for selection to assist in any portion of the development of the serialization solution be vetted for their ability to address regulatory as well as functional requirements. Refer to *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, Section 7 Supplier Activities, for a detailed discussion on this aspect of the process.

Another ISPE resource, the *JETT Acquisition Model*[13] (latest version), may be a valuable resource during this phase.

Validation and Maintenance

The reliance of accurate outward facing information underscores the need for a high degree of testing. Over time as equipment is swapped out, software version updates are installed and other changes take place, consideration must be given to the risk that the updated integrated system will continue to provide accurate, reliable, and legible data.

Here again it is important to point out that *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* is a valuable resource. As written in Section 3 Life Cycle Approach – "Compliance with regulatory requirements and fitness for intended use may be achieved by adopting a life cycle approach following good practice as defined in this

guide."[12] It is important to recognize that just as the concepts for managing ePedigree are in a current state of rapid evolution, so too, we must consider the current trends in the evolution of the Computer System Life Cycle (CSLC).

Recently there have been many documents (including *GAMP® 5*) and articles written on topics such as:

- Risk-based approach
- Leveraging vendor documentation
- Global corporate CSLC harmonization and standardization and more

It is important for the team involved in the testing and validation of a serialization system to be aware and take advantage of efficiencies that may be gained by paying attention to these trends and the company's related current philosophy and documented guidance in these areas.

At a high-level, the life cycle approach for a serialization project may look like the one shown in Figure 4.

Be sure to create and review a list of related questions such as:

1. Can we leverage the vendor(s) testing? If so, to what degree and how much internal documented testing can thereby be reduced, if any?
2. Have we performed a good risk assessment taking into consideration business and cGMP requirements?
3. Will the validation process merge well with system expansion to eventually include full track and trace?

System Security

When one considers the need for system security and then looks at the real-life aspects of an automated packaging line, several important considerations come to mind.

First, packaging line operators must have the basic computer and system skills required to operate the systems effectively and efficiently. Second, if operators are simultaneously responsible for multiple pieces of computerized equipment, especially those that may be considered cGMP, what are the implications of identification, control, and collection of an electronic signature, and perhaps other 21 CFR Part 11 rules. Third, depending once again on the simultaneous responsibility of an operator logged into multiple systems, consideration must be given to an operator's ability to visibly monitor what may be happening on those systems.

Business Continuity

With saleable package unit-level serialization and data aggregation during the packaging process, we will be in a situation that requires a very robust integrated series of systems. Not only will we need for the packaging equipment to run reliably and flawlessly, but the systems that are providing, gathering, and using business-critical ePedigree data (including serial numbers) in real time also must be reliable and accurate. When any system involved in the process of generating data for application to serialized package units fails, there must be a process in place to manage the situation. For many companies not accustomed to managing electronic data in real time on the packaging line, business continuity may be a very new, but very real concern.

Be sure to create and review a list of related questions such as:

1. Do we have adequate procedures in place (perhaps by product) to manage the business process for unexpected "system down" situations?
2. Are all of the parties that will be involved in the process trained?
3. Have we performed system audits and/or mock tests to challenge the procedures and look for ways to improve them?
4. In the event of a computer system disruption, how can we continue a packaging operation that is in process?
5. If the computer system disruption is expected to last a

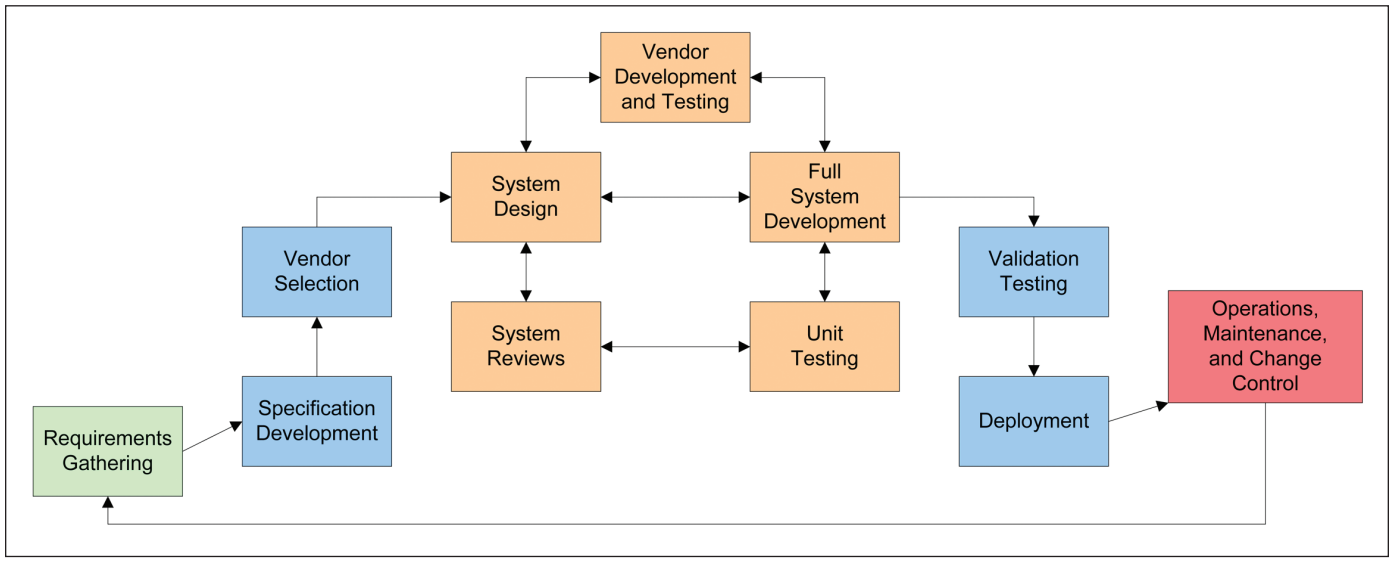

Figure 4. Computer system life cycle.

long time (i.e., days and not hours), is there a plan for continuing operations using a backup process? And if so, how do we recover when normal operations can resume?
6. What constitutes an event that results in a business continuity scenario?

Certainly, there are hundreds of questions to address in order to prepare for various levels of disruption up to and including a "disaster."

Disaster Recovery

When a disaster event occurs, the company must have a strong plan in place to cope with it and to minimize the impact. There are an unlimited number of approaches that may be taken, but the important take away is that every company must have a plan in place that is effective and reevaluated from time to time. The key to success in disaster recovery as well as business continuity is to have an effective communication process in place. This is because the number of possible scenario forms is limitless and the plan may or may not have taken into consideration the exact real-life situation. Therefore, the plan, as written, may very well need to be adjusted contemporaneously with the event in order to reduce the short or long term impact(s).

Other Operational Topics

With *GAMP® 5* as a guide, other topics to consider include how:[12]

- the system will be handed over to the users
- the system will be measured and monitored from a performance perspective
- incidents will be documented and corrective and preventive measures will be captured and coordinated
- system changes will be managed
- system audits will be conducted
- electronic records will be maintained, retrieved, and archived

Summary

By now, nearly everyone in the life sciences industries understands that serialization to meet the needs of an integrated ePedigree system will soon be as much a business requirement as making safe and effective products. Although much of the higher level technology has yet to be designed, applying traceable serial numbers to products on the packaging line is reasonably well known and understood. The speed and effectiveness of achieving the baseline requirements will be critically important to all life science manufacturers and packagers over the next two years.

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This article presents a marketing strategy that is implemented using existing or new primary and secondary packaging systems.

Pharmaceutical Packaging with Brite Stock Manufacturing

by Mel Bahr

Introduction

As a business strategy, a Brite Stock packaging line might be right for your company. These lines can be beneficial for both Rx and Over the Counter (OTC) products as an economical method of production for global markets or for private branding for the big box stores. The inventories created, effectively may be used as "Just in Time" or "Make to Order," at the same time providing customized labeling and insert requirements for each market. Although this topic also could include "Processing of the Product," this article will focus on the primary packaging of the product and the subsequent secondary packaging.

Today's business trend includes the consolidation of companies which invariably result in the combining of previously competing products. By harmonizing the primary packaging, and perhaps secondary, these products can continue to be produced economically for the supply chain.

The decision to "Brite Stock" often begins as a market strategy to sell more product (increase revenue) and maintain capital expenditures by utilizing existing plant and equipment assets. The effects of product life, potential quality impact, and product mix ups are all factors that need to be evaluated. It is not the intent of this article to include regulatory or quality impact factors as this is best evaluated on a case by case basis.

Defining "Brite Stock"

The traditional concept and definition of Brite Stocking is believed to have originated from food canning product lines. Filled, unlabeled canned product is produced then stored in inventory for future can labeling and case packing. The filled cans are labeled to a manufactures specific brand or as a generic product. Variable shipping packaging such as case packs and bundling is easily accommodated. The term "Brite" is due to the storage of the unlabeled can.

Today's definition, as applied to a pharmaceutical packaging line, would include a variety of primary packages, including at least bottles, vials, ampules, blisters, and pouches. The primary packaging system will need to include a method of coding or marking the package for later verification (typically a bar code applied by a non-contact printer). The secondary packaging operation would include labeling, printing, inserts, cartons, cases, bundling, and final package labeling. This portion of the line also will need to include verification systems (bar code readers or vision systems) that are similar to those required for "Track and Trace" systems.

A deviation to the traditional "Brite Stock" is an online buffering (small accumulation) of the product between the primary and secondary packaging that allows for a change to the secondary packaging without input stoppage. See Example three below.

Advantages

This manufacturing process has the advantage of maximizing the primary packaging efficiencies by increasing utilization of equipment and labor. Using Overall Equipment Effectiveness (OEE) principles:

- Availability is increased by reducing the frequency of product and or lot/batch changeovers. Line cleanout, tweaking, and fine tuning of changeover is a major time loss of equipment uptime.
- Performance of the primary packaging equipment is increased due to the reduction in line stoppages due to downstream equipment issues.
- Performance of the secondary packaging equipment is increased as it is not dependent

on performance of the primary equipment or lack of product at the input.
- Primary and secondary packaging equipment often function best at different rates. Each piece of equipment can be fine tuned without affecting the other portion of the operation.

A typical manufacturing goal would be 100% utilization of the primary packaging equipment. Seldom does the output rate of the primary packaging equipment match the secondary packaging equipment. For example, a blister thermoformer that is capable of producing 400 blisters per minute may need to be reduced in speed when inserting one blister per carton whereas if the put up is a ten pack, the cartoner will be underutilized. If this were a Brite Stock line, the thermoformer would continuously produce at an output of 400 blisters per minute 24/7 whereas the cartoner might package the product in a single shift.

Another example could be a bottling line that is producing at high speed. The secondary packaging is divided between a single bottle in a carton and bundled packs. A Brite Stock operation allows each of these outputs to happen individually or concurrently and each at their maximum speed with increased flexibility. In this situation, it makes it possible for the cartoner and bundler to be lower cost, slower speed units, neither by themselves matching the maximum output of the bottling filling and capping equipment.

The cost advantages are from the increased revenues (maintaining fixed overhead costs), reduced capital expenditures (utilizing the same facility and equipment assets), and increased efficiencies due to separation of primary and secondary packaging.

Disadvantages

These lines require a method or system to "store" the product. This may be as simple as bulk storage in a large container (filled plastic bottles), stackable products in paperboard trays (blisters and pouches), stackable plastic trays (vials and ampules), or on a pallet (glass bottles). The storage containers could be an additional cost.

Securing the appropriate facilities (and its control) and space for the storage of the unlabeled productcan be a challenge. This could be partially offset by reducing the finished goods storage if a "Just in Time" process is implemented.

The addition of equipment (such as tray loaders for blisters, pouches, vials, and ampules) to automate the "storing" is a possible additional cost.

Printing, marking, or coding units will be required for later identification of the unlabeled product in secondary packaging. Refeeding of the primary package into the secondary packaging line also will be required.

Identification systems will be required to verify the product as it is entering the secondary packaging line. The identification systems will typically be bar code readers and or vision systems and will require vigorous testing and operational controls (SOPs) to be in place.

The cost disadvantages are additional equipment (if storage is automated), the storage containers, unlabeled product coding (marking for identification), storage facilities, refeeding, identification, and verification of the unlabeled product entering secondary packaging.

Example One: Bottle in a Carton – *Figure 1*

The requirement is for a system that provides a liquid filled product in a bottle with the unit of sale being a carton. The market requirement is for an OTC product where the liquid product is the same for all SKUs, but the final packaging is for a variety of private and generic brands. The production speed is 250 bottles per minute.

Primary Packaging Basic Functional Equipment

- Bulk bottle unscrambler and cleaner
- Laser printer for the bottom of the bottle
- Vision system, verify printed code
- Liquid filler
- Capper
- Bulk storage container

Secondary Packaging Basic Functional Equipment

- Bulk filled bottle unscrambler

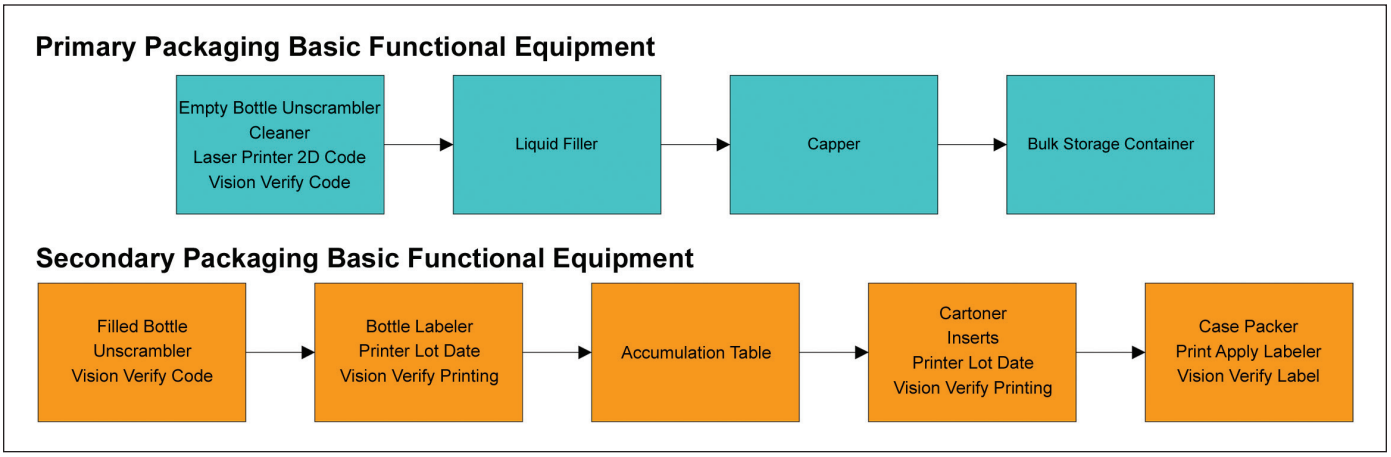

Figure 1. Example one: bottle in a carton.

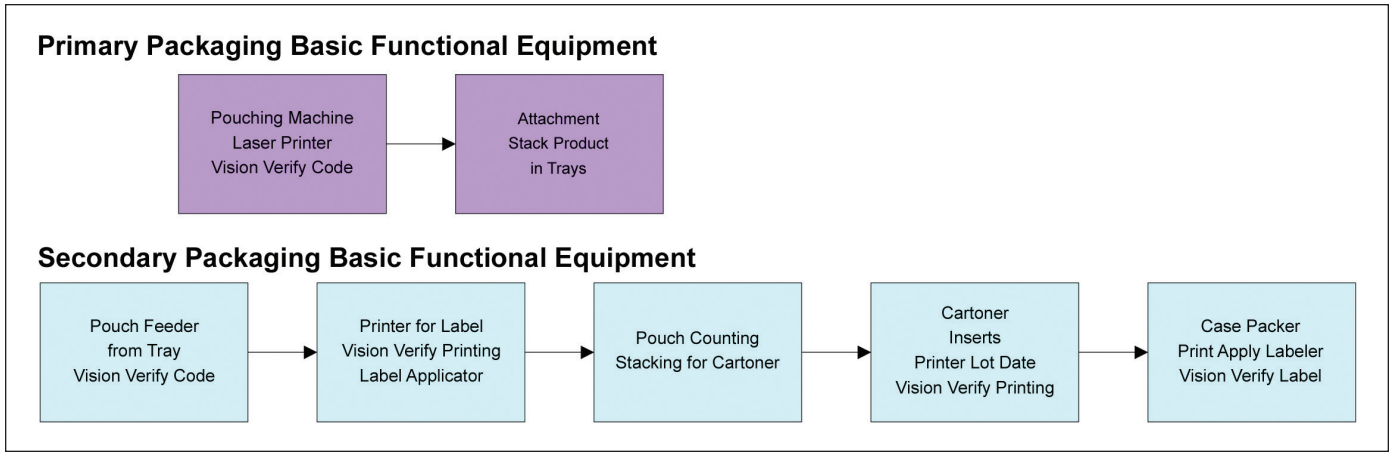

Figure 2. Example two: stackable pouches in a carton.

- Vision system, verify printed code on bottle bottom
- Bottle labeler
- Printer for bottle label
- Vision system, verify printed code
- Accumulation table (increases OEE)
- Cartoner with insert feeder
- Carton lot/date printer
- Vision system, verify printed code
- Case packer
- Print and apply labeler
- Vision system, verify printed code

Overview of Operation

- *The primary packaging* operation is to receive bulk plastic bottles, clean them, print a 2D code on the bottle bottom, verify that code (reject prior to printing), fill the bottle with a liquid, cap the bottle, and bulk store the bottles in large totes. This portion of the operation has a cycle rate of 250 BPM.

- *The secondary packaging* operation is to sort and orientate the filled bottles from the bulk storage containers. The 2D bar code is verified (reject prior to labeling); the label is printed with the lot/date code (and verified) prior to applying to the bottle. An accumulation table is used to increase the uptime of the system. The cartoner adds a wraparound insert as the bottle is loaded; the carton has the lot/date code printed (and verified). The cartons are arranged in a pack pattern, loaded into the case, and then the case label is printed with the lot/date code (and verified) prior to applying it to the case. The input to the labeling system runs at approximately 310 BPM (allows for planned stops for roll change) and the cartoner runs at 300 BPM. This increased speed allows for commodity changes for various SKU changes.

Example Two: Stackable Pouches in a Carton – *Figure 2*

The requirement is for a system that provides a transdermal or thin film filled pouch with the unit of delivery being a carton. The market requirement is for either an Rx or OTC product with a variety of SKUs produced based upon pouch quantity in the carton, product, and country of sale. The primary packaging production speed is 1200 pouches per minute.

Primary Packaging Basic Functional Equipment:

- Pouching machine
- Laser printer for the pouch
- Vision system, verify printed code
- Attachment to stack product into trays

Secondary Packaging Basic Functional Equipment:

- Pouch feeder from tray
- Vision system, verify printed code on pouch
- Printer for label
- Vision system, verify printed code
- Label applicator for pouch
- Pouch counter for cartoner infeed
- Cartoner with insert feeder
- Carton lot/date printer
- Vision system, verify printed code
- Case packer
- Print and apply labeler
- Vision system, verify printed code

Overview of Operation:

- *The primary packaging* operation is to manufacture pouches which require a number of complex roll stock feeding units. This system is very time consuming to changeover for product or format. Startup after a routine stoppage is also time consuming and wastes a substantial number of products before good useable items are produced. Once producing product, it is undesirable to stop the pouching machine. During the manufacturing process, a 2D code is printed on the pouch. The pouches are stacked into a chipboard tray that can be manually handled and stacked on a pallet. This portion of the operation has a cycle rate of 1,200 PPM. This output is used to feed several secondary operations.

- *The secondary packaging* operation feeds the pouches from

the trays into a labeler. The 2D bar code is verified (reject prior to labeling); the label is printed with the lot/date code (and verified) prior to applying it to the pouch. A counting system allows for a variety of put ups into cartons. The cartoner adds a wraparound insert as the pouches are loaded. The carton has the lot/date code printed (and verified). The cartons are arranged in a pack pattern, loaded into the case, and then the case label is printed with the lot/date code (and verified) prior to applying it to the case. The input to the labeling system runs at approximately 150 PPM.

Example Three: Bulky Pouches in a Carton – *Figure 3*

The requirement is for a system that provides a pouch with a medical device in it with the unit of sale being a carton. The market requirement is for an Rx product with a variety of SKUs produced based upon pouch quantity in the carton and country of sale. All of the production of the pouching machine goes through the cartoning machine. Due to the complexity of the product and the sealing requirements of the upstream equipment, it is very undesirable to stop for SKU changes; therefore, an online accumulation system is used between the pouching and cartoning machines. SKU changes (product count and orientation in carton as well as specific country requirements) are made to the cartoner while the pouching machine is running (filling up the buffer); these changes must be made in less than 10 minutes (buffer capacity). The production speed is 200 pouches per minute.

Primary Packaging Basic Functional Equipment

- Pouching machine
- Laser printer for the pouch
- Vision system, verify printed code
- Attachment to count and stack pouches into the accumulation (buffering) system

Secondary Packaging Basic Functional Equipment

- Accumulation (buffering system) for approximately 10 minutes of pouch machine runtime
- Pouch feeder from accumulation system
- Cartoner with insert feeder and quick accurate changeover features
- Carton lot/date printer
- Vision system, verify printed code
- Case packer
- Print and apply labeler
- Vision system, verify printed code

Overview of Operation

- *The primary packaging* operation is to manufacture the pouches filled with the same medical device. A complex and critical pouch sealing is required; therefore, equipment startup is time consuming and wasteful of product. This product is also expensive to rework. Therefore, once producing product it is undesirable to stop the equipment. During the manufacturing process a 2D code is printed on the pouch. The pouches are counted and stacked into an accumulation system that is online with the cartoner. This portion of the operation has a cycle rate of 200 PPM. The output is fed to a single secondary operation.

- *The secondary packaging* operation feeds the pouches from the accumulation system into the cartoner. The cartoner adds a wraparound insert as the pouches are loaded. The carton has the lot/date code printed (and verified). The cartons are arranged in a pack pattern, loaded into the case, and then the case label is printed with the lot/date code (and verified) prior to applying it to the case. The cartoner has a cycle rate in excess of 250 PPM, which will empty the filled buffer before the next SKU change.

Summary

Applying a "Brite Stock" strategy to a pharmaceutical operation may not be as simple as the original "food canning line" defined above. Innovation and ingenuity will be required to develop the proper solution. This strategy has the potential to expand your existing products into new markets (global or private brands), continue to offer lower volume products (profitable) by harmonizing and standardizing packaging, and increase the overall efficiency of producing your product (make more product with the same equipment and labor).

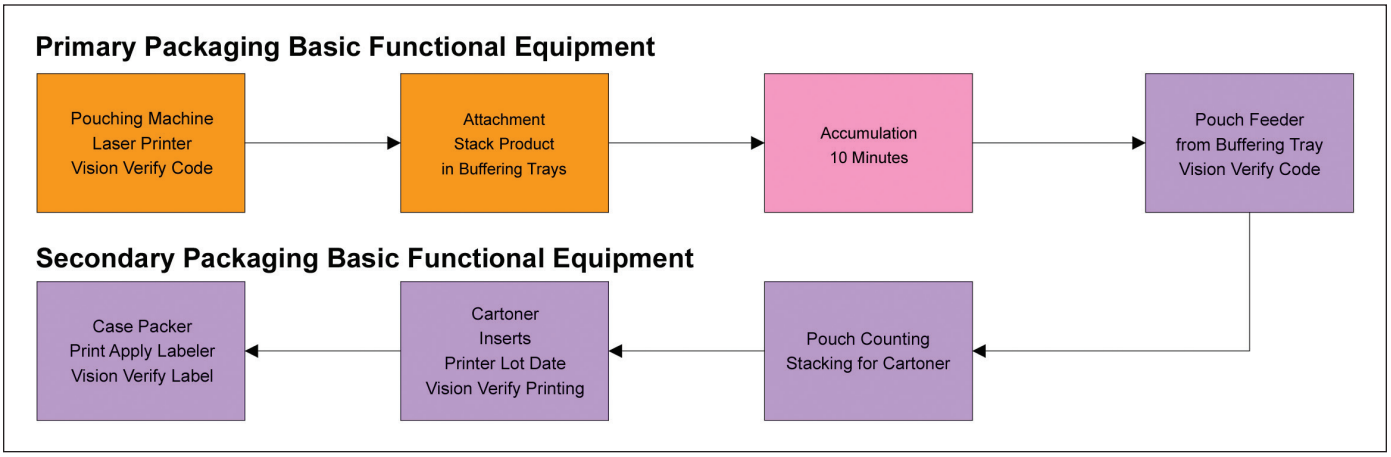

Figure 3. Example three: bulky pouches in a carton.

All of these increase revenue, which is more important than just cutting costs.

About the Author

Mel Bahr attended the University of Minnesota and began his career in designing and manufacturing of packaging machinery as an electrical engineer. He expanded his career to include engineering management and operations. He is the founder of MGS Machine Corporation. MGS has two plant manufacturing campuses in Maple Grove, Minnesota which manufacture a variety of equipment for the secondary packaging industry. One of its main focuses is the pharmaceutical industry. He has been involved in producing more than 40,000 pieces of machinery that have been installed globally. Many of these have been complete end of line systems. He is also named on a number of patents related to equipment design. Bahr is a member of ISPE and currently serves as Chair of the Packaging Community of Practice. He also contributed to the *ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Facilities.* He can be contacted by telephone: +1-763-493-8805 or email: mel.bahr@mgsmachine.com.

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Coding Solutions: An Essential Component for Serialization

by William P. Bonaccorsi

This article presents feedback from some of the leading healthcare companies regarding techniques and provides guidance for selecting proper coding.

Introduction

It appears that significant momentum and consensus is building toward defining requirements for a US-based track-and-trace program.[1] "With the RxTEC Act, pharmaceutical supply chain members are proposing a phased-in approach to track-and-trace with a federal law imposing uniform requirements on all states. The act was developed by the Pharmaceutical Distribution Security Alliance (PDSA), manufacturers, wholesalers, and pharmacy chains joining to offer an alternative model for tracing prescription drug distribution. The bill thus represents a consensus approach from different supply sectors facing different requirements in a track-and-trace scheme."[1] Obviously, there is still plenty of work to do to gain approval from all associated groups, but there is traction toward defining a specific path forward. And although final details of the forthcoming legislation have yet to be fully defined, most field experts agree that, at a minimum, item-level packaging will require serialized "codes" beginning in 2015. More specifically, manufacturers and re-packagers are advised under FDA's guidance, Standards for Securing the Drug Supply Chain – Standardized Numerical Identification (SNI) for Prescription Drug Packages, to create package-level SNIs the SNI is a serialized National Drug Code made up of the NDC and a unique serial number.[2] With pending legislation looming, the thought of implementing a comprehensive track-and-trace serialization program can be daunting.

As a result, many companies in the healthcare industry are already in the process of implementing various components or complete serialization programs. This article examines various pharmaceutical applications and provides guidance for selecting proper coding. It also brings attention to the risks associated with not devoting enough attention and resources to the coding evaluation process. Table A provides guidance for matching coding technologies to common applications and packaging types found in the healthcare industry.

Required implementation of item-level serialization is not until January 2015. This requires the equipment and technology to be validated in 2014, and therefore, needs to be employed and in testing during 2013. How to get started? Figure 1 provides several components included in a comprehensive serialized solution.

Although the various components involved range in technological complexity and level of implementation difficulty, each component is equally critical to the success of an overall serialization program. In other words, the weakest link in the chain will determine overall performance. Data management often attracts the highest level of attention and concern as this is perceived as the most complex part of the program. Less consideration is placed on components such as coding technologies used for printing serialized codes (i.e., data ma-

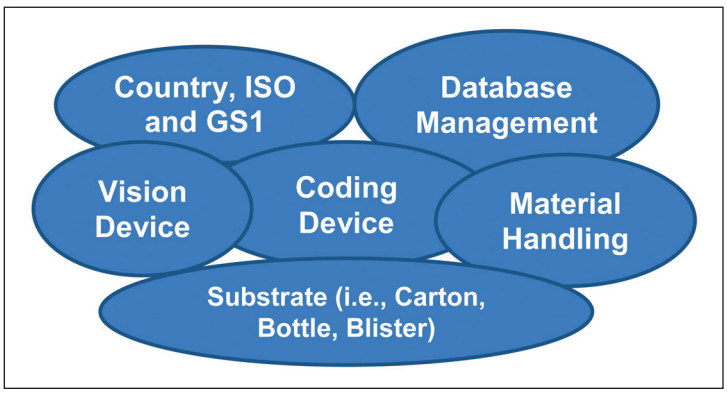

Figure 1. Track-and-trace components.

trix bar codes) onto products. The consequence of this "lack of attention" in this area can result in the broken link that causes a loss of productivity or worse. Although a holistic approach to implementation of a track-and-trace program is important, it is difficult to tackle the entire initiative at once. Many of the leading companies have realized this and are setting priorities for their journey toward a track-and-trace solution. These priorities vary among companies and the following are examples of the various approaches underway:

- Prioritize by application type – if the same application occurs on multiple lines and sites, deciding on the right coding, material handling, and vision aspects can prove to be a productive method.
- Prioritize by selecting one or two track-and-trace components at a time – for example, Step 1 is to equip all relevant production lines with equipment to print serialized 2D data matrix code. Step 2 might be implementing vision devices.
- Emphasize scalability and adaptability – implement a complete program on one production line with high priority on building a system that is scalable and adaptable to multiple (national and global) sites and local requirements.

As mentioned previously, there are aspects associated with the track-and-trace initiatives that are nearly certain to occur, including the need for data matrix codes printed on item-level and lot-level packaging. For this reason, many companies have designated this component of the track-and-trace solution as a higher priority. Regardless of which piece is deemed as highest priority/priorities, it is important that steps toward track-and-trace are currently underway.

Guidelines to Selecting an Effective Coding Solution

An advantage of identifying effective coding solutions for healthcare packaging is that there are common applications among manufacturers, the majority of which have been implemented in production. However, nuances involved in the process prevent a "cookie cutter" approach and require a more scientific method of investigation. Although there are coding and marking experts available to provide guidance, it is important for any organization (Original Equipment Manufacturer (OEM) and end users) to have "internal" knowledge of the variables at play when selecting a coding solution. Understanding these details up front will help when engaging suppliers and exploring the right coding solution to meet your organization's needs.

Factors That Impact the Coding Process

Packaging Substrate

Technological advancements in coding equipment and consumables have resulted in significantly improved versatility, speed, adhesion, and code quality. However, every coding technology has limitations. For example, HDPE, a common material used on plastic tablet bottles, presents a coding challenge for CO2 laser technology. CO2 light waves used in laser passes through the material versus being absorbed and creating a mark with strong contrast. As a result, most untreated HDPE cannot be marked with CO2 laser. Coated cartons, which have generally been deemed a "walk in the park" for laser marking, also necessitate careful evaluation. The reality is that carton composition plays a critical role in marking effectiveness. Cartons vary in coating types, ingredients, and quality. This variation does impact code quality, and in turn, readability. These factors considered, defining carton specifications with your supplier(s) is a critical step. In addition, developing an open relationship between your carton and laser suppliers can be extremely productive, as is sample testing the range of cartons used any time a new carton is introduced. It's not uncommon for a company that has been successfully printing on cartons for years to have a marking issue suddenly arise. Often, the root cause evaluation determines that a new carton or new carton ingredient was introduced. Proactive off-line sampling can pay tremendous dividends. The top laser printer suppliers have facilities to assist in this process, and can conduct print testing that emulates your own operating conditions, including production speeds and message specifications.

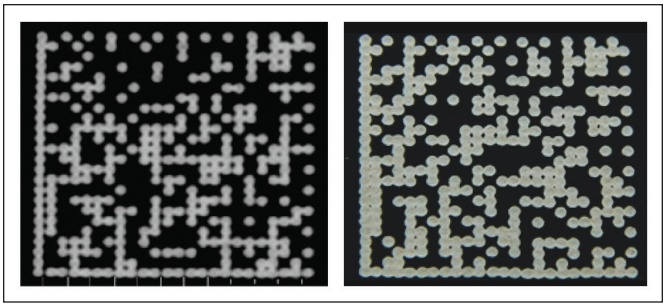

Figure 2. Comparison of 2D codes on different substrates.

Figure 2 shows two similar codes on a like substrate. The 2D code on the right produces a much higher, consistent read rate. This is only discovered through an effective sampling process.

Additional Substrate Related Questions:

- Can the substrate be modified to better interact with the coding device?
- Will the substrate impact code quality (shape, coating type, dyne level)?
- Will subsequent product handling affect substrate and code?

Purpose of Code

There are several drivers involved in coding initiatives. There are legislative, consumer, and internal drivers. Understanding the purpose of the code is critical for scoping in the coding project. This concept may seem elementary, but is often not fully understood at the OEM or end user level(s). There are many resources available that provide guidance for coding requirements, including International Society for Pharmaceutical Engineering (ISPE)[3], Healthcare Distribution Management Association (HDMA)[4], GS-1, Pharmaceutical Distribution Security Alliance (PDSA)[5], and Domino Printing Sciences.

Once the specific drivers and requirements are understood, whether internal, consumer, or legislative, there are industry consultants at key coding companies that can provide additional support in many areas, including sharing of best practices. The deep research and definition provided up front can eliminate unnecessary work and frustration during implementation. Discuss your requirements with your coding supplier to make sure they understand your needs. If they are not familiar with them, it is probably time to select another partner who does.

Additional Purpose of Code Related Questions:

- What information is included in the message?
- With which "standard(s)" must the code comply?
- Does the code need to be permanent or will it be removed?
- Will the printer offer a standard format for my code re-

Technology	Overview	Benefits
CO_2 Laser 	Marking is achieved by using a laser system to etch or vaporize the surface layer of the material leaving an indelible permanent mark. Domino has developed scribing laser coders that can print text, graphics and variable data onto a variety of substrates including plastic, glass, paper, and cartons. As there are no inks or fluids used, laser systems are environmentally friendly and very cost-efficient systems for your coding requirements.	- Superior letter-quality print - High reliability due to few moving parts and proven CO_2 laser system technology - Consistent quality on stationary and high-speed lines - Print in any orientation - Unlimited graphical capabilities - Minimal maintenance, making laser coding environmentally friendly
Continuous Ink Jet (CIJ) 	Continuous Ink Jet technology uses electrically charged ink droplets to create high quality characters based on a grid formation. Using a wide range of ink jet inks that have been developed for specific industry applications, that can print **text, graphics, bar codes, and variable data,** such as product identification directly onto substrates including: blass, plastic, rubber, paper.	- High speed printing that keeps up with the fastest production environments - Non-contact printing that enables uneven and flexible surfaces to be coded - Wide array of ink formulations that adhere to a wide array of substrates - Range of ink colors including opaques and UV invisible
Thermal Ink Jet (TIJ) 	Thermal Ink Jet printers use print cartridges with a series of tiny electrically heated chambers constructed by photolithography. To produce an image, the printer runs a pulse of current through the heating elements causing a steam explosion in the chamber to form a vapor bubble, which propels a droplet of ink out of the nozzle placing them precisely on a surface to form text, barcodes, or graphics onto the substrate. Use of fast drying inks for coding non-porous materials such as: paper, coated carton, plastics.	- High quality (up to 600 dpi) – providing superb image and text quality including 2D data matrix codes - Ease of use – requiring no special training to operate and maintain. Cartridges are clean, and easy to install - Reliability – Thermal Ink Jet solutions provide unrivalled reliability, resulting in minimum maintenance - change of cartridge changes whole printhead without requiring a service engineer - Flexibility – provides the ability to run multiple printheads, the ability to print in black or color
Thermal Transfer Over Print (TTO) 	Printing is achieved by placing a thermal ribbon between a heated printhead and the substrate to be marked. With the three items in contact, the printhead is moved over the length of both the ribbon and the substrate. Heat from the printhead is passed through the ribbon, causing ink to melt and be released from its underside. The ink adheres to the substrate and then cools rapidly, resulting in a permanent print.	- High speed printing for flexible packaging - Clean technology that can be used in all production environments - Extremely high print quality (300 dpi) allowing high definition bar codes and graphics - Large print area allows pack printing as well as coding in the same operation - Reliable and simple to use - Large ribbon range offers a wide selection of print properties including resistance to scratch, heat and solvents - Monochrome printing in a wide range of colors - Ribbon control technology maximizes uptime
Print and Apply Labeling Machine (PALM) 	Print and Apply Labeling machine (PALM) is designed to be used online and automatically print and apply labels to products as they move along a production line or within a warehouse or logistics facility. The print engine uses a thermal print head to create the image on the label, either directly (Direct Thermal) or by transferring ink from a ribbon onto the label material (Thermal Transfer). The printers are capable of printing text, including dates, serial numbers, use by information, as well as logos, graphics, and all types of barcodes.	- High speed labeling for delicate and rigid surfaces - Primary, secondary and pallet coding solutions - Fully modular to meet varying pallet labeling requirements - High resolution printing ensures supply chain compliance - Seamless integration into production lines - Simple label selection ensures operator independence

Table A. Coding and labeling technology overview.

quirements, i.e., a company unique off-set expiration date code?

Data Management

This article won't attempt to tackle how to implement a data management system; however, it's critical that coding technology is fully compatible with the data management system. Answers to some basic questions can provide the best chances for this situation. How will messages be entered into the coding system? Will they be loaded manually by the operator, automatically downloaded from an ERP system, or via other means? Is there a plan to initially enter messages manually and move to a more automated process down the road?

Integrators will often create drivers to create the link from the data management to printer process; however, these drivers are sometimes written without the complete range of printer capabilities. There have been situations where drivers were rewritten to add the full capability of the printer, and this modification opened functionality that resulted in significant efficiency improvement. Fully exploring short-term and long-term communication and application requirements combined with a deeper understanding of printer capabilities positions teams best for success.

Additional Database Related Questions:

- Is the coder required to provide feedback to data source or host equipment?
- How easy is the coder to integrate (i.e., what protocol is used)?
- Has the integrator built a fully capable driver for the coding device or is it limited?

Technology Match: The following identifies key applications and substrates used in the pharmaceutical segment. The chart is designed to provide guidance in matching the best coding technology with the application.
(This chart should be referred to as a general reference. Print sample testing is always recommended).

Packaging Type and Substrate	CO_2 Laser	CIJ	TIJ	TTO	DOD	P&A Labeler	Comments	Challenges
Blister Lid Stock – 2D Code	✸	✸	✸	✸	✸	✸	CIJ is the best option. DOD can be used to print bar code and add branding	Important to have designated
HDPE Bottle	✸	✸	✸	✸	✸	✸	CIJ is best option. Tight control on vibration and proper lighting for vision is critical.	Print quality consistency can be impacted by production-line vibration. Sample print testing is important.
Pet Bottle	✸	✸	✸	✸	✸	✸	Laser works well at even at high-speeds. Bottles with flat walls and larger print area are easier to code.	Printing on a curved surface presents a challenge for CJI.
Carton – Human Read	✸	✸	✸	✸	✸	✸	Laser is preferred. Proper extraction required.	Not all cartons are equal. Be selective and run print samples.
Carton	✸	✸	✸	✸	✸	✸	High quality stock results in better bar code grades at low laser power. Lower quality stock has inverse results.	Requires a TIJ system that is compatible with solvent based inks.
Ampules	✸	✸	✸	✸	✸	✸	CIJ is often the best option. Provides invisible ink options.	Beware of ink adhesion with CIJ. Chemicals involved in the filing and mfg process may remove codes.
Syringes	✸	✸	✸	✸	✸	✸	CIJ works well for printing Human Readable codes.	Printing measurement marks is difficult, but has been done with CIJ.
Pouches-Paper	✸	✸	✸	✸	✸	✸	CIJ, Laser and G-Series are good options.	Consistent print quality for CIJ bar codes

✸ Best Solution ✸ Possible Solution ✸ Not Recommended

- Is there a programming software developer's kit available with the coding device?
- How is "rejected" product identified and managed?

Hardware Implementation

Adding serialized coding capabilities to an existing production line (versus adding an entirely new production line) is common. This allows the manufacturer to leverage existing assets to the fullest. Although there are certain advantages to this scenario, a "retrofit" solution requires a unique set of questions to be addressed. For example, how much vibration is present in the area the coding will take place, and does the printer supplier provide vibration-related specifications? These issues can certainly be addressed proactively and efficiently, but understanding the situation in advance is critical. Ownership of various aspects of the implementation is also best determined prior to implementation. Definition of who will be responsible for the integrating the laser into the vision system is a key consideration when outlining the implementation plans leading into the project. With respect to vibration, does the coding company have a program to determine what the impact will be on production? Some do and some don't.

Additional Hardware Implementation Related Questions:

- Will the coding solution be installed in as new equipment or retrofit?
- Who will handle integration?
- What speeds, pitch, product control is required in order to meet production goals?
- How is "rejected product" removed from production?

In summary, implementing a track-and-trace solution can take years and can be overwhelming. However, breaking down the program into components and setting priorities facilitates a manageable and productive process. It's critical that all components of the program are given thorough investigation. Partnering not only with OEMs and integrators, but with strong coding companies is crucial. If you haven't already, the time to start is now.

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Bill Bonaccorsi is the Director of Marketing and Senior Team Manager at Domino North America. Bonaccorsi is based in the Chicago area (Gurnee, IL) at Domino's N.A. Corporate Office. He earned a Bachelor's degree from DePauw University as well as an MBA in international business from Saint Louis University's Boeing Institute. Bonaccoris's 21-year career in the packaging and printing industries has been devoted to helping companies define and reach their goals in product handling and enhancement with marking and coding throughout. During his time at Domino North America, he has held various management positions that include North American-wide Product Manager and Manager of the National Accounts program for some of the largest producers on the continent. He lives in the Chicago area with his wife, son, and daughter. He can be contacted by email: bill.bonaccorsi@domino-na.com.

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Calcium Alginate Microparticles As a Non-Condensing DNA Delivery and Transfection System for Macrophages

by Mansoor Amiji, PhD and Shardool Jain

Introduction

Inflammation is a defense mechanism adopted by the body in response to the variety of stimuli, including pathogens, injury, and autoimmune responses.[1,2] The primary functions of macrophages in inflammation include antigen presentation, phagocytosis, and modulation of the immune response through production of various cytokines and growth factors.[1,3] In case of inflammation caused by exposure to pathogens, the process of phagocytosis is mediated by specific receptors expressed on the surface of macrophages and other immune cells. Additionally, the attachment of antibodies and complement fragments, by a process called *opsonization*, to the microbes greatly enhances the phagocytic ability of macrophages.[1] The classical macrophage activation state is characterized by killing of intracellular pathogens and tumor resistance and can be induced by interferon-γ(IFN-γ) alone or in conjunction with microbial products such as Lipopolysaccharide (LPS) or cytokine, such as Tumor-Necrosis Factor alpha (TNF-α). The alternative state can be induced by cytokines, such as IL-4 and IL-13, and mainly results in anti-inflammatory responses and resolution of injury. Activation of macrophage via the classical pathway is marked by high antigen presentation capacity, high IL-12, IL-23, nitric oxide (NO), and reactive oxygen species production. On the other hand, alternate activation stage is characterized by an increase in the IL-10 and IL-1ra cytokines, mannose and scavenger receptors, arginase production, and decrease in the production of inducible nitric oxide synthase enzyme.[4-6]

Therefore, it is evident that macrophage activation will have a significant impact on the progression of pathologic conditions, such as growth and spread of malignant tumors, sepsis, chronic inflammation in rheumatoid arthritis, lysosomal storage disease, atherosclerosis, and major infections including HIV/AIDS and tuberculosis. Therefore, development of therapeutic delivery strategies aimed at macrophage-specific processes has potential for treating a variety of conditions.

Alginate is a random block copolymer made up of (1 → 4) linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues and occurs in nature as a structural component of marine brown algae (*Phaeophyceae*), where it comprises 40% of the dry matter. It also occurs as a component of capsular polysaccharide in soil bacteria.[7] Alginate is considered by the United States Food and Drug Administration (US FDA) as a *"generally regarded as safe"* or GRAS material and has found applications in various industries including food, pharmaceutical, and cosmetic industries.[8] Many of the applications of alginate rely on the ability of the polymer to form cross-linked hydrogels in the presence of di- and trivalent cations, such as calcium ions (Ca^{2+}).

In order to form Ca^{2+} ions cross-linked alginate particles, the electrolyte has to be introduced in a very controlled fashion using the diffusion (external gelation) method. In this process, Ca^{2+} ions are allowed to diffuse from a large outer reservoir into alginate solution. This technique exhibits rapid gelation kinetics and is suitable for immobilization purposes where each drop of alginate forms a single gel bead with entrapped bioactive agent. The formulation parameters, such as sodium alginate molecular weight and concentration, stirring

conditions, and rate of Ca^{2+} ions addition can be further optimized to form particles in the nanometer range.[10]

Ca^{2+}-alginate hydrogel particles also have been used as a non-viral gene delivery system because of their biocompatibility and ability to protect the plasmid DNA from enzymatic and pH-induced degradation. Douglas *et al*[11] reported that inclusion of alginate to chitosan-based nanoparticles improved the transfection efficiency of encapsulated plasmid DNA by four-fold as compared with control. Also, it was shown via cell viability assay, gel-retardation assay, and transfection studies that an alginate-chitosan/DNA based system exhibited lower toxicity, protected the DNA from DNase I degradation, which was not achieved by chitosan based nanoparticles alone, and improved the transfection efficiency in the 293T cell. Additionally, at 48 hours post-administration, this group was able to show that the transfection efficiency of alginate-chitosan nanoparticles was as high as Lipofectamine™. In the same context, Jiang, *et al*[12] aimed at improving the transfection efficiency and lower the cytotoxicity of poly(ethyleneimine) (PEI)/plasmid DNA complex by coating with anionic biodegradable polymer, alginate. The group reported that coating with alginate improved the transfection efficiency to the C3 cells by 10-30 folds in comparison to the non-coated PEI/DNA complex. In addition, the alginate/PEI/DNA complex showed a reduced erythrocyte aggregation and lower cytotoxicity profile to C3 cells in comparison to PEI/DNA complex alone.

Previously, non-condensing polymeric systems that can physically encapsulate plasmid DNA, such as type B gelatin, have been shown to afford more efficient and sustained transgene expression relative to cationic lipids and polymers.[13,14] Type B gelatin-based nanoparticles have been utilized for systemic and oral gene therapy using a variety of reporter and therapeutic plasmid DNA. We have postulated that the non-condensing system can retain the supercoiled structure of the plasmid DNA and allows for more efficient nuclear entry in non-dividing cells. Most importantly, these constructs are significantly less toxic to cells as compared to cationic lipid and polymeric transfection reagents. To further the application of non-condensing polymers for gene therapy, in this study we have developed Ca^{2+} alginate microparticles with encapsulated reporter plasmid DNA expressing GFP (i.e., EGFP-N1) and have evaluated the delivery efficiency and transgene expression using J774A.1 adherent macrophage cell line.

Materials and Methods

Materials

High viscosity grade sodium alginate was purchased from Protanal (Norway) and calcium chloride dihydrate was purchased from Sigma Aldrich (St. Louis, Missouri, USA), and were dissolved in de-ionized distilled water. Plasmid DNA expressing enhanced green fluorescence protein (i.e., EGFP-N1, 4.7 kb) was purchased from Clontech and amplified and purified by Elim Biopharmaceuticals (Hayward, Californiam USA). Rhodamine-B labeled dextran (Mol Wt. 70 kDa), the supercoiled DNA ladder (2-16 kb), were purchased from Invitrogen (Carlsbad, California, USA). Alginate lyase enzyme was purchased from Sigma Aldrich (St. Louis, Missouri, USA). Pluronics® F-108 was purchased from BASF chemicals (Mount Olive, New Jersey, USA).

Preparation of DNA-Encapsulated Alginate Microparticles

A stock solution with 1% (w/v) medium viscosity sodium alginate (Protanal® LF 20/200) solution was prepared. Similarly, a stock solution of 0.5M calcium chloride dihydrate (M.W. 147.02) (Fisher) was made. A 3 ml of sodium-alginate solution was filled into a 5 ml syringe fitted with a 30G1/2-inch needle. The alginate solution was added drop-wise into calcium chloride solution (27 ml) while stirring at 2,400 rpm using a 4-blade lab stirrer. Furthermore, these formulations were stabilized by adding Pluronics® F-108 (0.1% w/w of alginate) to the sodium-alginate solution prior to cross-linking with calcium. Pluronics® F-108 (PEO) is a copolymer which is made up of 56 residues of propylene oxide (PO) and 122 residues of ethylene oxide (EO). The resulting particle suspension was centrifuged at 10,000 rpm for 35 minutes. The pellet was washed twice with deionized water. 5 ml of de-ionized water was added to the pellet and to the resulting suspension, 0.1% (w/w) mannitol (Acros Organics) was added as a cryoprotectant. The sample was then freeze-dried at -80°C and later lyophilized to get the particle cake.

Characterization of the Microparticle Formulations

Particle Size, Surface Charge, and Morphological Analyses: The particle size and surface charge (zeta potential) of the blank and DNA incorporated particles were measured using the Coulter Counter Coulter Particle Size Analyzer at Massachusetts Institute of Technology (MIT), Boston, Massachusetts, USA. The sample obtained after lyophilizing the freeze-dried formulation was analyzed by Scanning Electron Microscope (SEM) for surface morphology and size. The sample was mounted on an aluminum sample mount and sputter-coated with a gold-palladium alloy to minimize surface charging. SEM was performed using Hitachi Instruments' S-4800 environmental scanning electron microscope (San Jose, California, USA) at an accelerating voltage of 3 kV.

Determination of Plasmid DNA Loading and Stability: 20 µg of EGFP-N1 plasmid DNA dissolved in aqueous solution was added to alginate solution prior to cross-linking with calcium. Plasmid DNA encapsulation efficiency was measured using PicoGreen® dsDNA fluorescence assay (Invitrogen) following digestion of the polymer matrix of the microspheres with the enzyme alginate lyase (1 mg/ml) for 24 hours in phosphate-buffered saline (PBS, pH 7.4) at 37°C. Following centrifugation at 13,000 rpm for 30 minutes, the supernatant was collected and the released DNA was quantified using PicoGreen® fluorescence reagent with a Bio-Tek Synergy® HT (Winooski, Vermont, USA) microplate reader. The stability of encapsulated plasmid DNA, due to processing conditions, was assessed using agarose gel electrophoresis. Following extraction of the DNA from the freeze-dried sample of

nanoparticles using 1mg/ml alginate lyase and precipitation with ethanol, a sample was run on 1.2% pre-casted ethidium bromide-stained agarose gels (Invitrogen). Control lanes had 2-16 kb DNA ladder and the naked plasmid DNA sample. Following the agarose gel electrophoresis, the ethidium bromide labeled DNA bands were visualized with a Kodak FX imager (Carestream, Rochester, New York,USA).

Macrophage-Specific Uptake and Cytotoxicity Analyses

Cell Culture Conditions: J774A.1 adherent murine macrophage cell line was obtained from American Type Culture Collection (ATCC Manassas, Virginia, USA) and grown in T75 culture flask at 37°C and 5% CO2 using Dulbecco's modified Eagle medium (DMEM Cellgro®, Mediatech Inc., Manassas, Virginia, USA) modified with 10% fetal bovine serum (FBS Gemini Bio-Products, West Sacramento, California, USA) and combination penicillin/streptomycin antibiotics. Cells were allowed to divide until they reached desired density. Cell count was measured by placing 20 µL of the cell suspension mixture on a heamocytometer slide and the cell viability studies were performed using Trypan blue dye exclusion assay.

Macrophage-Specific Particle Uptake and Cellular Internalization: In order to evaluate the uptake and cellular internalization of calcium-alginate microspheres, rhodamine-B dextran was encapsulated at 1% (w/w) concentration using a similar procedure as described above for plasmid DNA. Particles were incubated with 20,000 J774A.1 macrophages, plated on glass cover-slips, in a 6-well microplate in the presence of DMEM supplemented with 10% FBS. The cells were treated with microspheres in a time-dependent fashion from 1-6 hours; however, only 6 hour time point has been shown here. After particle treatment, the cells were placed on the glass cover slips, placed in the 6-well microplate were removed and rinsed with sterile PBS, and inverted on a clean slide for qualitative analysis of uptake and cellular internalization using fluorescence microscopy. Bright field and fluorescence images were acquired with a BX51-TRF Olympus (Center Valley, Pennsylvania, USA) inverted microscope at 20× and 40× original magnifications.

Cytotoxicity Analysis Using MTT Reagent: Blank and plasmid DNA-encapsulated alginate particles were incubated with 10,000 J774A.1 macrophages in 96-well microplates for cytoxicity analysis in the presence of DMEM supplemented with 10% FBS conditions. (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazole) reagent (MTT Promega, Madison, Wisconsin, USA) that is converted to water-soluble formazan derivative by viable cells was used to assess cytotoxicity of the formulations. Untreated cells were used as negative control, while poly(ethyleneimine) (PEI; Mol. wt. 10 kDa), a known cytotoxic cationic polymer at a concentration of (1 mg/ml), was used as a positive control. A known amount of micro-particles sample with and without encapsulated plasmid DNA (20 µg) were suspended in 200 µL of culture media and incubated with the cells for 6 hours. Following a washing step with sterile PBS, the wells were treated with MTT reagent and the stop mix is then added to the culture wells to solubilize the formazan product, and the absorbance of the chromogenic formazan product in viable cells was measured at 570 nm BioTek Synergy HT microplate reader. Percent cell viability was calculated from the absorbance values relative to those of untreated cells. The samples were tested with n=8 replicates.

EGFP-N1 Plasmid DNA Transfection Studies

Calcium alginate microspheres with encapsulated plasmid DNA expressing reporter GFP (i.e., EGFP-N1) were added to J774A.1 macrophages in a 6-well micro-plate, in the presence of DMEM supplemented with 10% FBS, at a dose equivalent to 20 µg of DNA per 200,000 cells. Naked plasmid DNA and DNA-complexed with the cationic lipid transfection reagent Lipofectin® (Invitrogen, Carlsbad, California, USA) were used as controls. Following 6 hours of incubation, the wells were rinsed with sterile PBS to remove excess particles and 2 mL of FBS supplemented DMEM was added. Periodically, starting from 24 hours to 96 hours post-administration, quantitative analysis of transgene expression was carried out with a GFP-specific enzyme-linked immunosorbent assay (ELISA). Transfected cells were harvested, lysed, and the cell extract was used for determination of GFP concentrations relative to the total intracellular protein concentration obtained using a BCA Assay (Thermo Scientific-Pierce, Rockford, Illinois, USA). A 96-well microplate was coated with 100 µL of anti-GFP mouse monoclonal antibody (Novus Biologicals, Littleton, Colorado, USA) diluted at a concentration of 1:2400 and incubated for 2 hours at 25°C. The antibody-coated microplate was then washed 5-times with PBS-T washing buffer (Sigma-Aldrich, St. Louis, Missouri, USA) and then blocked with 200 µL of blocking buffer (Thermo Scientific-Pierce, Rockford, Illinois, USA) for 2 hours at room temperature. The microplate was again washed 5 times and 100 µL of cell lysate was added and incubated at 4°C overnight. Following extensive rinsing with the washing buffer, 100 µL polyclonal secondary antibody conjugated to alkaline phosphatase (Novus Biologicals, Littleton, Colorado, USA) was added and incubated for 1 hour at room temperature. Lastly, 100 µL of the substrate was added to the wells and the chromogen was measured at 409 nm using the microplate reader. A calibration curve was constructed using GFP (BioVision, Mountain View, California, USA) and the levels of transfected GFP in macrophages were calculated as ng per mg of total cellular protein.

Qualitative analysis of GFP expression as a function of time after incubation of J774A.1 macrophages with EGFP-N1 plasmid DNA-encapsulated alginate particles was determined by fluorescence microscopy. Naked plasmid DNA and DNA-complexed with Lipofectin® were used as controls, Followed by treatment with 20 µg equivalent dose of DNA per 200,000 cells for 6 hours in a 6-well microplate, in the presence of DMEM supplemented with 10% FBS, having glass cover slips in each well, and the cells were incubated at 37°C. At pre-determined time intervals from 24 hours to 96 hours post-treatment, the cover slips were removed, rinsed with

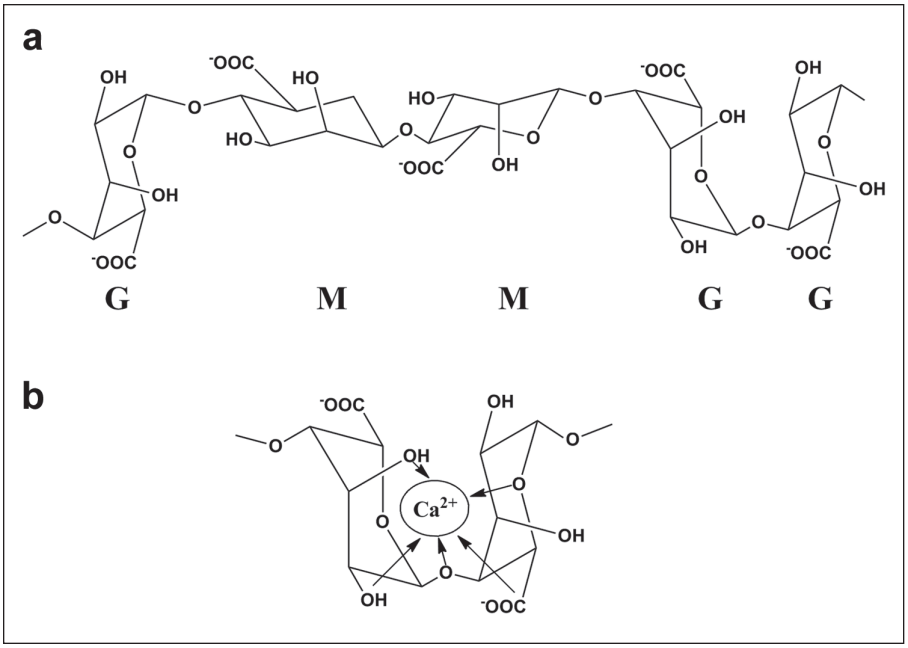

Figure 1. (a) The chemical structure of alginate showing two repeating monomer units – mannuronic acid (M) and guluronic acid (G) and (b) ionic gelation with divalent cations, such as calcium ions, leads to the formation of "egg box" structure.

sterile PBS, and placed on a glass slide. GFP expression in the cells was visualized by fluorescence microscopy using an inverted Olympus microscope.

Statistical Data Analysis

Statistical significance of results was determined using one-way ANOVA and Tukey's Multiple Comparison Test with a 95% confidence interval ($p < 0.05$).

Results

Preparations and Characterization of Calcium Alginate Microparticles

As a GRAS material, alginate has been used in a variety of applications. In this study, we have prepared Ca^{2+} ion cross-linked alginate microparticles for macrophage-specific gene delivery and transfection. Figure 1 shows the chemical structure of the repeat G and M units of alginate, the "egg box" model, that is used to describe the Ca^{2+} ion cross-linked alginate matrix.

Table A shows the particle size and surface charge of both the blank and DNA encapsulated optimized calcium alginate microparticles modified with 0.1% (w/w) F-108 Pluronics®. The particle size of the optimized DNA encapsulated formulation was found to be ~800 nm and surface charge was found to be on average -13.5 mV, whereas the particle size of the blank formulation was ~1 µm and the surface charge was -8.6 mV. Furthermore, the SEM results in Figure 2 confirmed that the optimized DNA-loaded formulation was found to be smooth and spherical in shape with an average particle size of about 1 µm.

Figure 3 shows the stability of encapsulated plasmid DNA due to processing conditions using agarose gel electrophoresis. Lane 1 is 2-16 kb super-coiled double stranded DNA ladder, lane 2 is precipitated naked EGFP-N1 plasmid DNA showing open and circular bands, lane 3 shows the plasmid EGFP-N1 DNA extracted from the supernatant of calcium-alginate microspheres treated with 1mg/ml of alginate lyase for 24 hours at 37°C. Lane 4 shows the pellet obtained after centrifuging the particles treated with alginate lyase. As evident, no plasmid DNA bands were observed in this lane indicating that alginate lyase treatment for 24 hours was sufficient enough to completely degrade the polymer and as a result, the total amount of encapsulated plasmid DNA was released and collected in the supernatant. Overall, these results show that the plasmid DNA can be efficiently protected in the micro-particle matrix.

In addition, the plasmid DNA loading studies using pico-green analysis revealed that the plasmid loading efficiency was around 65%.

Microparticle Uptake and Cytotoxicity in Macrophages

Figure 4 represents the fluorescence images obtained for control (untreated cells) and rhodamine-labeled micro-particles at 20× and 40× magnifications. The studies were conducted in a time-dependent fashion; however, the fluorescence images for only a 6 hour time point have been shown here as appre-

Formulation	Hydrodynamic Diameter (µm)	Zeta Potential (mV)
Blank PEO-Modified Alginate Microparticles	1.02 ±0.23*	-8.60 ±1.60
Plasmid DNA-Encapsulated PEO-Modified Alginate Microparticles	0.87 ± .07	-13.5 ±2.30
*Mean ± S.D. (n =3)		

Table A. Particle size and surface charge analyses of blank and plasmid DNA-encapsulated calcium ion-crosslinked poly(ethylene glycol) (PEO)-modified alginate microspheres.

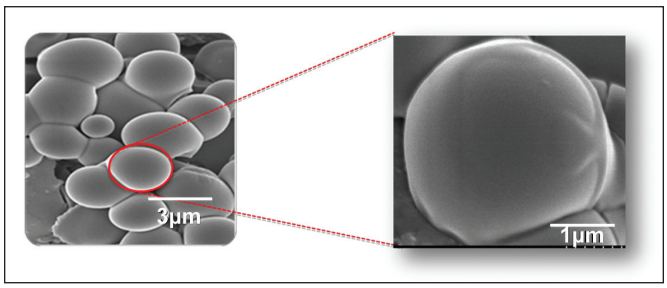

Figure 2. Scanning electron microscopy image shows spherical uniformly-sized plasmid DNA-encapsulated calcium alginate microspheres. Higher magnification image of one of the microspheres shows smooth surface morphology.

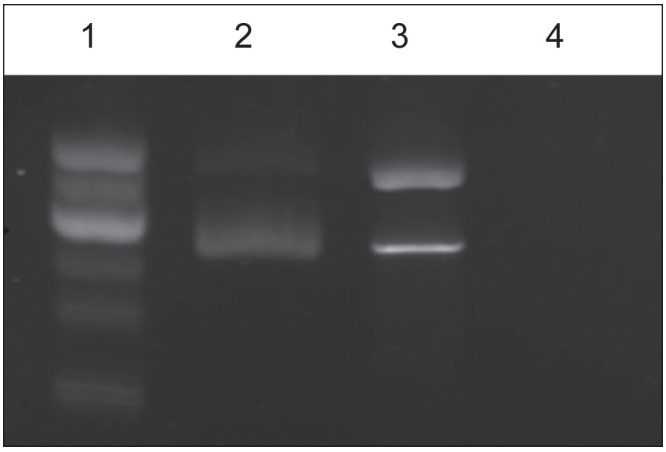

Figure 3. Evaluation of plasmid DNA stability by agarose gel electrophoresis. Lane 1 is 2-16 kB DNA ladder, lane 2 is naked EGFP-N1 plasmid DNA after precipitation showing two bands corresponding to open circular and supercoiled DNA, lane 3 is EGFP-N1 plasmid DNA extracted from the microsphere formulation after incubation with 1 mg/ml alginate lyase for 24 hours, and lane 4 is the pellet obtained after centrifuging the formulation treated with 1 mg/ml alginate lyase.

ciable amount of signal was observed only at this point. The particles were suspended in the complete DMEM media and incubated with the cells for 6 hours and subsequently cells were viewed under fluorescence microscope. These images confirmed that alginate based microspheres were efficiently phagocytosed by the J774A.1 macrophages at 6 hours post-administration. Based on this data, it was decided that for subsequent toxicity and GFP transfection analysis, particles will be incubated with the cells for 6 hours.

In order to assess potential cytotoxicity, if any, with the control and EGFP-N1 plasmid DNA-encapsulated alginate particles, the formulations were incubated with J774A.1 macrophages. In viable cells, the enzymes convert the yellow MTT reagent, in the presence of phenazine methosulfate, to a purple-colored formazan product that has an absorbance maximum at 570 nm. The cell viability results, as shown in Figure 5, confirm that neither the blank nor DNA-loaded formulations induced any significant cytotoxicity. The cell viability was maintained at approximately 100% in both cases. In comparison, PEI-treated cells, at a concentration of 1 mg/ml, caused significant cell cytotoxicity and cell viability was significantly reduced to about 35% after 6 hours of incubation.

Quantitative and Qualitative Transfection Analyses

A GFP-specific ELISA (Figure 6) was used for quantitative determination of the transgene expression in J774A.1 macrophages upon treatment with control and DNA-loaded calcium-alginate microparticles. The results show the intracellular GFP per total protein concentrations as a function of time ranging from 24 hours to 96 hours post-administration. On average, highest GFP expression (i.e., 0.65 ng/mg) was observed at 24 hours post-administration. In comparison, Lipofectin® and naked plasmid showed on average transgene

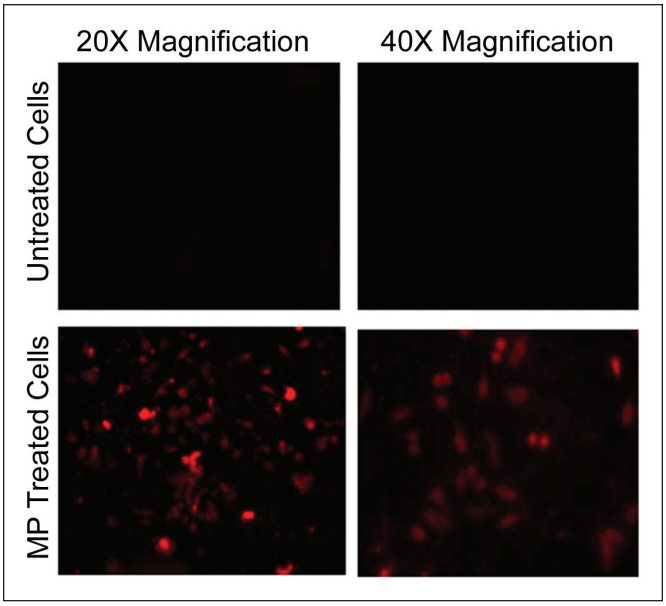

Figure 4. Cellular uptake and intracellular localization of rhodamine-labeled calcium alginate microsphere in J774A-1 macrophages. Top panel images are of untreated cells at 20× and at 40× magnification, whereas bottom panel images are of cells treated with rhodamine-labeled microspheres at 20× magnification and at 40× magnification.

expression of 0.41 ng/mg ($p < 0.001$) and 0.05 ng/mg ($p < 0.0001$), respectively, at this time point. For the subsequent time points, the GFP levels still remained significantly higher in the calcium-alginate microsphere treatment group as compared to positive controls including Lipofectin® and naked plasmid DNA.

Figure 7 shows the qualitative GFP expression analysis using fluorescence microscopy images of J774A.1 macrophages transfected with EGFP-N1 plasmid DNA in the control and alginate microparticle formulations. The GFP expression

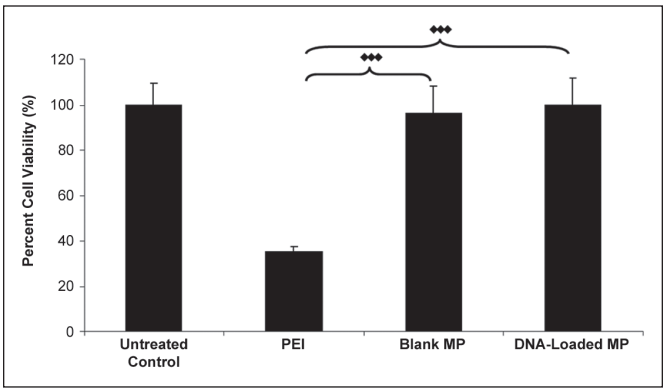

Figure 5. Cytotoxicity analysis of calcium alginate microspheres in J774A-1 macrophages evaluated by MTT (formazan) assay. The cytotoxicity of the plasmid DNA loaded formulation in macrophages was compared to untreated cells. Poly(ethyleneimine) (PEI, Mol. wt. 10 kDa) served as a positive control. The cell viability of the / untreated cells was considered 100% and the values obtained in the rest of the treatment groups were normalized to control values and presented as percent viability. The values reported are mean ± SD. ($n = 8$). Statistical significance of results was determined using one-way ANOVA and Tukey's Multiple Comparison Test with a 95% confidence interval ($p < 0.05$).

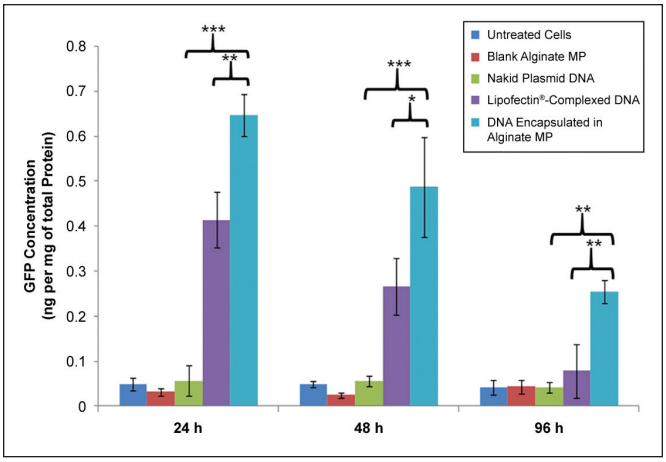

Figure 6. Quantitative evaluations of EGFP-N1 plasmid DNA transfection using green fluorescent protein (GFP)-specific ELISA in J774A-1 macrophage cells after 24 hours, 48 hours, and 96 hours post-transfection with control and DNA-encapsulated calcium alginate microparticle formulations. The plasmid DNA dose was maintained constant at 20 μg per 200,000 cells. The amount of GFP is expressed in (ng) per mg of total cell protein, which was measured using the BCA assay. The values are reported are mean $\pm$SD (n = 3). Statistical significance of results was determined using one-way ANOVA and Tukey's Multiple Comparison Test with a 95% confidence interval ($p < 0.05$).

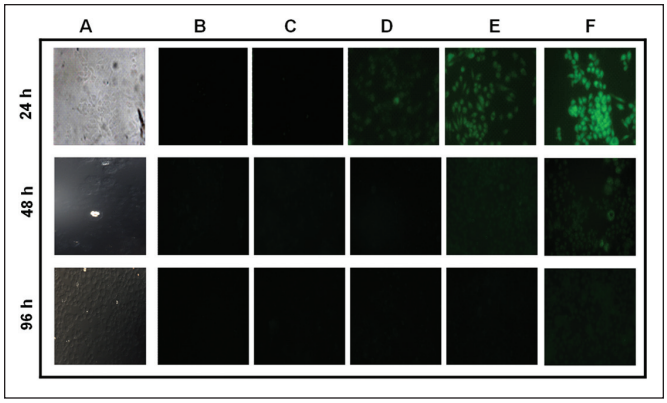

Figure 7. Qualitative evaluation of EGFP-N1 plasmid DNA transfection in J774A-1 macrophage cells after 24 hours, 48 hours, and 96 hours post-transfection with control and DNA-encapsulated calcium alginate microparticle formulations. Differential interference contrast (DIC) images of treated cells (A), and fluorescence images of untreated cells (B), and cells treated with blank microspheres (C), naked EGFP-N1 plasmid DNA (D), EGFP-N1 plasmid DNA complexed with Lipofectin® (E), and EGFP-N1 plasmid DNA encapsulated in calcium alginate microspheres. The plasmid DNA dose was maintained constant at 20 μg per 200,000 cells. All of the images were acquired at 40× original magnification.

was evident in both the Lipofectin® and alginate formulation was evident by 24 hours of particle administration. In addition, much lower fluorescence intensity also was observed in the naked plasmid treatment group. The same trend was observed at 48 hours, where the Lipofectin® and formulation treated groups again showed significant fluorescence intensity. However, at 96 hours of particle administration, the signal intensity from the alginate particles treated group was much higher as compared to Lipofectin®. The signal intensity for the naked plasmid DNA dropped significantly from 24 hours onward. These results indicated that DNA-loaded calcium-alginate particles can afford higher transgene expression for up to 4 days post-transfection.

> "These results provide encouraging evidence for development of a macrophage-targeted anti-inflammatory gene delivery system with potential to treat many acute and chronic debilitating diseases."

Discussion

Gene therapy has become an exciting prospect for the treatment of the inflammatory diseases as the traditional methods lack the ability to efficiently deliver proteins and nucleic acids, especially in case of chronic inflammation where therapeutic level of the drug needs to be maintained for an extensive period of time.[15,16] However, for effective gene delivery the payload needs to be protected from the intracellular (endosomes or phago/lysosome compartment of cells) and extracellular (serum proteins/enzymes) barriers. Therefore, researchers have utilized both viral and non-viral vectors to improve the transfection efficiency of plasmid DNA.[17] However, a major drawback with viral counterparts is the associated oncogenecity and immune-genecity. Similarly, cationic condensing non-viral gene delivery vectors, such as Lipofectin® and PEI that form electrostatic complexes with the negatively charged DNA, can be highly cytotoxic to the cells or prevent release of the DNA for nuclear entry.[18,19] Therefore, the motivation behind using this system stems from the superior safety/toxicity profile and the non-condensing nature, based on physical encapsulation of plasmid DNA, of the anionic alginate matrix.

Using high viscosity grade sodium alginate, we were able to optimize formulation to reproducibly obtain particles of around 1 µm in diameter. Plasmid DNA encapsulation efficiency was optimized to be around 65% and the stability of plasmid DNA was confirmed due to processing conditions - *Figure 4*. Cell uptake of alginate particles with encapsulated rhodamine dextran was evaluated using fluorescence microscopy in J774A.1 adherent cells. Cytotoxicity analysis showed that the blank and DNA-loaded particles did not induce overt toxicity to the cells at doses that were subsequently used for DNA delivery and transfection - *Figure 5*.

DNA delivery and transfection were performed with EGFP-N1 plasmid. The quantitative GFP expression by ELISA and qualitative analysis by fluorescence microscopy showed that the alginate microparticles were most effective

as gene delivery vectors in J774A.1 macrophages - *Figures 6 and 7*. Although the exact mechanism of calcium alginate matrices in promoting phago/lysosomal escape has not been well examined, the report from You, *et al*[20] suggests that the Ca^{2+} ions used for cross-linking alginate may be sequestered by intracellular phosphate and citrate ions leading to an increase in the osmotic pressure, which will facilitate swelling and rupture of the phago/lysosomes.

Conclusions

Macrophages play an important role in acute and chronic inflammatory reactions in the body. In this study, we have investigated calcium ion crosslinked alginate microparticles as a non-condensing DNA delivery system for transfection in macrophages. Using reporter plasmid DNA expressing GFP, we have showed enhanced uptake by macrophages and the system was found to be relatively non-toxic to the cells in comparison to positive control, such as PEI. The quantitative and qualitative analysis of GFP expression was highest with calcium alginate microparticles as compared with all other controls, including Lipofectin®-complexed DNA. These results provide encouraging evidence for development of a macrophage-targeted anti-inflammatory gene delivery system with potential to treat many acute and chronic debilitating diseases.

Acknowledgements

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Traditional Lot Traceability Approaches Are Not Sufficient to Enable Upstream/Downstream Correlation Analysis for Quality by Design (QbD)

by Victor Shashilov, PhD and Justin Neway, PhD

Introduction

As Quality by Design (QbD) initiatives gain acceptance across life sciences process development and manufacturing organizations, there is an increased need to understand the dynamics of the critical portions of the process stream more fully. For example, detailed accounting of the fractional contributions of upstream process steps to downstream process steps is required at points of splitting and pooling in the process stream to conduct statistical correlations between upstream process parameters and downstream process outcomes. These fractional contributions are compounded in processes that have multiple points of splitting and pooling.

Splitting and pooling of batches is common in both process development and full scale commercial manufacturing. In commercial manufacturing, batches are often split and pooled to increase throughput and optimize equipment usage where downstream steps are slower than upstream steps or where upstream equipment has lower capacity than downstream equipment. For example, several upstream lots can be mixed into a single granulation batch in order to fully utilize the capacity of the granulator. Each granulation batch can then be split between several tablet presses, such that the total throughput of the tableting step is high enough to maintain the required load of the coating equipment and keep the hold time for the material coming from the granulator within the specified limits. In process development situations, batches are typically split into subsequent unit operations where sub-batches are run through different sets of experimental conditions and then recombined into downstream steps where the downstream equipment has higher capacity than the upstream equipment. The complexity of lot genealogy in the PD environment rapidly increases with the number of unit operations and the number of experimental conditions.

Traditional lot traceability tools are often used to track the linkages between process inputs and outputs. They are intended primarily for recall management and do not provide sufficient detailed information or flexibility on their own to allow correct calculation of such correlations. Spreadsheets are sometimes pressed into service to help calculate compounded fractional contributions across multiple process steps, but for this application, they are error-prone and hard to manage, and they become impractical very rapidly as the number of splitting and pooling points in a process grows.

Better, more automated and flexible tools are needed to perform these calculations so that useful process models can be built to link upstream Critical Process Parameters (CPPs) to downstream Critical Quality Attributes (CQAs) in processes where splitting and pooling occurs, an important requirement for achieving the goals of QbD. This article will explore the following three approaches for making such correlations and highlight the advantages and limitations of each:

1. The traditional spreadsheet-based approach
2. The manual SQL approach
3. A new on-demand SQL genealogy approach

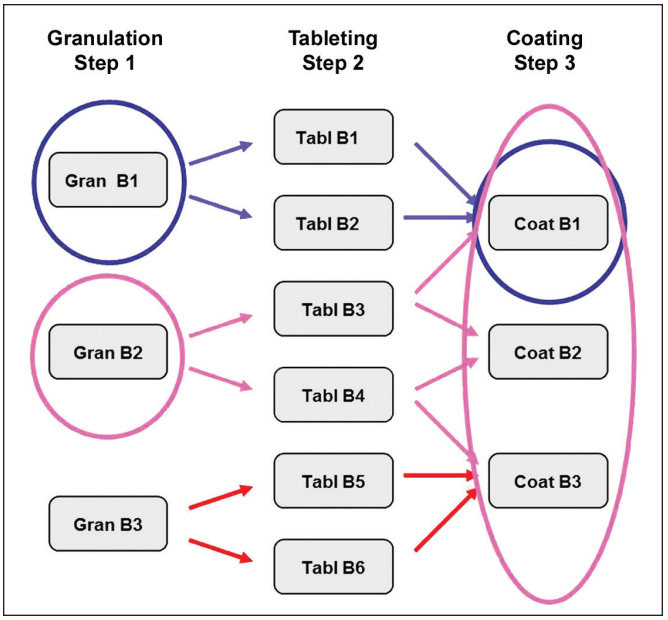


Figure 1. A simple process genealogy context shown as batches are mixed and split from left to right.

that offers opportunities for automation and the ability to handle complex process genealogies with comparative ease and simplicity

The Difference between Traditional Lot Traceability and a Full Accounting of the Process Stream Genealogy

Traditional lot traceability is typically used to manage situations where a defect has been identified in an incoming material or upstream in-process material that could jeopardize the quality of the final downstream product. By using a traceability matrix, a manufacturer can determine which final batches contain any amount of the defective upstream material. This information is used to support decisions about which lots of final product to quarantine for further testing or which shipped product lots to recall. Figure 1 illustrates an example of this type of traceability matrix. In traditional lot traceability situations, the focus is in knowing which downstream lots contained any amount of the defective upstream material, as opposed to knowing the exact amount of the defective upstream material that ended up in each downstream lot.

In many situations, it is desirable to correlate variations in upstream process conditions or materials to variations in downstream process outcomes to establish whether or not there is a relationship between them (e.g., whether or not the upstream process parameter can be considered for further evaluation as a CPP driving a downstream CQA). To enable such correlations, it is first necessary to calculate the fractional contributions of each upstream step to each downstream step across all the process steps between the upstream variable and the downstream outcome. This reveals the amount of the upstream material or condition that is associated with each downstream outcome instance. These upstream amounts or conditions are then used as #1 parameter values in the correlation calculation using the corresponding values for each downstream outcome as #2 parameters values. Furthermore, if the number of #1 parameter values does not match the number of #2 parameter values as shown in the more complex example in Figure 2, additional steps must be taken so that there are equal numbers of upstream and downstream parameter values available for the correlation calculation. The fractional contribution calculations can be very cumbersome and error-prone when using spreadsheet methods. Instead, methods based on the use of well-designed Structured Query Language (SQL) queries are a more practical way of accounting for the splitting and pooling genealogy during such investigations because they allow users to make these nested calculations more easily and reuse their work with less potential for introducing errors.

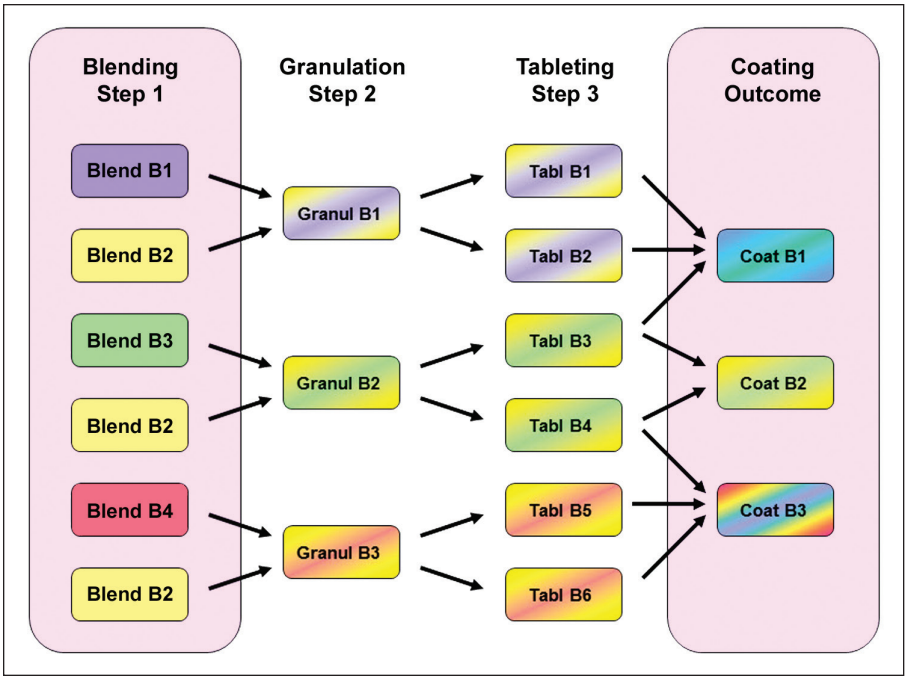


Figure 2. A more complex process genealogy context showing how batches can be split and pooled from left to right with fixed and varying cardinality, and how the number of upstream input batches can be unequal to the number of downstream outcome batches.

Upstream/Downstream Analysis

The following two examples illustrate some of the complexities inherent in upstream/downstream data analysis:

In the first example, a nutrient supplement is added to a seed fermentor and there is a need to determine whether a significant difference exists between the resulting process yields from batches

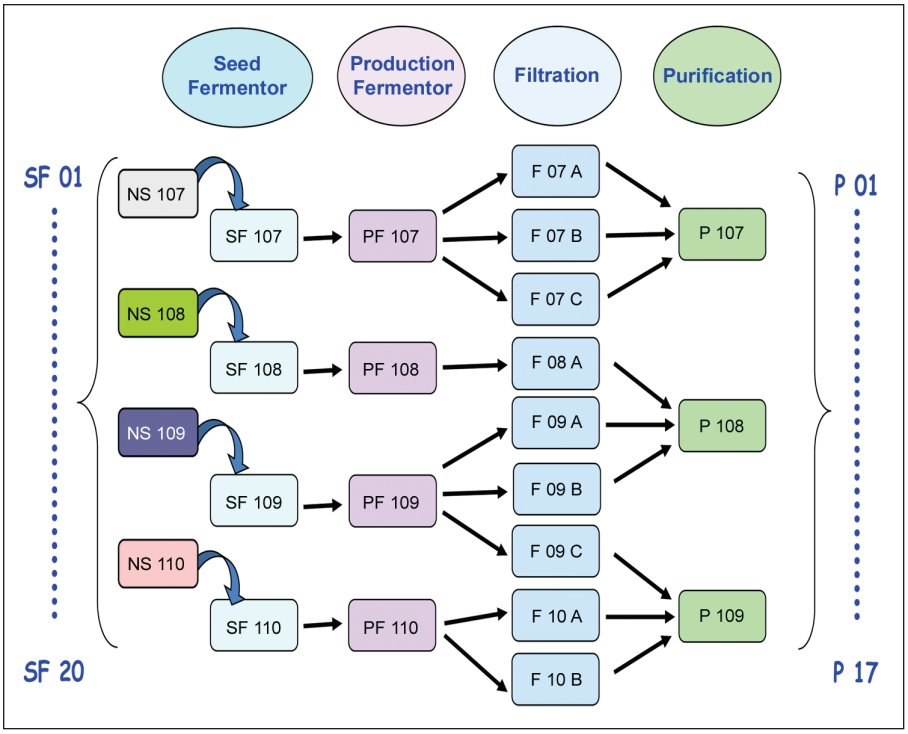


Figure 3. A nutrient supplement supplied by four different vendors is added at the seed fermentation step with four batches split into eight by the filtration step and then combined into three batches at the purification step.

produced using supplement from four separate vendors. To make this determination, lots need to be traced across four steps, including: (1) the seed fermentor step, (2) the production fermentor step, (3) the filtration step, and (4) the downstream purification step. Nutrient supplements supplied by four different vendors are added at the seed fermentation step. To reduce the total hold time for this degradation-prone protein, the four batches are split into nine at the filtration steps for parallel processing and then combined into three batches at the purification steps as shown in Figure 3.

To determine whether the specific vendor of the nutrient supplement has an effect on the yield of the product, the mixing at the purification step needs to be taken into account and included in calculations of the fractional contributions of each vendor's supplement into each of the final purification batches.

The second example illustrates additional important considerations for correlating CPPs to CQAs in a process with a more complex lot genealogy as shown in Figure 4. In this case, there is a need to determine whether a correlation exists between the osmolality of the media that is fed into each seed fermentation step and an impurity found in the final product lots. Splitting and pooling in the process stream needs to be taken into account along with the number of incoming media lots and the number of final purification lots, which have different total numbers. Using a manual spreadsheet-based approach for such calculations would require a significant amount of time and effort, but *could* be done using the following steps.

Three Approaches for Upstream/Downstream Correlations Analysis

The Manual Spreadsheet Approach

To manually correlate a parameter from Step A (Par A) to a parameter from Step X (Par X), the following steps are required:

1. Construct the lot genealogy chart.
2. Starting with Step A, for each pair of adjacent steps, perform calculations as in #3.
3. These calculations need to be repeated for each step and each batch within the step.
   a. Calculate fractional contributions of the material from all the batches from the previous step feeding into the given batch.
   b. Calculate the weighted average of the weighted averages of parameter A, computed for batches in the previous step.

While it is possible to use this spreadsheet-based method for upstream/downstream analysis, calculations in each subsequent iteration use weighted averages obtained in the previous iteration; therefore, errors can accumulate rapidly. In a typical situation where the cardinality varies among batches, the number of fractional contribution calculations required to support the calculation of correlations between any two steps of Ns steps is roughly proportional to the square of the number of steps and the number of batches as illustrated in the following formula:

$$\text{Effort} \sim N_S^2 \bullet N_{batches}$$

Table A illustrates the relative effort involved in the manual spreadsheet approach as a function of the number of batches, process steps, and parameters at each step. As seen from the table, the effort rapidly grows with the number of steps and batches, which can make this approach impractical, even for processes of moderate complexity.

The limitations and risks of the manual spreadsheet approach include:

1. Prone to errors – mistakes are easy to make and difficult to find.
2. Error propagation – errors made in the beginning are carried over and accumulated.
3. Complexity – calculations become unmanageable for large numbers of steps and parameters and/or complex genealogies.
4. Time consuming – spreadsheets are, by nature, extremely inefficient.

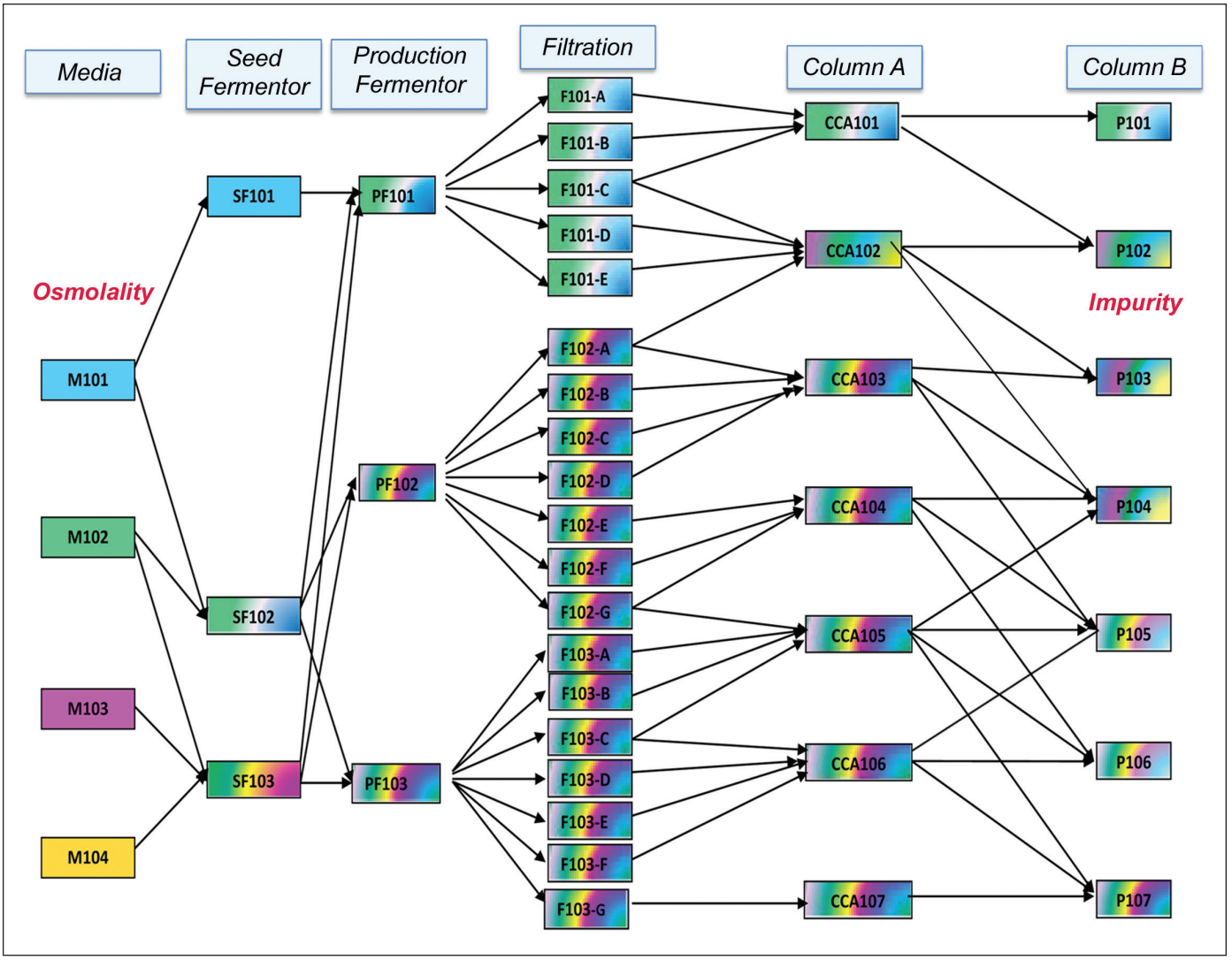


Figure 4. A more complex genealogy for which CPPs and CQAs need to be correlated during the fermentation process to determine whether there is a correlation between the osmolality of the media that is fed into the seed fermentation step to the impurity of the final product.

5. Difficult to validate – requires at least two people doing the same calculation independently and coming up with the same results every time.
6. Difficult to automate – all calculations have to be repeated from scratch for new batches and parameters.

The Manual SQL Approach

Another more useful method of dealing with the complexity of upstream/downstream analysis when there is splitting and pooling in the process stream is by taking a manual SQL query approach to model the lot genealogy using applications with data modeling capabilities, such as Oracle, Microsoft Access, or other enterprise applications that support SQL queries.[1] The approach considered here relies on the assumption that the end user is able to select any parameters from any two process steps for a correlation analysis without the need to write any SQL statements. To accomplish this, all the necessary data views need to be created in advance and then properly maintained when the structure of the source data or the manufacturing process changes. An example of a data view is shown in Table B. This data view maps media osmolality values ("Osmolality" field) to the impurity values in the production fermentor ("Impurity" fields). "Media," "Seed F," and "Prod F" columns compose the "lot tree." The lot tree in this example links media lots to production fermentor batches through batch IDs at the intermediate step – the Seed Fermentor ("Seed F") step.

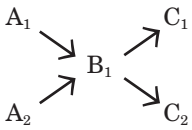
The complete mapping of the lot genealogy in this manual SQL approach relies on the creation of a set of genealogy "lot

# Steps	# Batches	Relative Effort
2	2	1
2	10	5
10	10	125
30	10	1,125

Table A. Relative effort encountered using the manual spreadsheet approach as a function of process complexity.

trees" as the first step. Lot trees require a set of views[1] called "mapping views." These views map the upstream steps to the downstream steps in all pairs of adjacent steps in the process. For each pair of non-adjacent steps A and B where a lot number change occurs, a pathway map or lot tree is created by sequential joining of mapping views.

Example 1. By way of illustration, consider a simple process with three steps (A, B, and C) and assume that a lot number change and pooling occurs between steps A and B and again between steps B and C along with splitting as shown below.



First, mapping views are constructed to link lot IDs of the adjacent steps. In this case, there are two mapping views: AB and BC. Each mapping view contains only two columns : lot IDs of step A and lot IDs of step B in view AB, and lot IDs of step B and lot IDs of step C in view BC, as shown below.

$$AB = \begin{matrix} A_1\,B_1 \\ A_2\,B_1 \end{matrix} \quad \text{and} \quad BC = \begin{matrix} B_1\,C_1 \\ B_1\,C_2 \end{matrix}$$

Now that the mapping views are available, non-adjacent steps can be mapped by constructing lot trees. In this case, there is only one pair of non-adjacent steps: A and C. These steps (A and C) can be linked in either a forward manner (i.e., from step A to step C) or backward manner (i.e., from step C to step A). In either case, the lot tree contains three fields: Lot IDs of step A, Lot IDs of step B, and Lot IDs of Step C as shown below:

$$AC = \begin{matrix} A_1\,B_1\,C_1 \\ A_1\,B_1\,C_2 \\ A_2\,B_1\,C_1 \\ A_2\,B_1\,C_2 \end{matrix} \quad \text{and CA} = \begin{matrix} C_1\,B_1\,A_1 \\ C_1\,B_1\,A_2 \\ C_2\,B_1\,A_1 \\ C_2\,B_1\,A_2 \end{matrix}$$

Lot trees AC and CA link lot IDs at step A to lot IDs at step C through lot IDs of the intermediate step (step B).

In the case of a three-step process, four views are needed (AB, BC, AC, and CA) to be able to map all pairs of adjacent and non-adjacent steps. If a similar approach is applied to a four step process (A-B-C-D) then three mapping views: AB, BC, and CD and six lot trees: AC, AD, BD, CA, DA, DB, need be created, which gives a total of nine views. Using the combinatorial theory[2] it can be shown that to allow for correlations between any two steps in an N-step process, the total number of views to be created is defined by formula 1 and is shown in Table C.

Formula 1 takes into account the fact that views obtained by forward joins (i.e., from step A to step B) and backward joins (i.e., from step B to A) will in general not be identical.

V

Osmolality	Media	Seed F	Prod F	Impurity	
Osm1	M101	SF101	PF101	Im1	
Osm1	M101	SF102	PF101	Im1	$W_{Im}=(2\cdot Im1+Im2+Im3)/4$
Osm1	M101	SF102	PF102	Im2	
Osm1	M101	SF102	PF103	Im3	
Osm2	M102	SF102	PF101	Im1	
Osm2	M102	SF102	PF102	Im2	
Osm2	M102	SF102	PF103	Im3	$W_{Im}=(2\cdot Im1+2\cdot Im2+2\cdot Im3)/6$
Osm2	M102	SF103	PF101	Im1	
Osm2	M102	SF103	PF102	Im2	
Osm2	M102	SF103	PF103	Im3	
Osm3	M103	SF103	PF101	Im1	
Osm3	M103	SF103	PF102	Im2	$W_{Im}=(Im1+Im2+Im3)/3$
Osm3	M103	SF103	PF103	Im3	
Osm4	M104	SF103	PF101	Im1	
Osm4	M104	SF103	PF102	Im2	$W_{Im}=(Im1+Im2+Im3)/3$
Osm4	M104	SF103	PF103	Im3	

Media	Osmolality	Impurity
M101	Osm1	W Im1
M102	Osm2	W Im2
M103	Osm3	W Im3
M104	Osm4	W Im4

Average (Impurity) group by Media

Table B. Data view for calculating weighted averages using the production fermentor as the universe.

Formula 1 $\quad N_{Views} = N_{steps} \bullet (N_{steps} - 2) + 1$

The major limitation and risk of the manual SQL approach is the rapidly increasing complexity as the number of steps and parameters increases. The equation from combination theory below shows that the total number of data views is proportional to the square of the number of steps and the square of the number of parameters, assuming for simplicity the same number of parameters in each step. (Note: Equation 2 is used to calculate the maximum number of required views in situations where each data view contains only two parameters.) The number of data views will be smaller if several data views are combined to contain multiple parameters from both steps mapped in the view.)

Equation 2 $\quad N_{Views} = \{N_{steps} \bullet (N_{steps} - 2) + 1\} \bullet N^2_{parameters}$

Thus, for a 30-step process, 84,100 views need to be created and maintained as shown in Table D.

Because the calculations involved in both the manual spreadsheet approach and the manual SQL approach are cumbersome and time consuming, the ideal solution lies in creating views and performing analyses on-demand, based on an easier method of selecting steps and parameters that maximizes flexibility and reuse while at the same time reducing the potential for errors. Thus, a tool is needed that provides the ability to refresh data and re-execute each analysis in a more automated fashion.

Due to the large amount of the data modeling effort required to enable ad-hoc correlations between any parameters and process steps, business users usually have to limit the number of parameters and process steps included in the data model and request changes to the data model each time the need for more data becomes obvious. Therefore, in most real time situations, the manual SQL approach doesn't deliver the ability to perform ad-hoc correlations between any parameters of a user's choice across complex lot genealogies. However, when such a capability is required, end users need to write fairly complex SQL queries against mapping views and data views,

# Steps	# Lot Trees
2	1
5	16
10	81
30	841

Table C. Number of lot trees as a function of the number of process steps.

which makes this approach error prone, time consuming, and difficult to validate.

The On-Demand SQL Genealogy Approach

A more practical alternative to the manual SQL query approach described above is the on-demand SQL genealogy approach, which eliminates the need to create and store large numbers of views, allowing the user to more easily perform correlations between any parameters across any number of steps at any time, and instead uses queries and genealogies that are automatically created on-demand. This approach saves time and minimizes opportunities for miscalculations and error propagation due to human error.

Figure 5 depicts a typical genealogy data modeling workflow, which is the same for the manual and on-demand SQL genealogy approaches.

- Step A is to create views (called *mapping views*) that map the relationships between all pairs of adjacent steps in the process. The lot genealogy information required to perform step A is typically available from such systems as Enterprise Resource Planning (ERP) systems, paper record systems, Manufacturing Execution Systems (MES), batch record systems, etc.
- Step B is to create *lot trees* by joining individual mapping views to map the relationships between any two non-adjacent steps in the process.
- Finally, lot trees are joined to data to produce the data views that are used to perform cross-step correlations (Step C).

In the manual SQL approach described above, all three steps

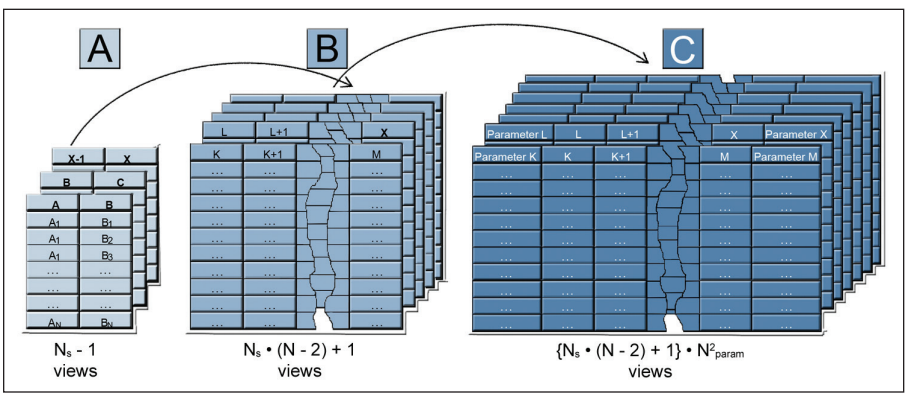


Figure 5. A typical genealogy data modeling workflow, which is the same for the manual and on-demand SQL genealogy approaches.

# Steps	# Parameters at each Step	# Views to Create and Maintain
2	1	1
2	2	4
5	3	144
10	5	2,025
30	10	84,100

Table D. Number of data views as a function of the number of process steps and parameters.

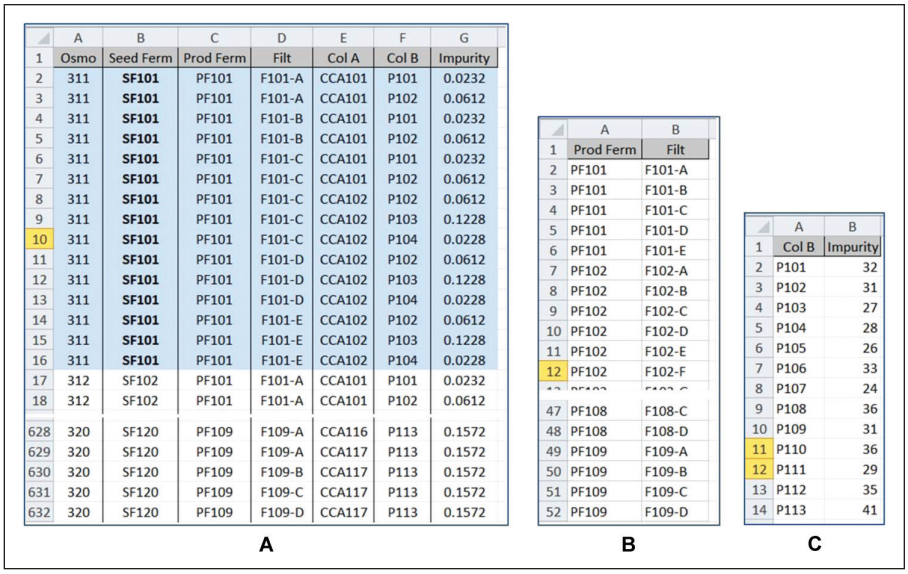
(A, B, and C) must be performed manually in advance, which results in the need to create a total of 84,100 views to support calculations between all pairs of parameters in the 30-step process as seen in Table D. In the on-demand SQL approach, only mapping views (step A) need to be constructed manually, while a corresponding set of re-usable lot trees (step B) and data views (step C) can be constructed by the software at the time of a user request. This is done by joining only those mapping views necessary for the query at the time the query is executed to map the step-to-step relationships for the portion of the process between the start and end points requested by the user. For example, in the 30-step process referred to in Table D, only 29 mapping views would need to be constructed as compared to the construction in advance of 84,100 views that would be required to support calculations between all pairs of parameters in the 30-step process as seen in Table D in the manual SQL approach.

Example 2. To compare directly the effort involved in the three approaches described here (manual spreadsheet, manual SQL, and on-demand SQL), consider the following example of a fermentation process shown in Figure 4. Batches in this process are frequently split and pooled between the unit operations (seed fermentor, production fermentor, filtration, and two column purification steps) such that the starting material from 20-seed fermentor batches ends up in 13 column B purification batches (note that Figure 4 shows only a subset of all the batches). The goal is to prepare all the required data tables needed to correlate parameters between any two of the five steps of this process by using the three methods described in this article.

A. Manual spreadsheet approach.
   1. Starting with the Seed Fermentor batch SF101 and looking at the lot genealogy map in Figure 4, all the sequences of batches that link batch SF101 to the Column B purification batches are manually entered (Figure 6A, rows for batch SF101 are highlighted in blue).
   2. Repeating step 1 for all 20-seed fermentor batches produces an Excel spreadsheet containing 631 rows (Figure 6A).

3. The spreadsheet created in step 2 can now be used to perform correlations between parameters from the Seed Fermentor and column B purification steps where the seed fermentor step defines the degrees of freedom (i.e., the seed fermentor step is the universe). To allow for correlations between all the other two out of five steps, 15 more spreadsheets would be needed, each containing a subset of the table shown in Figure 6A.

To summarize this manual spreadsheet approach, the total number of rows in the 16 spreadsheets in this example was 2,200 and each of the spreadsheets are created by manual manipulation of data in Excel. Any addition of new batches would require updating each of these 16 spreadsheets.



A

	A	B	C	D	E	F	G
1	Osmo	Seed Ferm	Prod Ferm	Filt	Col A	Col B	Impurity
2	311	SF101	PF101	F101-A	CCA101	P101	0.0232
3	311	SF101	PF101	F101-A	CCA101	P102	0.0612
4	311	SF101	PF101	F101-B	CCA101	P101	0.0232
5	311	SF101	PF101	F101-B	CCA101	P102	0.0612
6	311	SF101	PF101	F101-C	CCA101	P101	0.0232
7	311	SF101	PF101	F101-C	CCA101	P102	0.0612
8	311	SF101	PF101	F101-C	CCA102	P102	0.0612
9	311	SF101	PF101	F101-C	CCA102	P103	0.1228
10	311	SF101	PF101	F101-C	CCA102	P104	0.0228
11	311	SF101	PF101	F101-D	CCA102	P102	0.0612
12	311	SF101	PF101	F101-D	CCA102	P103	0.1228
13	311	SF101	PF101	F101-D	CCA102	P104	0.0228
14	311	SF101	PF101	F101-E	CCA102	P102	0.0612
15	311	SF101	PF101	F101-E	CCA102	P103	0.1228
16	311	SF101	PF101	F101-E	CCA102	P104	0.0228
17	312	SF102	PF101	F101-A	CCA101	P101	0.0232
18	312	SF102	PF101	F101-A	CCA101	P102	0.0612
628	320	SF120	PF109	F109-A	CCA116	P113	0.1572
629	320	SF120	PF109	F109-A	CCA117	P113	0.1572
630	320	SF120	PF109	F109-B	CCA117	P113	0.1572
631	320	SF120	PF109	F109-C	CCA117	P113	0.1572
632	320	SF120	PF109	F109-D	CCA117	P113	0.1572

B

	A	B
1	Prod Ferm	Filt
2	PF101	F101-A
3	PF101	F101-B
4	PF101	F101-C
5	PF101	F101-D
6	PF101	F101-E
7	PF102	F102-A
8	PF102	F102-B
9	PF102	F102-C
10	PF102	F102-D
11	PF102	F102-E
12	PF102	F102-F
47	PF108	F108-C
48	PF108	F108-D
49	PF109	F109-A
50	PF109	F109-B
51	PF109	F109-C
52	PF109	F109-D

C

	A	B
1	Col B	Impurity
2	P101	32
3	P102	31
4	P103	27
5	P104	28
6	P105	26
7	P106	33
8	P107	24
9	P108	36
10	P109	31
11	P110	36
12	P111	29
13	P112	35
14	P113	41

Figure 6. A) A data view created in MS Excel as part of the manual spreadsheet approach; B) An example of the mapping view required by manual and on-demand SQL methods; C) An example of a parameter view used in manual and on-demand SQL approaches.

B. Manual SQL approach.

1. Four mapping views are created, each containing ~ 50 records. An example of the mapping view linking the production fermentor and filtration batches is shown in Figure 6B.
2. Five parameter views are created, one for each process step, each containing two fields: batch IDs of the step and parameter values. Figure 6C depicts one of the parameter views created in this example.
3. To map batch IDs from non-adjacent steps, 12 lot trees are constructed by joining mapping views as appropriate. This step requires writing complex SQL queries.
4. To allow for correlations between each two out of five steps, 16 data views are constructed by joining parameter views to 12 lot trees from step 3 and to 4 mapping views from step 1)

To summarize this manual SQL approach, nine views are constructed with a total of 280 records, and 12 lot trees and 16 data views are built using complex SQL commands.

C. On-demand SQL approach.

1. Similar to the manual SQL approach, four mapping views and five parameter views are built that are identical to those for the manual SQL approach. No creation of lot trees and data views or writing of SQL statements is required as all lot trees and data views are constructed by the software at the time the user selects steps and parameters to correlate. Furthermore, in many industrial applications, the manual step of creating step views may not be required either because these views may already be available in such systems as, for example, MES or the electronic batch record.

Table E summarizes the effort required to provide the user with the ability to perform correlations between parameters at any two out of five steps in the example process. Notice that the manual spreadsheet approach is the most effort intensive and error prone and the on-demand SQL approach is the least laborious and does not require either manual data manipulation or SQL skills. The advantage of the on-demand SQL approach becomes more pronounced as the number of steps and batches increase.

To enable an upstream/downstream correlation, data must be joined with lot trees (Figure 5, step C); therefore, all of the corresponding data must be pre-organized by batch. Translating data into the batch context in the manual SQL approach usually takes significant additional data modeling effort, thus slowing down this type of analysis and making it more complex and error prone. On the other hand, the on-demand SQL approach described here also can embody built-in data contextualization capabilities to automate all of the data modeling query generation required to support upstream/downstream calculations.

Next, data is made available by accessing it directly from an on-screen hierarchical view of the process flow linked to an on-demand SQL generator which populates the "where clauses" in the SQL queries using the node names in the hierarchy

Method	Manual Spreadsheet	Manual SQL	On-demand SQL
# Records manipulated manually	2,200	0	0
# Views created manually or retrieved from database	0	9	9
# Views created with SQL statements	0	28	0

Table E. Effort involved to organize data for upstream/downstream correlation analysis in Example 2.

(Figure 7). In this example, the data is made available in a form that is contextualized by batch as the organizing principle of the hierarchical view (i.e., with all the parameter values organized so that they are associated with their corresponding batches to enable easy comparisons between batches). Other data organizing principles can be used for such hierarchies, such as production shifts, individual unit operations, raw materials, sample or test IDs, and other organizing identifiers used in enterprise data systems.

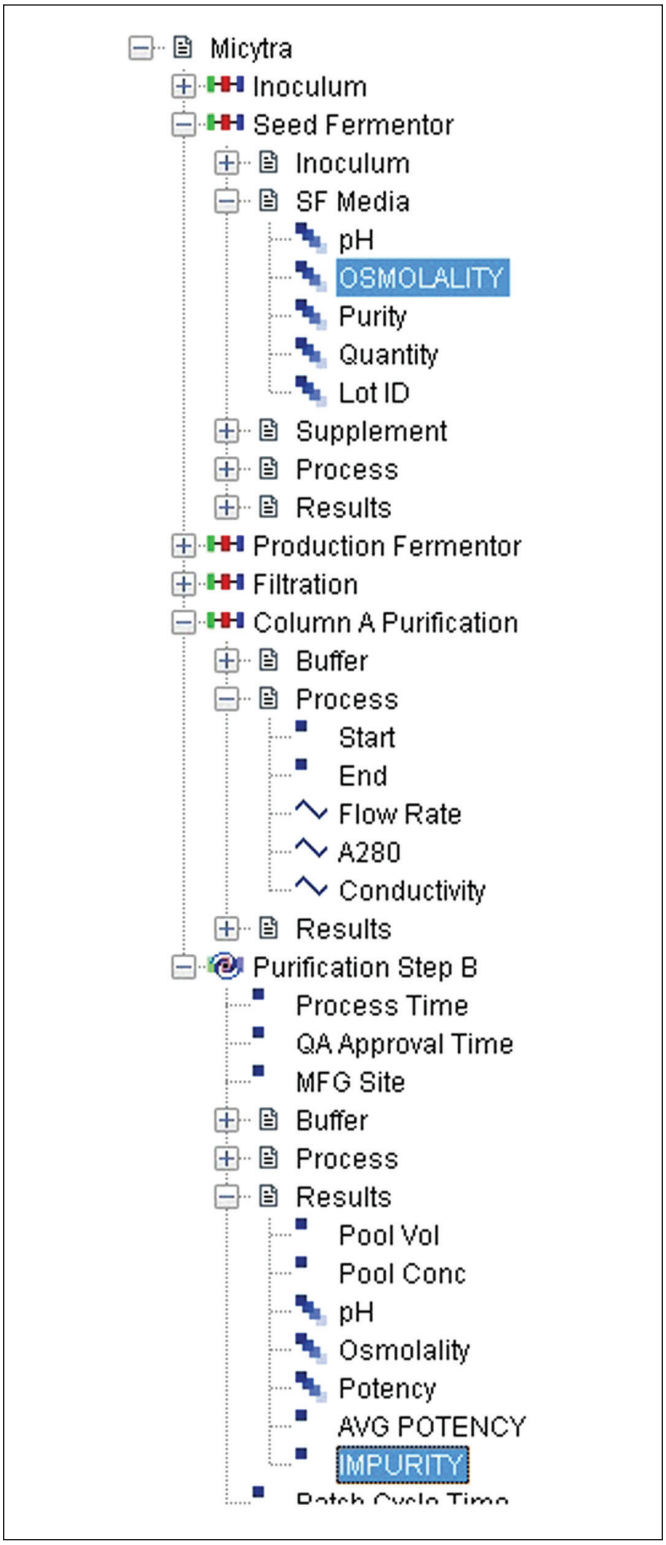


Figure 7. A hierarchy for a process with a complex lot genealogy between the seed fermentor and the final column purification step. To correlate the media osmolality to the impurity, the user selects two parameters shown by clicking them on the screen.

Finally, weighted averages based on the fractional contributions of upstream steps to downstream steps are automatically calculated as part of the batch contextualization function. Table B illustrates how the data should be grouped and aggregated to accomplish such batch contextualized averaging. In this case, weighted averages are calculated by using the cardinality of mixing between the media lots. Media lots are considered to be the "step universe" which is the higher-level organizing principle around which the other organizing principles are organized. The average impurity values across all production fermentations are calculated for each media lot in the "step universe" in this illustration. For each media lot in the "step universe," the weighted average impurity value is calculated by averaging impurity values across all replicate production fermentor lots in which that particular media lot was used. This type of mapping leads to:

1. Replicate parameters, defined as multiple impurity values associated with each media lot, in which each replicate value represents the endpoint of a pathway by which a given media lot contributes to the impurity outcome of each fermentor batch. (Note: These replicate values can be used to calculate the average impurity (weighted-by-cardinality) associated with each media lot.)

2. Equal numbers of input parameters and impurity outcomes as required for meaningful correlation calculations.

Similarly, data also can be grouped using the production fermentor batches as the step universe in order to calculate the weighted average osmolality values associated with each production fermentor batch. As a general rule, when correlating parameters between different process steps, the step with the smallest number of batches should be used as the step universe, to minimize the number of degrees of freedom and thus avoid the overestimating the correlation.

However, in some types of analyses, such as comparing raw material suppliers using Analysis of Variance (ANOVA), selecting the step with the smaller number of batches as the step universe can be impractical. Referring to the example of comparing vendors of nutrient supplements above (Figure 3), the seed fermentation step should be used as the step universe to avoid having to do calculations of the weighted averages of vendors that would be required if the purification step were selected. Figure 8 also illustrates that one of the vendors (shown in the middle of the figure) is associated with a significantly higher level of impurity in the filtered bulk.

The following steps can be used to correlate a parameter from step A (Par A) to a parameter from step X (Par X) using the SQL method:

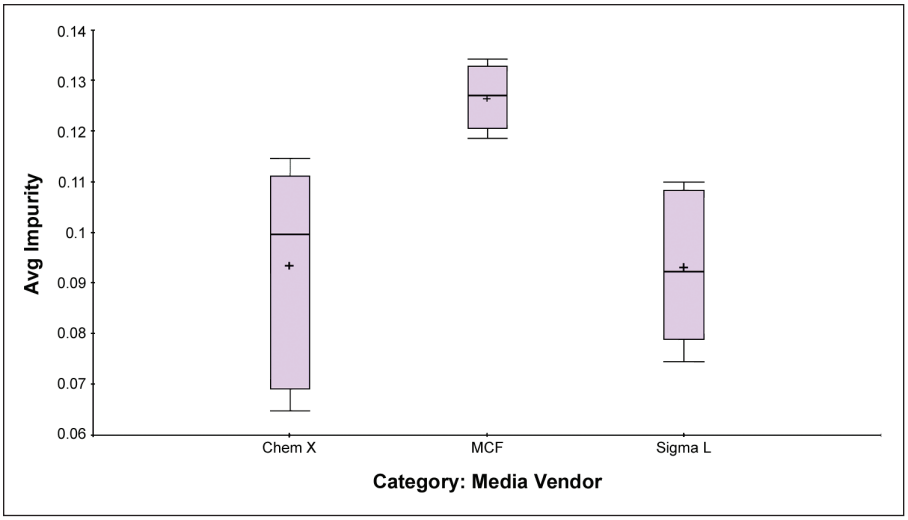


Figure 8. The nutrient supplement vendor shown in the middle of the figure is associated with a significantly higher level of contaminant in the filtered bulk using the seed fermentation step as the step universe.

1. Prepare Mapping Views so that each view maps two adjacent steps between A and X. This will require a total of X-A mapping views: [A]->[A+1], [A+1]->[A+2], … ,[X-1]->[X].

2. Create a lot tree by joining all X-A mapping views created in step 1.

3. Prepare views for **Par A** organized by the batch ID at step A and **Par X** organized by the batch ID at step A.

4. Join **Par A**, **Par X** views to the lot tree created in step 2.

5. Decide which step will be the organizational unit (discussed above).

6. Calculate the weighted average of the parameters by grouping the view created in Item 4 by the step universe batch ID.

7. Perform the analysis.

Conclusion

This study considered three approaches to performing upstream/downstream data analysis, focusing on the differences between them with regard to labor intensity, complexity, ability to account for splitting and pooling in the process stream, and their ability to inadvertently propagate errors. The manual spreadsheet approach was the most labor-intensive, complex, time consuming, and error prone way to perform upstream /downstream data analysis and was severely limited in its ability to account for splitting and pooling in the process stream genealogy without significant risks of inadvertent error propagation. In a complex manufacturing process with 20 to 25 unit operations containing four or five points of splitting and pooling in a process stream, the manual spreadsheet approach would need tens of thousands of spreadsheet rows to allow for the necessary calculations to correlate upstream inputs with downstream outcomes. Such a complex spreadsheet could probably not be used without a significant number of errors, thus providing questionable functionality. The manual SQL approach was potentially less error prone than the manual spreadsheet approach, but was still too labor intensive and complex to be useful as a practical tool for complex manufacturing processes. The on-demand SQL genealogy approach required an initial investment in the development and configuration of mapping views similar to that used in the manual SQL approach. Once the initial investment was made, this approach provided a high degree of reuse of the views along with minimal potential for errors, simplicity of use, and the ability to easily perform upstream/downstream correlations in complex manufacturing processes with multiple points of splitting and pooling in the process stream.

An important benefit of being able to easily perform upstream/downstream correlations in complex manufacturing processes is that significant barriers are removed to identifying potential cause-and-effect relationships between upstream process conditions and downstream process outcomes. Such relationships drive the formation of hypotheses that can be confirmed, extended, or refuted using mechanistic knowledge and/or experimentation. The information thus gained about the relationships between upstream process parameters and downstream process outcomes is a major component of process models used for process control, and also contributes in the development of sophisticated process models for use in Real Time Adaptive Control (RTAC).

A complex manufacturing process with multiple splits and recombinations in the process stream may be operating in a state of control until a process upset occurs (e.g., an unexpected change in a raw material which threatens to produce unacceptable downstream outcomes). In this situation, the control system must be supported by a process model to determine what adjustments to make (either automatically or with the help of manual intervention) to re-establish control of the process within the design space. Such a process model would be most efficiently prepared using the on-demand SQL approach described in this study so that the quantitative relationships between upstream parameters and downstream process outcomes is available to the control system to make the appropriate adjustments.

The on-demand SQL genealogy approach described in this study can be embodied in a computer software program that allows process models to be built efficiently and with minimum potential for errors. Such a software program could provide data values for process parameters contextualized by batch and organized to include the genealogy of the process stream. This would simplify and reduce errors in the work involved in understanding upstream/downstream parameter relation-

ships in complex processes that include splitting and pooling in the process stream, a critical success factor for building process models that link CPPs and CQAs.

In summary, lot traceability is an important capability for recall management, but it is not enough to support the development of sufficient process understanding for achieving the goals of QbD. A flexible capability for performing upstream/downstream correlations, such as the on-demand SQL approach described in this study, accounts for fractional contributions across process steps and makes it possible to draw statistically sound conclusions about the relationships between upstream process parameters and downstream process outcomes. This helps to make processes better understood and outcomes more predictable by linking CPPs with CQAs to shape useful process models that meet the goals of QbD.

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Bringing New Products to Market Faster

by Adam Fermier, Paul McKenzie, Terry Murphy, Leif Poulsen, and Gene Schaefer

This article presents ideas, concepts, and prototype experience on how to bring products faster to market through a more structured and integrated management of product, process, and analytical data based on proven industrial standards (S88/S95) and data warehouse technology.

Introduction

Large pharmaceutical organizations are currently being pressured to increase the efficiency and effectiveness of their business in terms of leveraging internal and external resources to deliver faster on design, execution, analysis, and reporting. Inconsistency and sometimes a complete lack of structure around key business processes has led to intensive allocations of resources spent on last minute efforts to complete regulatory filings and technology transfers on time. Inherent in these efforts is often a misplaced emphasis on gathering primary data rather than its transformation into information and knowledge and its subsequent analysis. Thus, these efforts are typically the result of an information "push" through the corporation as opposed to an information "pull" driven by a well-coordinated knowledge management strategy. The root cause of this push versus pull in the pharmaceutical industry is the fundamental lack of a scalable knowledge management strategy that can handle the lifecycle management of a novel medicine end to end.

Building a solid knowledge management strategy for the industry has many requirements and challenges. Fortunately, other data driven industries have tackled the knowledge management challenge by adopting industrial standards for batch execution and planning/modeling (i.e., ISA S88/S95 compliant).[1-5] However, the problem is how to assemble and contextualize the data scattered throughout many systems. Compounding this problem is that these systems are often a mix of validated and non-validated systems; therefore, it is imperative that the strategy encompasses a modular and scalable approach to the integration of information contained within these systems.

Data warehousing is a common informatics approach that can help meet the requirements set forth above where the data warehouse has a data model conforming to the standards. Bringing these two concepts of a data warehousing strategy in combination with what some have called recipe-based execution will enable the assembly of data rich systems into a common system defined here as a "Recipe data Warehouse" (RW). The RW strategy will allow the organization of data across multi-source execution systems and will drive more data rich decisions for products in a timely manner. This will ultimately lead to increasing the quality, capability, and capacity of the organization to execute our ultimate business deliverables: New Drug Application (NDA), Biologic License Application (BLA), technology transfer, and delivery of therapeutics to patients.

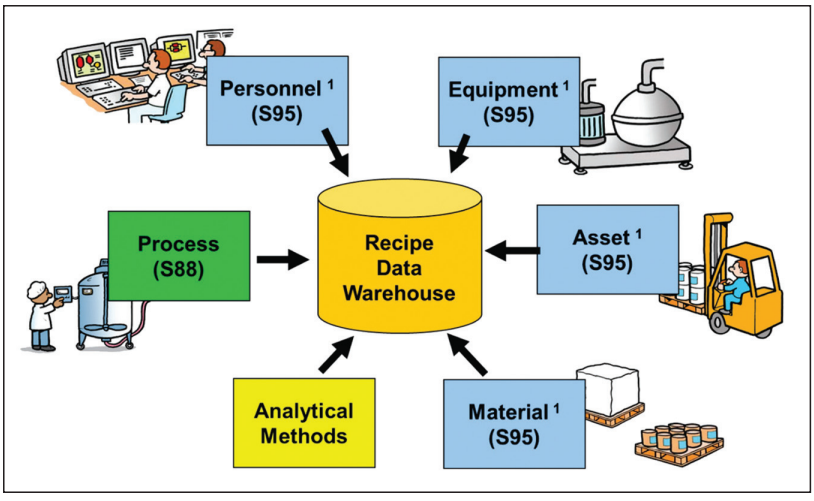

Figure 1. S88 & S95 recipe objects to be managed by recipe data warehouse.

Defining the Strategy

S88/S95 standards provide definitions around people, materials, and equipment as well as procedural models on how these are combined to make

products *Figure 1*. Typically, quality monitoring methods are not well defined in these standards; however, the associative resulting data from these methods could be easily stored. The core of the recipe data warehouse is based on a well structured and tested data model which must:

- Support the business objectives/planned system functions (S95)
- Provide modeling of recipes including specification of processes, personnel, equipment/assets, materials, and analytical methods (S88/S95)
- Align with current/best practice in pharmaceutical manufacturing, i.e., development of small and large molecule drugs
- Align with relevant S88/S95 models
- Include modeling of analytical methods/data, which is not well defined in S88/S95
- Adopt the S88/S95 object oriented thinking (use object classes and instances)
- Adopt the S88/S95 expandability/collapsibility concept (use recursive relations)
- Allow for stepwise development of a recipe based on recipe building blocks (use reference or inheritance)
- Enable ad-hoc addition of analytical measures that may initially not have been defined in the recipe
- Provide ability to capture in process or release data (discrete and continuous)

Putting all these requirements into a centralized recipe data warehouse can be daunting, but well defined strategies in data warehousing can help tremendously.[6] The strength of combining these two strategies is the common modular approach. The data warehousing strategy breaks the information management into four unit operations as outlined in Figure 2. Data source systems provide all source data for the recipe warehouse and in this strategy validation and compliance issues, including change control are addressed in these source systems. The data staging area is a complex, yet simplified manner to help conform to the S88/S95 data standard and designed to optimize data writing speeds. The data presentation area now pre-aggregates data from the data staging area designed to optimize read speeds. The data access tools provide a means to deliver standard reports as well as ad-hoc

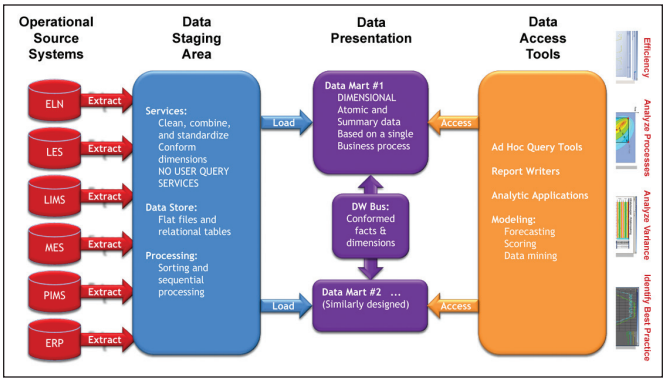

Figure 2. Overview on information management – pulling data from source systems.

to advanced trending/analysis. Like the data source systems, the data access tools are meant to be non-system specific to provide the modularity and flexibility required.

It is important to note that the data structure must be applied and/or understood within these data source systems to effectively leverage this strategy. The transformation from the data source systems into the recipe data warehouse is called Extraction-Translate-Load (ETL). It arguably is the most critical portion of the strategy as it will ultimately be required to handle the diversity of data models in the source systems and conform to one common system independent model.

Recipe Development Process – Driving Standards and Flexibility

The overall business objective is to bring new products faster and more efficiently to the market. To do this, the complete development process from discovery to commercial manufacturing of new drugs must be standardized and based on common recipe data models and tools. A key driving motivator behind this strategy is presented in Figure 3 where the organization prepares in a proactive nature to perform technology transfer between each critical clinical milestone. The strategic modification enables more flexibility to the organization as a whole whereby decisions and priorities can change significantly during the products lifecycle. The recipe data warehouse must support each overall step in the development of new drugs:

- Pre-Clinical Phase
- Clinical Trials Phase I
- Clinical Trials Phase II
- Clinical Trials Phase III
- Product Launch and Manufacturing

The product development process should be managed by QbD principles and include the following steps:

- Quality Target Product Profile (QTPP) development
- Prior knowledge collection and Critical Quality Attributes (CQA) identification
- Product and process development including Critical Process Parameters (CPP) identification
- Design space development, including Design of Experiments (DoE)
- Control strategy development, including real time release testing and process validation
- Continuous improvement supported by, e.g., Process Analytical Technology (PAT)

The recipe warehouse must include the necessary data to perform each of these steps thereby encapsulating the continuum of compliant data - *Figure 3*.

S88 Recipe Objects and S95 Complementary Objects

The recipe data warehouse will be based on a common language for exchange of information about products and recipes for manufacturing of products as described in the ISA standards

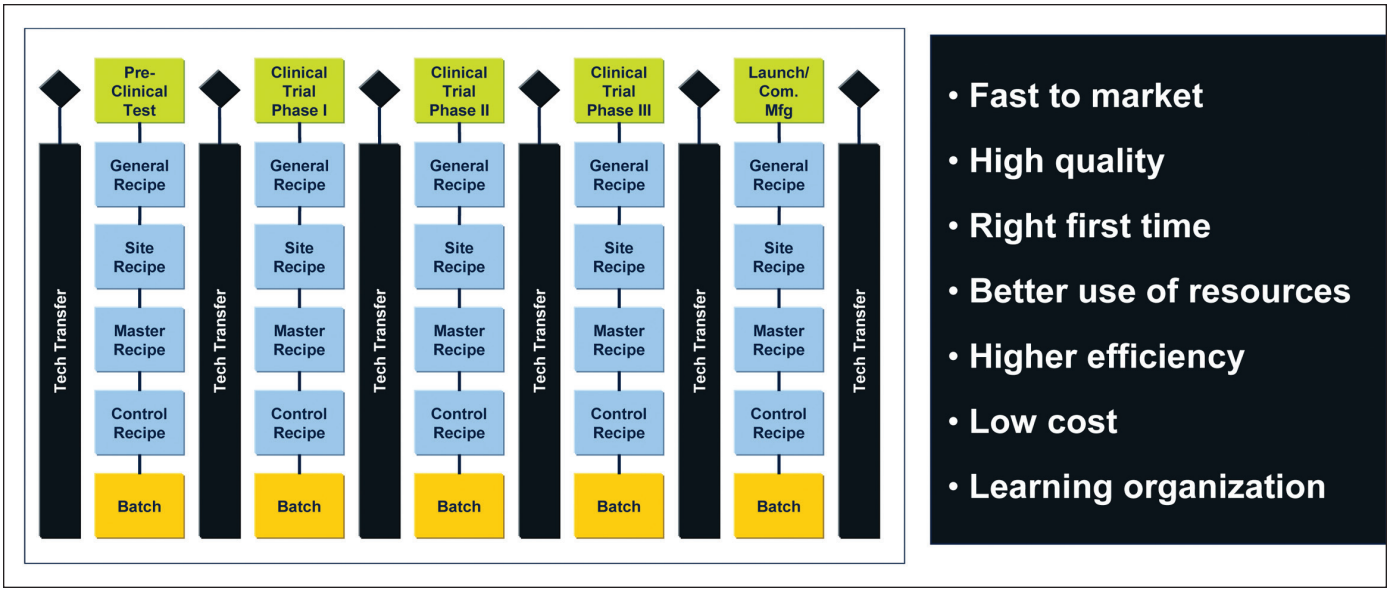

Figure 3. Recipe data warehouse must support tech transfer throughout complete development/manufacturing life cycle management.

S88 Batch Control,[1-3] and S95 Enterprise Control System Integration.[4-5] Alignment on these standards will help provide a common structure over the data which is maintained in multiple source systems.

Figure 4 describes the matrix of models described in S88. The horizontal slices address varying levels of repeatable units, operations, and parameters. The vertical slices then define varying levels of restrictions applied to these models which increase moving from the process model on the left side to the equipment model (physical model) on the right side. It is assumed that the equipment can be controlled by either a paper-based or a computer-based system, which get its product specific input from a recipe (equipment control). Fundamentally, it is important to note that the recipe establishes the link between the process and the equipment in this matrix format to provide for ultimate flexibility.

Implication of Vertical Slices in the Procedural Model

The evolution from a process view to an equipment/execution view is defined as procedural control which is synonymous to a control strategy. Hence, if your regulatory filings are aligned with these overall procedural models, it will help ensure you are indeed providing the most transparent process definitions to the agencies as well as providing flexibility for your commercial manufacturing. For example, a regulatory filing would outline a general recipe and include all Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) defined, and include a procedural definition as a mean to describe the products control strategy. Certainly, master and control recipes leveraged in development that helped define these CPPs and CMAs would be shared, but only to justify the overlaying general recipe for the product. In such a manner, commercial manufacturing and the agencies are provided clear definitions and processes for the control strategy.

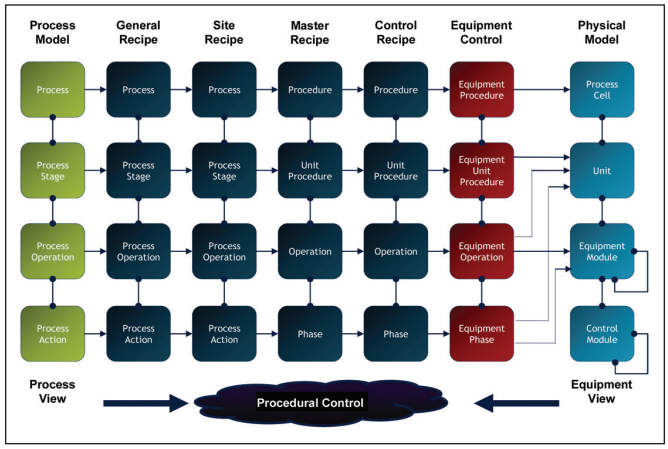

Figure 4. S88 procedural controls and model definitions.

S88 describes how process descriptions may be transformed into similar structure for a recipe. It is important to note again that the information captured in the recipe contains both the process execution as well as the quality testing methods/data. It is through this combination of information in one central location that facilitates effective definition of CPPs and CMAs.

Recipe Definitions

According to S88 Reference,[1-3] a recipe is "an entity that contains the minimum set of information that uniquely defines the manufacturing requirements for a specific product." It is used to describe products and how to produce products. In practice, you need varying degrees of information specificity for different recipients of the information in the organization. That's why S88 operates with four different recipe types as shown in Table A.

Process Models Equivalent to a Platform

Strictly speaking, process models are intended to be independent of product and materials. However, in discussions around alignment of platform definitions and recipe based definitions, we have taken the editorial liberty to enable some material

definitions/classes to be defined in these process models as well as equipment parameters and settings. This decision was made to help enforce some further standardization the corporation was looking for in the overall platform discussions.

Product Specific Recipes

Figure 4 describes the evolution from a general recipe to a control recipe. Note the clear equipment independency implied by these recipe definitions. This is important to note and follows on the conversations above around actual filing strategies/recommendations for products. The S88 standard,[1-3] defines four different recipe types:

- General recipe: a type of recipe that expresses equipment and site independent processing requirements.
- Site recipe: a type of recipe that is site specific.
- Master recipe: a type of recipe that accounts for equipment capabilities and may include process cell-specific information.
- Control recipe: a type of recipe which, through its execution, defines the manufacture of a single batch of a specific product.

Each of these recipes is further described in the S88 standard as shown in Table A.

Recipe Types
The ***General recipe*** is an enterprise level recipe that serves as the basis for lower-level recipes. It is created without specific knowledge of the process cell equipment that will be used to manufacture the product. It identifies raw materials, their relative quantities, and required processing, but without specific regard to a particular site or the equipment available at that site. The general recipe provides a means for communicating processing requirements to multiple manufacturing locations. It may be used as a basis for enterprise-wide planning and investment decisions.
The ***Site recipe*** is specific to a particular site. It is the combination of site-specific information and a general recipe. It is usually derived from a general recipe to meet the conditions found at a particular manufacturing location and provides the level of detail necessary for site-level, long-term production scheduling. However, it may also be created directly without the existence of a general recipe. There may be multiple site recipes derived from a general recipe, each covering a part of the general recipe that may be implemented at a specific site
The ***Master recipe*** is that level of recipe that is targeted to a process cell or a subset of the process cell equipment. Some characteristics of master recipes include the following: • The master recipe has to be sufficiently adapted to the properties of the process cell equipment to ensure the correct processing of the batch. • The master recipe may contain product-specific information required for detailed scheduling, such as process-input information or equipment requirements. • The master recipe level is a required recipe level, because without it no control recipes can be created and, therefore, no batch can be produced
The ***Control recipe*** starts as a copy of the master recipe and is then modified as necessary with scheduling and operational information to be specific to a single batch. It contains product-specific process information necessary to manufacture a particular batch of product. It provides the level of detail necessary to initiate and monitor equipment procedural entities in a process cell. It may have been modified to account for actual raw material qualities and actual equipment to be utilized.
Recipe Categories of Information
The ***Header*** in the recipe comprises administrative information. Typical header information may include the recipe and product identification, the version number, the originator, the issue date, approvals, status, and other administrative information.
The ***Formula*** is a category of recipe information that includes process inputs, process parameters and process outputs. A ***process input*** is the identification of a raw material or other resource required to make the product. A process parameter details information such as temperature, pressure, or time that is pertinent to the product but does not fall into the classification of input or output. A ***process output*** is the identification and quantity of a material and/or energy expected to result from one execution of the recipe. ***Equipment requirements*** constrain the choice of the equipment that will eventually be used to implement a specific part of the procedure. In general and site recipes the equipment requirements are typically described in general terms, such as allowable materials and required processing characteristics. At the master recipe level, the equipment requirements may be expressed in any manner that specifies allowable equipment in process cells. At the control recipe level, the equipment requirements are the same as the allowable equipment in the master recipe.

Table A. Glossary of recipe terms as defined in S88.[1]

Implication of Horizontal Slices in the Procedural Model

According to S88, each of these vertical slices is further matrixed to describe in a structured way by splitting the process up into process stages, process operations, and process actions - *Figure 5*. To complete the process description a set of parameters describing required materials, equipment and personnel and specifying process variables may be assigned to each process action.

According the S88 standard, [1-3] the recipes contain the following categories of information: header, formula, equipment requirements, and procedure. Each of these categories is further described in the S88 standard as shown in Table A.

Recipe Data Warehouse Development – S88/S95 Meets Kimball

Combining the S88/S95 data standards with the informatics strategy outlined by Kimball, we have called this system the "recipe data warehouse"[6] recognizing the importance of the relationship between recipes and informatics (i.e., information management) strategies. The combined data model is proposed in Figure 6 recognizing some key staging areas isolating the source systems and target systems. Source systems are exist-

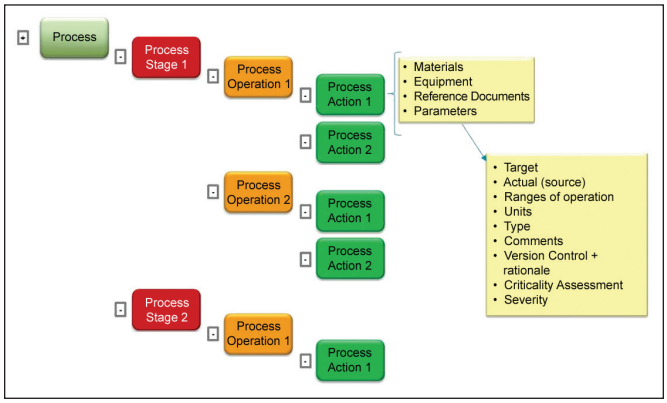

Figure 5. S88 based recipe structure.

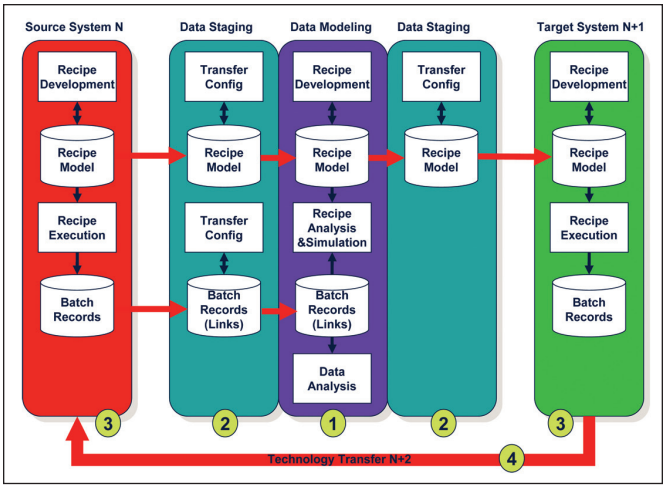

Figure 6. Recipe data warehouse conceptual system architecture.

ing systems that are used to create or modify existing product recipes in the central recipe data warehouse or to produce batches based on existing product recipes where the batch data will be used for data analysis by the central recipe data warehouse. Target systems are existing systems that use existing product recipes to produce batches (experiments, lab production, commercial production, etc.). The numbers in parenthesis below relate to Figure 6.

The conceptual architecture illustrates both the central recipe data warehouse (1) the data staging for connected systems (2), and the connected systems (3) as well as the conceptual workflows (4) related to defined business processes which creates, modifies, uses, or analyzes the recipe data (e.g., material, equipment, people and process definitions, and in process data as well as release/stability data).

It is anticipated in the generic model that all, some, or none of the current systems can act in the role of both being a source system or a target system (3).

Data staging is intended for each connected system to enable standardizing and normalizing on data structures in the central recipe data warehouse and de-coupling these structures from the native data structures used in and by the connected systems themselves.

The core of the architecture is the Central recipe data warehouse (1), which holds the following types of data:

- Standardized/normalized product recipes
- Tools for recipe development, including recipe building blocks
- Meta data for recipe analysis and simulation
- Meta data for linking to batch data in any defined source system (3)
- Tools for analyzing recipe/batch data

It is important to realize that a significant portion, if not all of our current data is stored in a manner that does not comply with recipes and sources range from excel workbooks, custom databases, emails, pdf documents, paper records, etc. So a huge value in building a unified, system independent model is that it helps to capture and contextualize this disparate data today.

The transformation or mapping from/to the specific systems of the generalized data models and structures used in the central recipe data warehouse is done by data staging.

The data staging is intended to be an integrated part or the central recipe data warehouse with centralized configuration of the transformations. This gives a good de-coupling of the connected systems from the central recipe data warehouse and it furthermore gives a robust and consistent basis for managing the data transformations.

For some of the current systems, a full and complete data transformation may not be possible or GMP and other regulations may prevent a direct storing of data into the central recipe data warehouse. In such cases, the data staging could include a user interface component for committing of the transformed data. Data staging has to cover both product recipe data and batch data transformations.

Data staging has for some of the existing systems to be bi-directional to enable business process workflows. This is illustrated by the data staging between the source systems and the data modeling for transforming data that creates or modifies existing data in the recipe data warehouse. Data subsequently leaving the warehouse would go through a similar staging environment where appropriate mapping to system specific definitions would be defined. The inbound and outbound data staging is clearly not identical and must be treated as separate transformations with specific and individual configurations for each of the connected systems.

User interface components shall be included for configuration of the data transformation and eventual data commitment functionality.

Workflows which can be for optimizing, fine tuning, and development of recipes is illustrated by the target system (N+1) which loads an existing production recipe (or recipe component) from the central recipe data warehouse. This recipe is then modified before or during recipe execution and batch data is collected during this execution.

There may now be a desire to update the production recipe to a new "version" in the central recipe data warehouse, and the "arrow" with "technology transfer N+2" indicates that this specific system used for the recipe execution now changes from being a target system to also being a source system. In this way, many of the existing systems can be used as both a source and a target system.

A special methodology which could be used for recipe development is simulation of processes. Simulation of processes is based on Process Models which can be developed based on historical batch data by use of standard software products.

Once such process models have been developed, these can be used by software engines to simulate the modeled process with a variance on inputs (recipe modifications).

In the current concept illustrated above, such simulation is intended to be included as applications in the central recipe data warehouse, but such simulations also could be seen as just another set of source and target systems. In the latter case, this may require that additional data staging components are made for batch data from the central recipe data

warehouse to the target system to enable the process model to operate (recipe execution) on real batch data. (This data staging component is not illustrated).

Other Functions

The recipe data warehouse may eventually comprise data for use in quite a number of other applications. Figure 7 shows the envisioned functions.

The core function of the recipe data warehouse is called recipe authoring. Recipe authoring is the stepwise development/refinement of the recipe from the initial idea of the product to commercial manufacturing of the product to be supplied to the patient.

The recipe authoring process will be based on selection and combination of predefined recipe building blocks kept in a library. Different kinds of building blocks will be kept for specification of processes and related resource requirements (personnel, equipment, methods, and materials). The building blocks must represent the best practice in the complete development organization.

The development of new recipes will take advantage of the object oriented approach using object classes and object instances as described in S88, e.g., you may have a class of equipment called fluid bed dryers in your library and based on that class, you may create an instance of a fluid bed dryer called fluid bed dryer 23 linked to a specific recipe operation.

The recipe authoring will be supported by a graphical front end based and recipe representations standards like Sequential Function Charts (SFC) as described in S88.

Parts and bits of a recipe may be developed outside the recipe data warehouse in one of the source systems linked to the recipe data warehouse and then transferred to the recipe data warehouse through a standard based interface (recipe upload).Based on the data kept in the recipe data warehouse, the users may perform a number of different analysis and simulations:

- Simple views/reports, based on SQL queries in the database
- Advanced statistical analysis/reporting, based on statistical analysis methods, like statistical process control, Multivariate Data Analysis (MVA), Principal Component Analysis (PCA), etc.
- Risk assessment/reporting, based on entry of experience based or theoretical risk probability and risk consequence figures
- Advanced process modeling, based on pre-defined rules/equations for material and energy balances
- Advanced what-if analysis/simulation, based on process modeling methods

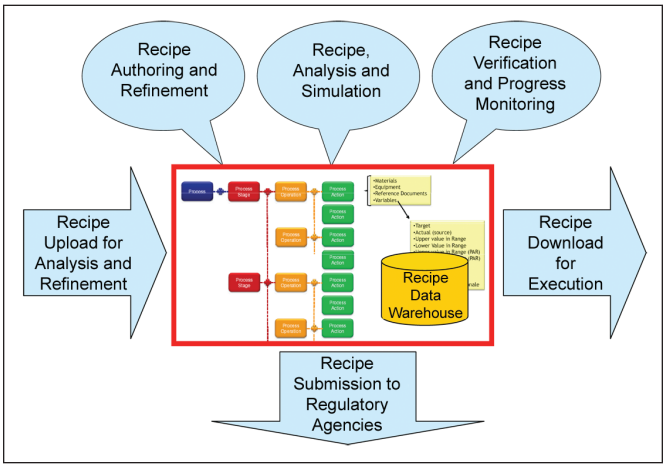

Figure 7. Recipe data warehouse – envisioned functions.

These analysis/simulation/reporting tools will be implemented by linking third party standard software packages to the recipe data warehouse. The recipe authoring process will be supported by various types of recipe verification functions:

- Automatic verification for consistency, based on recipe building rules
- Automatic verification of completeness, based on comparison with pre-defined recipes
- Automatic verification of regulatory/GxP compliance, based on check against pre-defined specification of regulatory/GxP requirements

Further, the recipe authoring process will be supported by a progress monitor describing Key Performance Indices (KPIs) for maturity and readiness for submission/approval:

- Monitor dynamically progress on recipe development
- Compare different versions of recipe and track changes

The progress monitoring tool would provide management with an excellent overview of the product development progress.

Eventually the recipe data warehouse may be used to download recipes for execution in a target system (recipe download). A target system could, for example, be a batch control system in a commercial manufacturing facility. This would require quite detailed modeling of not only the process and the related resource requirements, but also modeling of conditions for transitions and constraints for use of particular equipments.

The recipe data warehouse may store data from execution of recipes or provide on-line links to such data kept by external source systems making it possible to use historical data for the analysis and simulations described above. Historical data may exist in large amounts and may be kept in special historian databases and it may be smart to keep such data in these special databases and just establish links to the data when needed for analysis.

Eventually, the recipe data warehouse may be used for submission of files for approval by regulatory authorities like FDA. Two levels of support may be envisioned for submissions:

- Automatic provision of data for file submissions to regulatory authorities, for example:
  - Collating information over time for a given unit operation would link to S3.2.6 – process development history

  - Information for the current master recipe would link to S3.2.4 process description
  - Specific information gathered during certain instances of the control recipe would link to S3.2.5 process validation and would for the core data set for ongoing process verification, especially useful when combined with the general or site recipe definition(s) for products manufactured at multiple sites
- Manage/track changes related to submitted files

The recipe data warehouse may be used for transfer of recipe data between different systems used for:

- Modeling/specification
- Batch control/execution/reporting
- Quality control/LIMS

Transfer of data between source and target systems would require validation of the recipe data warehouse.

Current Recipe Data Warehouse Experience

A prototype of the recipe data warehouse was built based on S88 and S95 standards and consistent with the published data models.

Standard S88 recipe process models for manufacturing processing and testing thereof was undertaken to drive a common platform of definitions for solid dosage and large molecule synthesis. These process models were loaded into the recipe data warehouse and subsequently used as a framework to abstract general, site, master, and control recipes from previously collected process and analytical data.

Implementation of the concept presented here required a significant amount of data manipulation as the current structure was as diverse as the number of experiments. Thereby, a significant amount of work was undertaken to transform executed batch records and associative analytical data into the recipe structure described above. More than 300 control recipes were converted and stored in the recipe data warehouse. Once the data was loaded, some query tools were developed to help retrieve and visualize the information from the warehouse as depicted in Figure 8.

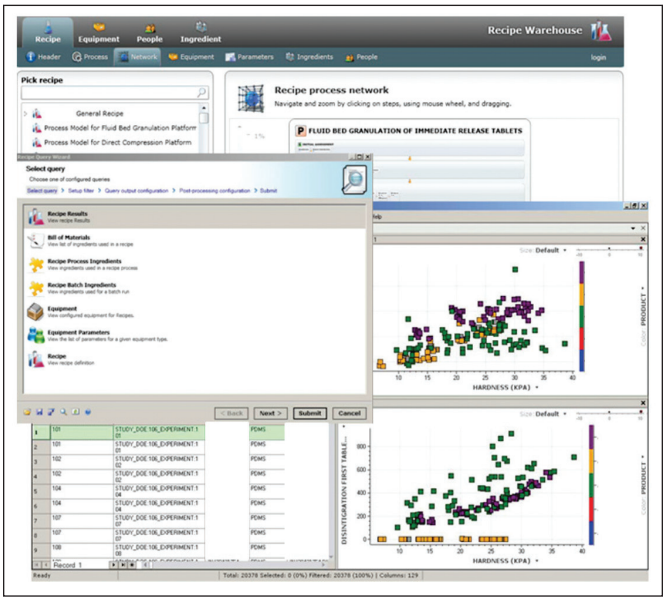

Figure 8. Recipe data warehouse – user interface.

Further Development Plans

Any data warehousing approach requires the organization to look at a continuous improvement of the data model, analysis, and reporting to help ensure learning is leveraged across the lifecycle of the product and across products. As such, the recipe data warehouse future will include expanding the data integration into quality control systems as well as business management tools. Through the combination of product knowledge and resource allocation, the acceleration goals of the organization can be reached, ultimately delivering value to the patients.

Conclusion

The pharmaceutical industry is awash with data, resultant from recipe execution. This data is generated via analytical and process recipe execution, but lacks context to support swift product lifecycle management. As such, recipe based execution requires a strategic approach toward the data management associated with said execution in order to change the current data paradigm from reactive to proactive with respect to releasing the inherent knowledge. To achieve the sustainability and ultimate vision of recipe based execution a system strategy coined "recipe data warehouse" is outlined here. The strategy leverages both external (S88/S95) and internal best practices by which a novel data warehouse was generated to address both. Through the implementation of such a system, the business benefits can be realized via the embracement of scientific and engineering methods. Empowering employees in the corporation will without doubt lead to a sustainable, scalable, and flexible environment to execute on the complex nature of commercializing new medicines for our patients.

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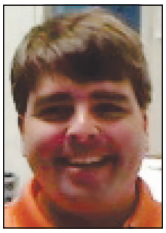

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This article presents and analyzes the results of a survey regarding the use of Non Investigational Medicinal Products (NIMPs).

Results and Analysis of the ISPE Survey Regarding Use of Non IMPs in Global Clinical Trials

by Lee Miller and Karen Main on behalf of the IP COP Non IMP Task Team

Summary

The purpose of the survey was to acquire data on the current use of materials which may be considered outside the scope of the regulatory filing requirements for Investigational Medicinal Products (IMPs) within clinical trials. The general survey was prepared by the members of the Investigational Product Community of Practice (IP COP) non IMP Task Team, administered by ISPE, and distributed to the IP COP and other investigational products (clinical supply) professionals. Generally, the data agrees that there is varied practice among survey participants regarding the Non Investigational Medicinal Products NIMP definition, use, and filing. This confirmed the need for a general Good Practice Guide[1] for such materials to supplement the document issued by the EMA describing requirements for clinical trial dossiers containing NIMPs.[2]

Background

ISPE's IP COP brings together investigational materials/products professionals to collaborate and interact to address issues of common concern. The IP COP is governed by a Steering Committee of committed volunteers who are subject matter experts in diverse fields related to investigational products. The COP is global with a strategic vision that supports industry professionals with interest or professional experience in all aspects of the investigational product (clinical product supply) supply chain. The IP COP consists of a global Council as well as regional Steering Committees in North America, Europe, and Japan. Joint Task Teams are oftentimes formed to organize guidance and respond, as needed, to proposed regulations.

After discussions at the 2010 ISPE Brussels Conference, the IP COP formed a global "**non IMP Task Team**" charged with preparing a guidance document targeted to provide practical guidance to harmonize the definition and use of Non Investigational Medicinal Products (NIMPs). The Task Team comprising members from Europe and North America met periodically with the goal of producing an ISPE Good Practice Guide entitled "Harmonizing the Definition and Use of Non IMPs." In doing so, the team collected data from an online ISPE sponsored survey performed among its professional community. Analysis of this information, along with detailed recommendations from the Task Team and extended group is anticipated to result in the final ISPE Good Practice Guide, to be issued toward the end of 2012 (draft issued May 2012). The detailed results of the survey are described in this article.

Survey

The non IMP Task Team, with the help of ISPE, composed and issued an online survey with the goal of understanding how the pharmaceutical industry manages NIMPs. The electronic survey was distributed to the ISPE IP COP as well as several other clinical supply related pharmaceutical professional groups during Q2 2011. Fifty-seven participants completed the survey.

Survey Rationale

The non IMP Task Team was formed in order to respond to the perceived general confusion as to the classification of investigational products, and the perception that some clinical supply professionals may overcomplicate clinical trials through submitting dossiers for products as IMPs in cases when they could be managed as NIMPs. One of the first objectives of the

Task Team was to collect information via the ISPE survey methodology to allow for data input from those clinical supply professionals not directly represented on the global team.

The following are the specific questions, the responses, and the non IMP Task Team's interpretation of the results.

Question 1: On average how many clinical trial protocols does your organization sponsor per year?

Of the survey responders, approximately 37% are from organizations that sponsor 100 or more clinical trial protocols per year. An additional 14% sponsor more than 50, but less than 100 clinical trial protocols per year. This would imply that at least half of the survey responders represent large, active pharmaceutical companies. Approximately 22% of the survey responders sponsor less than 25 clinical trial protocols per year. This group may represent smaller pharmaceutical companies and Contract Research Organizations (CROs).

Question 2: How many protocols has your organization managed that include clinical trial materials that are filed and handled as NIMPs?

The survey participants were asked to quantify the number of protocols their organizations supported that contained clinical trial material that was filed and managed as NIMPs - *Figure 2*. Approximately 55% have some experience with filing and handling clinical trial material as a NIMP. This further breaks down to approximately 29% of survey responders supporting 25 or fewer protocols and approximately 26% supporting more than 25 protocols containing a NIMP. This result was surprising. Based on the experiences of the non IMP Task Team, there was an expectation that a lower percentage of clinical trials would contain clinical trial materials filed as NIMPs. However, 31% of the survey responders did not distinguish between NIMPs and IMPs. There were seven write-in comments, six of which were "do not know." One was from a member of a CRO stating that their organization does not perform NIMP filings, but that their organization had provided NIMPs by request of the sponsor. One stated their organization only considered clinical trial material a NIMP if it was purchased directly by a patient. This result reiterated the premise that the Task Team held: general practical knowledge around the requirements of NIMPs and IMPs was needed.

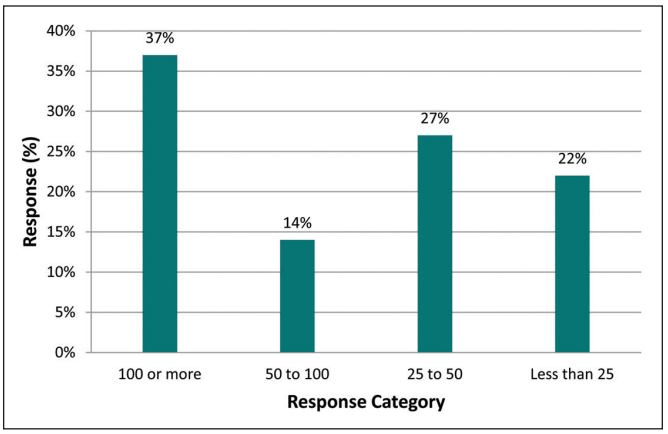

Figure 1. Data from Question 1 (N = 49).

Question 3: Which NIMP category do you have experience with using in clinical trials that was filed and/or handled as a NIMP?

The following six different categories of NIMPs were provided:

1. ***Background medication*** – standard of care to treat the indication that is the object of the study and provided to all participants.
2. ***Challenge agent*** – administered to the participant to produce a physiological response necessary to assess the IMP.
3. ***Concomitant medication –*** standard of care to treat an indication that is NOT the object of the study.
4. ***Endpoint medication*** – administered to participants to measure the effect of the IMP or other end point.
5. ***Rescue medication*** – administered to participants in an emergency situation.
6. ***Infusion solutions –*** (ancillary items): saline, sterile water for injection, etc.

Infusion solutions was included to capture additional practical information.

For this question, responders had an opportunity to select more than one category. Three of the six categories were selected in a majority of the responses. *Background medication* was selected in approximately 22% of the responses, *concomitant medication* in approximately 20% of the responses, and *rescue medication* in approximately 16% of the responses. Infusion solutions, defined as, but not limited to, saline or sterile water for injection, were only selected in approximately 13% of the responses. This may suggest that these types of globally available clinical trial materials are not included with study medication as a kitted unit. Rather, the sponsor may require the clinical study sites to supply these clinical trial materials locally, experiencing a cost and resources savings. It is logical that the sponsor may decide to include infusion solutions in the patient kit if the IMP requires a specific type or manufacturer of infusion solution that was not globally available.

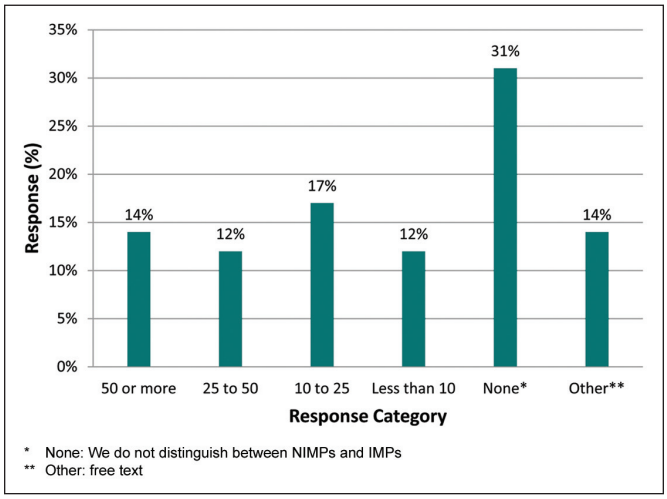

Figure 2. Data from Question 2 (N = 49).

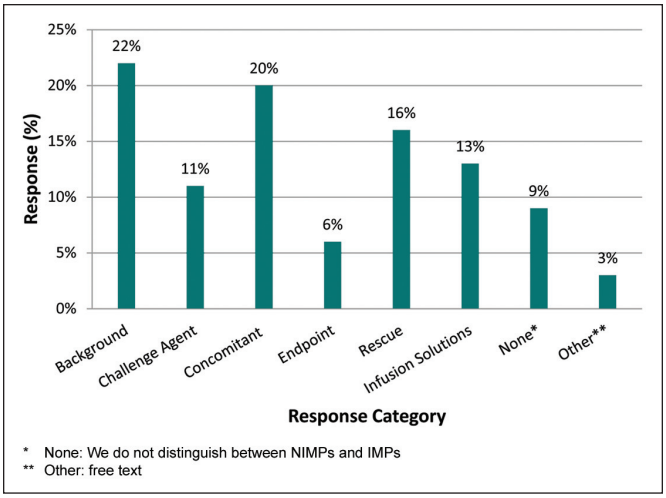

Figure 3. Data from Question 3 (N = 128).

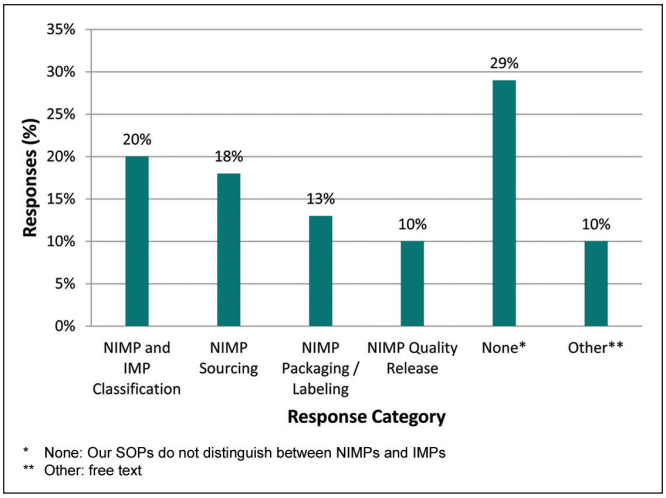

Figure 4. Data from Question 4 (N = 77).

Approximately 9% of the responders for this question selected "none of the above," and approximately 3% selected "other" and included a write-in comment. Of the four write-in comments, three provided additional information of no consequence. One further explained that their organization had expereince with filing a background medication, but that it was not provided to all treatment arms. However, no additional NIMP categories were provided, suggesting that the six categories presented were sufficient to capture the practical need.

Question 4: Does your organization have procedures and processes that address the following?

- NIMP and IMP classification
- Sourcing processes specific to NIMPs
- Packaging and labeling processes specific to NIMPs
- Quality release processes specific to NIMPs
- None: our SOPs do not distinguish between NIMPs or IMPs
- Other

Question 4 was written to gain some insight into whether the colleagues surveyed relied on standard operating procedures specific to NIMPs. Responders had an opportunity to select more than one category. Approximately 20% of responders have a procedure or process for classification of a NIMP versus an IMP and 18% have one for sourcing a NIMP. However, there is noticeable decrease for NIMP versus IMP-specific procedures when considering downstream activities like packaging, labeling, (~13%), and release (~10%). Based on the results from this question, there is a higher propensity toward having NIMP specific procedures and processes at the beginning stages of the clinical supply chain. Despite having procedures on sourcing NIMPs, it is inferred that these same organizations may rely on already established SOPs and GMPs for the downstream activities (i.e., packaging, labeling, and release). In addition, nearly 30% do not have unique procedures or processes specific to NIMPs, which roughly correlates with the results from question 2.

There were eight write-in comments (~10% "other"), five of which were of no consequence. Of the three remaining comments, the responders stated their organization 1) prepares a protocol-specific guide documenting the use of the NIMP, 2) uses a database to capture NIMP related information, and 3) is currently working on a NIMP-related SOP.

Question 5: Which functional area is responsible for classification of study medication as either a NIMP or an IMP?

- Research
- Clinical Supply
- Regulatory Clinical
- Quality
- None: we do not distinguish between NIMPs or IMPs
- Other

Approximately 31% of the survey responders do not distinguish between the two categories, hence reiterating the necessity for investigational material to be defined more clearly. Approximately 22% use a combination of functional areas (clinical supply, regulatory, quality, and clinical) via clinical supply team discussions to make this determination, as detailed in the responses for the "other" category. Of the organizations that leave the decision up to one functional

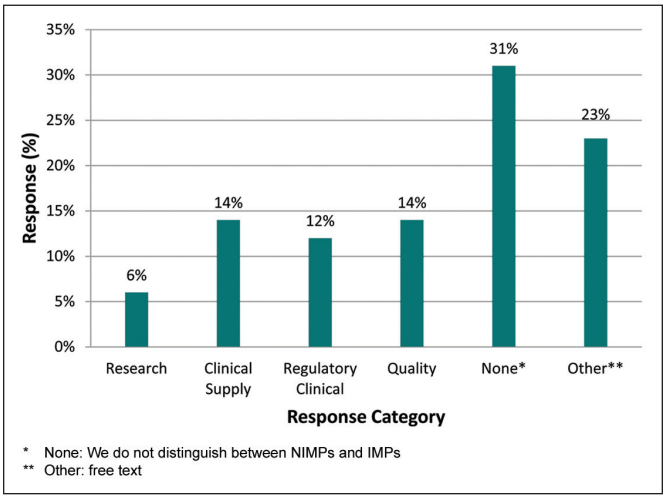

Figure 5. Data from Question 5 (N = 49).

area, there is nearly an even split between clinical supply (14%), regulatory (12%), and quality (14%). Of note in this survey, many companies vary in the definitions of functions within their organizations, and for this reason the question may have been misinterpreted.

During discussion of these results, the IP COP non IMP Task Team provided additional information that most members had good experience when the clinical/medical functional group were involved early in these discussions. The clinical team provides expert opinion on determining if the clinical trial material is considered a "*standard of care*" or "*background therapy*" as defined in the clinical protocol. Furthermore, in some circumstances, the clinical trial material could be used off-label as a NIMP if a national guidance document recommends its off-label use as being well established. However, there is a risk that some Health Authorities (HA) may not accept this argument.

Responses from this question suggest that a significant percentage (31%) of respondents do not distinguish between NIMPs and IMPs, creating the hypothesis that classifying material NIMPs may pose a risk for approvals, and further suggesting that there may be a bias to treat material in question as an IMP. This is an important topic for all clinical supply professionals, and will be further discussed in the ISPE Good Practice Guide issued by the IP COP non IMP Task Team.

Question 6: How does your organization typically source NIMPs that are licensed in the country where the clinical trial is taking place?

- Sponsor centrally sources the NIMPs
- Sponsor locally sources the NIMPs
- Clinical trial sites locally source the NIMPs
- None: we do not distinguish between NIMPs or IMPs
- Other

Question 7: How does your organization typically source NIMPs that are NOT licensed in the country where the clinical trial is taking place?

- Clinical trial material would be considered an IMP in the country in which it is not licensed
- Sponsor centrally sources NIMPs
- Sponsor locally sources NIMPs
- Clinical trial sites locally source NIMPs
- None: we do not distinguish between NIMPs or IMPs
- Other

Questions 6 and 7 asked those surveyed how they typically source NIMPs and allowed for more than one response per question. The results suggest that the respondents are using various methods, in combination, to source NIMPs that are licensed in the country where the clinical trial is taking place. Approximately 26% of the responders source the NIMP centrally. Central sourcing is defined as purchasing a NIMP for a clinical trial from one single country with the intention of using it in other countries in the clinical study. The survey showed a split (22 %) between the sponsor sourcing the NIMP locally or allowing the clinical trial site to source it locally. An additional 14% of the responders use locally sourced clinical trial material that already exists in the clinical trial site's inventory. Five responders provided write-in comments

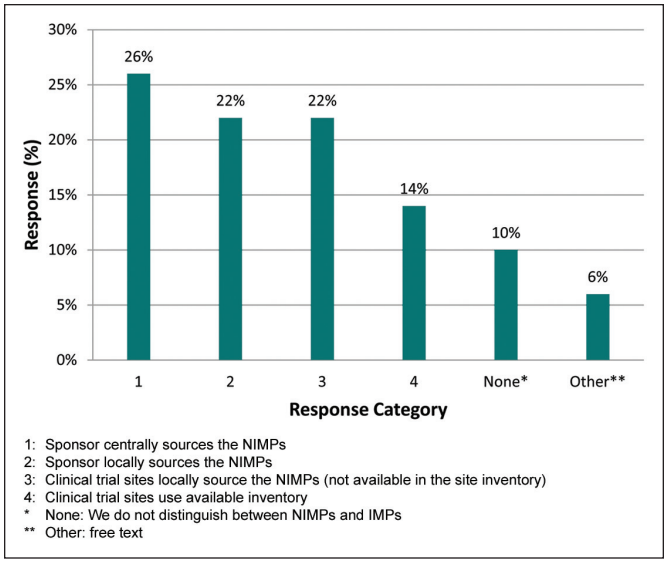

Figure 6. Data from Question 6 (N = 108).

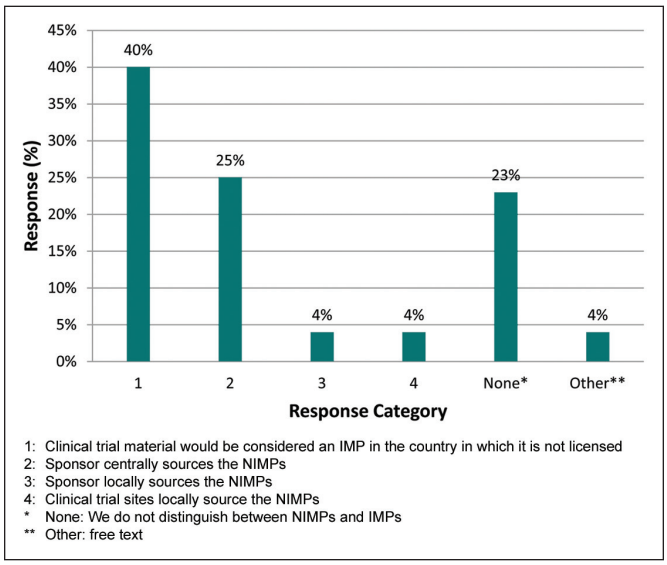

Figure 7. Data from Question 7 (N = 52).

(~6% "other") that their organization uses a combination of approaches with local regulations having a strong influence, and one write-in comment described the patient's physician (not the trial investigator) providing the NIMP by prescription.

When the NIMP is **not** licensed in the country in which the trial is taking place, approximately 40% of the responders re-categorize the clinical study material as an IMP. An additional 25% of responders continue to refer to it as a NIMP, but source it centrally through the sponsoring organization. The two write-in (4% "other") comments were of no consequence.

Question 8: Has your organization been challenged by a country Health Authority when classifying a clinical trial material as any of the following categories?

- Background medication: standard of care to treat the indication that is the object of the study and provided to all participants

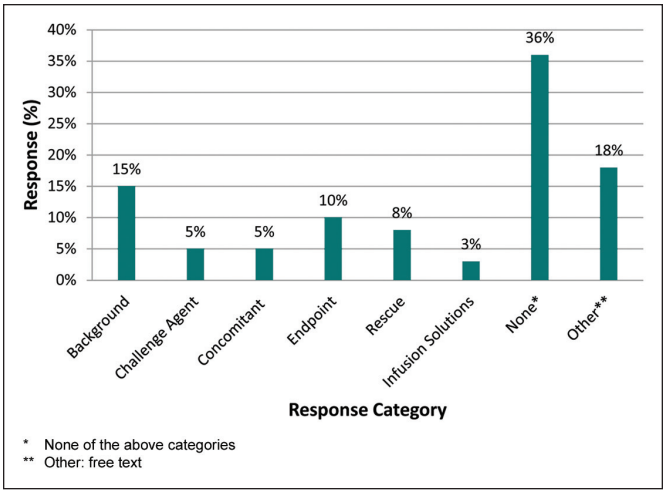

Figure 8. Data from Question 8 (N = 39).

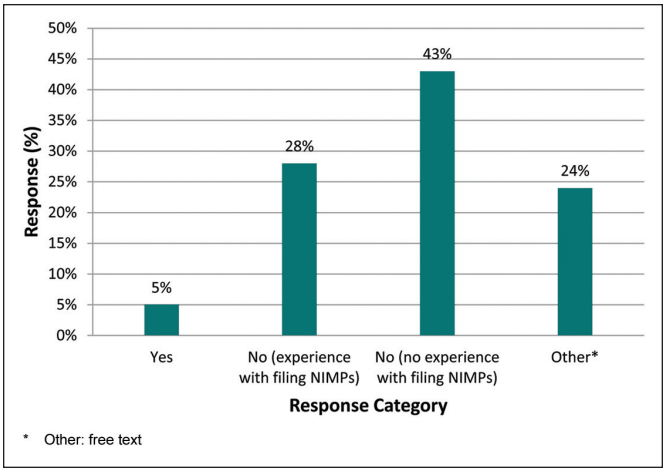

Figure 9. Data from Question 9 (N = 42).

- Challenge agent: administered to the participant to produce a physiological response necessary to assess the IMP
- Concomitant medication: standard of care to treat an indication that is NOT the object of the study
- Endpoint medication: administered to participants to measure the effect of the IMP or other end point
- Rescue medication: administered to participants in an emergency situation
- Infusion solutions (ancillary items): saline, sterile water for injection, etc.
- None of the above (clinical trial materials are always handled as IMPs)
- Other

Question 8 asked the survey responders if their organization was ever challenged by a country Health Authority (e.g., FDA, MHRA), and if so, to identify the category of NIMP that was the focus of the challenge. It is important to note that not all functional areas of an organization are privy to interaction with country Health Authorities. In addition, throughout the survey, approximately one third of the responders had indicated that their organization handles all clinical trial material as IMPs. Therefore, these organizations will not experience NIMP related challenges from the Health Authorities.

Approximately 15% of responders indicated that their organization has been challenged by a country Health Authority for a clinical trial material categorized as a *background medication*. The *background medication* is the most widely utilized NIMP category according to the survey responses in question 3. The second most widely used NIMP category according to the survey responders was *concomitant medication*. However, concomitant medication was not selected as being commonly challenged by the Health Authority.

The higher incidence of Health Authority challenges associated with *background medication* compared to other NIMP categories could be explained by considering the definition of *background medication*. The *background medication* is administered to each of the clinical trial participants (independent of treatment assignment) to treat the indication that is the object of the study. Therefore, it may be under greater scrutiny by the governing agencies.

Of the seven write-in comments (18% "other"), five responders stated that they did not know if their organization was ever challenged by a Health Authority concerning use of a NIMP, one stated "no," and one stated that as a CRO they would not have been notified if the sponsor had been challenged.

Question 9: Has your organization received a NIMP related finding during a GMP/GCP inspection?

Slightly more than 70% of the survey responders have not experienced this situation. Of those, only a third (28%) actually file clinical trial materials as NIMPs, the remaining 43% do not distinguish between NIMPs or IMPs. Only approximately 5% of the responders had experienced a NIMP related finding.

A majority of the write-in comments (24% "other") stated that the responders were not aware of any findings, but could not confidently select "yes" or "no."

Question 10: How does your organization typically package commercially available NIMPs?

- Keep the commercial primary and secondary packaging (i.e., use as is)
- Remove from the commercial secondary packaging and re-package in a clinical image secondary package, which is completed at the sponsor or contract research organization
- Remove from the commercial secondary packaging and re-package in a clinical image secondary package, which is completed at the clinical trial site
- None: we do not distinguish between NIMPs or IMPs
- Other

Approximately 42% of the survey responders keep the primary and secondary packaging in its commercial image. Nearly 13% remove the commercial secondary packaging and re-package in a clinical image secondary package at the sponsor's facility or a CRO. Approximately 5% of the survey responders selected that the re-packaging activity would be done at a clinical site. This low percentage is likely due to that fact that a re-packaging operation is considered GMP and most clinical sites may not be licensed accordingly. Upon

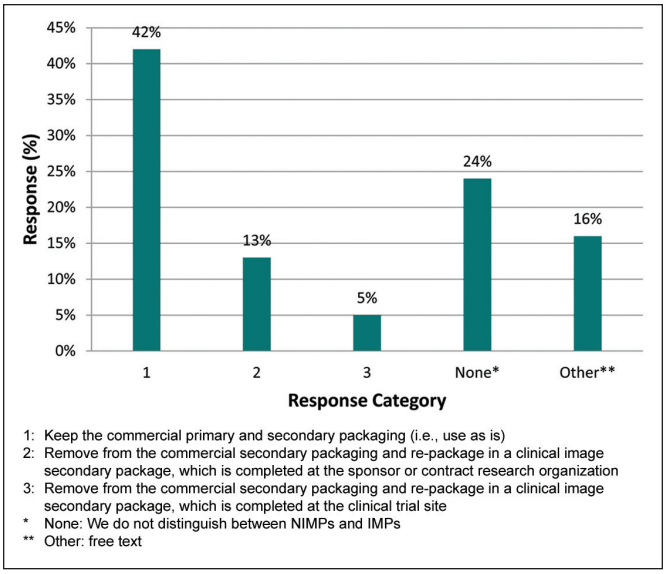

Figure 10. Data from Question 10 (N = 62).

review of the write-in comments, approximately 5% stated that their organizations apply a flag label to the outer carton of the commercial NIMP such that the label can be peeled back to expose the commercial text or an ancillary label is applied to meet specific country requirements.

Question 11: How does your organization typically label commercially available NIMPs?

- Commercial label only, no clinical labeling or caution statements added
- Additional label is applied to the commercial package to specify the study number or add caution statements
- Full clinical label is applied to the secondary commercial packaging
- Full clinical label is applied to the clinical image secondary packaging
- None: we do not distinguish between NIMPs or IMPs

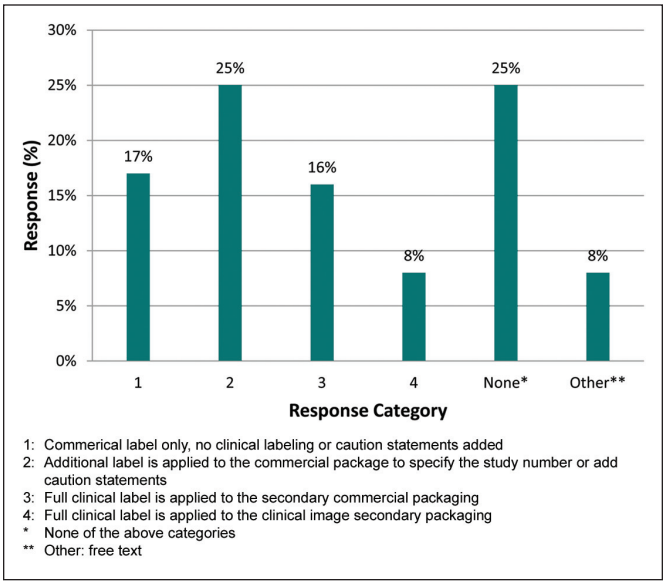

Figure 11. Data from Question 11 (N = 63).

Considering all the survey responses to question 11, which allowed for multiple responses, 49% of respondents add some kind of clinical label to the NIMP commercial packaging. Approximately 17% do not use any additional labeling. The lack of additional labeling suggests that these organizations are using locally procured commercial NIMP that is packaged in the appropriate language for the country in which the clinical trial is taking place. The write-in comments (8% "other") were of no consequence. Excluding 25% of responders that did not distinguish between NIMPs and IMPs, the percentage of responders that add some kind of label increases to 66% and those organizations that do not supplement the commercial labeling increases to approximately 23%.

Conclusion

It is difficult to make statistically significant conclusions from a small electronic survey to a diverse clinical supplies population. However, this survey does confirm that the use of investigational materials in clinical trials, and the distinction in the clinical supply chain from NIMPs, is challenging. The ISPE IP COP non IMP Task Team intends to meet this challenge with a document to summarize current regulatory guidelines and incorporate practical operational guidance for use of NIMPs.

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Dr. Karen Main has more than 30 years of experience in the pharmaceutical industry. In her present position, she is responsible for the site leadership for Pharmaceutical Development Wilmington and the US R&D Supply Chain function. Previously, she led the US/UK Investigational Products Group, encompassing IMP management, outsourced and internal packaging, labeling and distribution. Prior, she headed the US Product Development function where she was responsible for the formulation development, clinical supply manufacture, and technology transfer, as well as pharmaceutical contributions to global regulatory documentation for new drug entities. She has authored the CMC dossiers for four approved NDAs/MAA and multiple IND/IMPDs. Dr. Main is a Registered Pharmacist and received her BS magna cum laude from Rutgers College of Pharmacy. She went on to receive her Masters and Doctoral degrees in pharmaceutical chemistry from Rutgers University, certificates in pharmaceutical manufacturing (Stevens Institute of Technology) and supply chain management (Rutgers Business School). Dr. Main holds patents in sustained release technology, formulations, and has authored many scientific papers, including the chapter "Analysis of Medicinals" in the reference text Remington's Pharmaceutical Sciences. Dr. Main has been a frequent invited speaker at scientific conferences in the US and Europe, past Chair of the Drug Product Technical Group at PhRMA and the PhRMA Technical Leadership Committee, and served on the Expert Working Group for ICH Q8. She can be contacted by email: karen.main@astrazeneca.com.

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Come and Experience the New ISPE

ISPE President and CEO Nancy S. Berg introduces the Society's new mission and explains the buzz about a progressive new experience planned for the ISPE 2012 Annual Meeting and events throughout the year.

by Nancy S. Berg

The annual meeting of any professional society is typically the culmination of a year's work of its membership, the platform from which the society speaks to industry and its members, a time for learning and networking – it is the gathering of the clan. One of my primary objectives is to help influence a progressive new experience for our members not only at the Annual Meeting, but throughout the year. Those who attended our all-new CGMP Conference in Baltimore in June witnessed the new educational format, high energy sessions, extensive regulatory and industry leader participation, and productive networking. You can be a part of the same ISPE experience at the upcoming ISPE 2012 Annual Meeting, 11 to 14 November in San Francisco, California, USA.This year's Annual Meeting features comprehensive conferences, the addition of some special sessions and "discussion" groups, and meetings of the entire organization, including ISPE's Communities of Practice (COPs), Committees and Councils, Chapter and Affiliate leaders, the Board of Directors, and the International Leadership Forum (ILF). Regulatory agencies from more than 15 countries have been invited to speak, to serve as panelists and as discussion leaders, demonstrating to industry and members the important role ISPE has in facilitating collaboration, stimulating advancement of ideas and technology, and building solutions to business, technical, and regulatory challenges.

Big Event

More than 150 members have influenced the development of ISPE's 2012 Annual Meeting. The four-day technical conference will include more than 125 presentations featuring investigational products, quality systems, supply networks, global regulatory initiatives, project management, advanced technology, emerging markets and more. Speakers will cover sustainability issues and Greenfield projects, innovation in laboratory operations, and transforming and managing the product lifecycle – and these are just a few highlights. Sessions are designed for members new to the industry, those working in intermediate and advanced level roles as well as industry leaders. This year, our keynote speakers include Dr. Stephen P. Spielberg, FDA's new Deputy Commissioner for Medical Products and Tobacco, and Murray Aitken, Executive Director, IMS Institute for Healthcare Informatics – both plan to share global views on industry and regulatory scenes, discuss trends, and share impressions on how ISPE should help in responding to challenges in our ever changing and very complex business and regulatory environments.

The International Leadership Forum (ILF) also will meet during the ISPE 2012 Annual Meeting. ILF members operate in leadership roles in their enterprises and lead quality, research, production, finance and other business functions, as well as R&D, clinical and manufacturing operations. This year, the ISPE Annual Meeting features the return of the "Executive Series" programs on 12 November. These programs are open to all delegates and include presentations on new technology, sustainability, enterprise risk management and other key topics identified by the ILF in the Global Positioning Strategy (GPS) document as integral to our industry's future.

Advance Look at New ISPE Mission

During the Annual Meeting, ISPE will communicate updates to its strategic plan. Stay tuned for more information on our approach to building and sustaining member value, and plans to take a more active leadership role in industry issues. As you can read below, our new

mission statement reflects our blended membership and how industry views their business operations today:

By 2015, ISPE will be recognized globally as the leading technical organization for professionals engaged in producing quality medicines and pharmaceutical devices throughout the product lifecycle.

Rest assured that the new mission represents an anticipated evolution of the Society's focus and there will not be a radical departure from our traditions or in our areas of expertise, such as manufacturing operations, facilities, advanced technology, GAMP, supply chain, or others. Looking forward, ISPE must be reflective of industry and we are anticipating continued growth as we build upon areas of the product lifecycle, such as quality management, supply management, and other organizational processes and systems.

Business Aside.

We are now in the third quarter of what is proving to be another year of change for the pharmaceutical industry. As your association, we understand your hectic schedules and work challenges. In fact, it is that understanding that motivates us to create an Annual Meeting that is both business-focused and enjoyable. This year's event is locally hosted by our San Francisco Chapter; these members are supporting tours of local pharmaceutical and biotech facilities, offering advice and support around local tours for our international delegates and attending family members, and championing the early morning ISPE Fitness events (a 5k charity run and ISPilates – ISPE's own 6 am pilates classes). During the event, we also will host a meeting for "Team ISPE," our own volunteer cycling team that will train to ride in "America's Most Beautiful Bike Ride" (2 June 2013). This century ride (100 miles) around Lake Tahoe in California/Nevada, USA, is in conjunction with the Leukemia & Lymphoma Society's Team in Training Program (LLS-TNT). Many of you and your companies already support this event. Those interested in being a part of our team will train with a national cycling coach and work with fundraising mentors as part of the LLS "Virtual Team." As members of ISPE, we support our patient customers and industry by giving back, and in this event, cycling for a cure. Some may recognize the personal connection – my husband, Tim, is a lymphoma patient and has been an honored patient rider in this challenging event. Email me at NBerg@ISPE.org for details.

Join Us

Plan now to attend the 2012 Annual Meeting to be a part of the new ISPE Experience. ISPE members are leading the industry and staying ahead of issues and resolving them. A comprehensive promotional brochure will be mailed to you shortly, but you also may take advantage of registering online now at www.ispe.org/2012annualmeeting. I look forward to meeting you in San Francisco this November.

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International

Chinese SFDA Commissioner Yin Li Meets WHO Director-General Dr. Margaret Chan[1]

On the morning of 17 July 2012, Yin Li, Commissioner of the State Food and Drug Administration (SFDA), met with the visiting Dr. Margaret Chan, Director-General of the World Health Organization (WHO). Main directors of SFDA's Department of International Cooperation, Department of Drug Registration, Bureau of Investigation and Enforcement, National Institutes for Food and Drug Control, relevant director of Department of Drug Safety and Inspection, and WHO Representative in China Dr. Michael O'Leary attended the meeting.

Korea Food and Drug Administration Signs a Memorandum of Understanding with Indonesian National Agency of Drug and Food Control[2]

On 12 July 2012, the Korea Food and Drug Administration signed a Memorandum of Understanding (MOU) with National Agency of Drug and Food Control in Jakarta, Indonesia. Under this MOU, the two agencies agreed to cooperate in the areas of food, drug (API, vaccines, biopharmaceuticals), herbal medicines, cosmetics, and health functional foods and work to enhance safety of imported food and drugs in a collaborative manner.

EU Commissioner Dalli Visits the US[3]

Health and Consumers' Commissioner John Dalli discussed a variety of issues covering all three pillars of his portfolio (health, consumer policy, food safety) during an official visit to the United States from 27 to 29 June 2012. The Commissioner participated at the third Trilateral European Union-China-United States Consumer Product Safety Summit together with counterparts from the US and China: Inez M. Tenenbaum, Chairman of the US Consumer Product Safety Commission (CPSC) and Sun Dawei, Vice Minister of the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ). The topic of the Summit was "Product Safety Surveillance from Factory to Front Door: A Cooperative Effort."

The Commissioner met with Health Secretary Kathleen Sebelius and Deputy Bill Corr to discuss, among other subjects, ageing and Alzheimer's disease, eHealth, healthcare reform, and tobacco. Tobacco also was a topic discussed during his bilateral with Margaret Hamburg, Commissioner of the US Food and Drug Administration (US FDA). Further meetings were scheduled with Kathleen Merrigan, Deputy Secretary of the US Department of Agriculture (USDA), to discuss animal health and livestock exports, as well as with Rich Cordray, Director of the Consumer Financial Protection Bureau, to exchange information on financial consumer protection activities on both sides. Other appointments included breakfast with the American Association of Retired People, lunch with the European American Business Council, and meetings with the Consumer Product Safety Commission and the United States Trade Representative's office.

ICH

E3 Q&As on Structure and Content of Clinical Study Reports Available on the ICH Website[4]

In June 2012, the ICH E3 Implementation Working Group finalized under Step 4 of the ICH Process a set of questions and answers addressing content and structure, appendices, and terminology. This supplementary questions and answers document intends to clarify key issues which were identified since the ICH E3 Guideline was published in the three ICH regions. The ICH E3 Q&As document is available for download from the E3 Section on the Efficacy Guideline page at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

Asia/Pacific Rim

Japan

Japan Publishes "Answers to the Questions on Generic Drugs" in Japanese[5]

This document addressing issues concerning generic drugs can be found at http://www.mhlw.go.jp/bunya/iryou/kouhatu-iyaku/dl/02_120713.pdf. It is available only in Japanese.

Europe

European Union

European Medicines Agency Sees Benefits of Interaction with Japanese Regulators[6]

The European Medicines Agency has increased its level of interaction and cooperation with medicines regulatory authorities in Japan over the past three years, according to the report on interactions.

Since November 2009, when the Japanese authorities seconded their first liaison official to the Agency, there has been an increase in information exchange and interaction on areas of mutual interest, with Japanese and European representatives attending conferences and meetings in each others' territories.

European Medicines Agency Releases Two Further Modules on Good Pharmacovigilance Practices for Public Consultation[7]

The European Medicines Agency has released two further modules of the guideline on good pharmacovigilance practices (GVP) for public consultation until 21 September 2012. The modules are: Module IV: Pharmacovigilance Audits; Module XV: Safety Communication. GVP are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). They apply to marketing-authorization holders, the Agency, and medicines regulatory authorities in EU Member States and aim to improve safety for patients by strengthening the monitoring of the safety of medicines across the EU. They cover medicines authorized centrally via the Agency as well as medicines authorized at national level.

New Rules on Importing Active Pharmaceutical Ingredients into the EU – Information Leaflet[8]

The European Union (EU) has reformed the rules for importing into the EU active substances for medicinal products for human use. As of 2 January 2013, all imported active substances must have been manufactured in compliance

with standards of Good Manufacturing Practices (GMP) at least equivalent to the GMP of the EU. The manufacturing standards in the EU for active substances are those of the "International Conference for Harmonization" – ICH Q7. As of 2 July 2013, this compliance must be confirmed in writing by the competent authority of the exporting country. This document also must confirm that the plant where the active substance was manufactured is subject to control and enforcement of good manufacturing practices at least equivalent to that in the EU. The template for such written confirmation can be found overleaf. This must accompany the active substance being imported into the EU. The leaflet can be found at: http://ec.europa.eu/health/files/documents/active_pharmaceutical_ingredients_leaflet_en.pdf.

European Regulators Back First Gene Therapy Drug[9]

European regulators have recommended approval of the Western world's first gene therapy drug – after rejecting it on three previous occasions – in a significant advance for the novel medical technology. More than 20 years since the first experiments with the ground-breaking method for fixing faulty genes, scientists and drug companies are still struggling to apply gene therapy in practice. The decision by the European Medicines Agency (EMA) is a win for the drug's maker, the small Dutch biotech company uniQure, and a potential lifeline for patients with the ultra rare genetic disorder lipoprotein lipase deficiency (LPLD).

Adoption and Publication of Commission Implementing Regulation on Pharmacovigilance Activities in the EU[10]

Following its adoption on 19 June, the Commission Implementing Regulation (EU) 520/2012 on the performance of pharmacovigilance activities has been published in the Official Journal of the European Union. This Implementing Regulation complements the 2010 pharmacovigilance legislation, which started to apply in July 2012, by providing the more technical details that have to be observed by marketing authorization holders, national competent authorities, and EMA in the daily practice of applying the new legislation. It is therefore an important piece in the new framework, which will promote and protect public health by strengthening the European system for monitoring the safety and use of medicines. The text of the Implementing Regulation is at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF.

European Medicines Agency Finalizes Guidance on Medicines Containing Monoclonal Antibodies[11]

The European Medicines Agency has finalized two documents providing pharmaceutical companies with guidance on how to develop medicines containing monoclonal antibodies. The guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical aspects provides information on the requirements for companies developing medicines containing monoclonal antibodies that are similar to medicines already authorized. The second document, the guideline on immunogenicity assessment of monoclonal antibodies intended for in-vivo clinical use addresses issues related to the body's development of antibodies against these medicines, which could lead to reductions in their effectiveness or rare, serious side effects.

European Medicines Agency Management Board Completes Framework for Conflicts of Interests[12]

The European Medicines Agency's Management Board adopted a new "breach of trust procedure" to deal with cases of incorrect or incomplete declarations of interests of Board members. The adoption of the latest procedure completes the Agency's framework on dealing with potential conflicts of interests of its scientific experts, committee members, Management Board members, and staff.

EMA Annual Report 2011 Shows Continuously High Level of Activities[13]

The report shows continuously high levels of activities in almost all of the Agency's business areas. There was a slight increase in the number of applications for initial marketing authorizations for medicines for human use, from 91 applications in 2010 to 100 applications in 2011. Most of this increase was due to applications received for new medicines: this number rose by more than 40% from 34 in 2010 to 48 in 2011. The number of applications received for initial marketing authorization for veterinary medicines declined slightly, which is likely to reflect the delayed impact of global recession and the consolidation seen in recent years in the veterinary sector. Significant advances were made in terms of transparency. In March 2011, the European Union Clinical Trials Register went live. The launch of this database was welcomed by patients, consumers, and healthcare professionals organizations as an important step toward increasing transparency of medical research and facilitating availability of information about clinical trials taking place. Later in the year, the Agency launched a new database of European experts, which allows the public to access an expert's declaration of interests online. However, nowhere was the impact of the Agency's much more proactive approach to transparency more dramatic as in relation to handling of access-to-documents requests. During the course of the first full year of operation of the new access to documents policy, the Agency released more than a million pages in response to requests.

Denmark

Danish Health and Medicines Authority Announces New Opening Hours from 2 July 2012[14]

As part of the merger announced earlier this year, the Danish Health and Medicines Authority introduced new opening hours as of 2 July 2012. From 2 July 2012, the following will apply:

- Premises and telephone lines will

be open Monday-Friday, 9:30-15:00.
- Goods can be delivered Monday-Friday, 8:30-15:00.

In addition, a special service hotline will be taking calls for Medicine Prices every other Monday between 15:00-16:30 (in weeks when the pharmaceutical companies must notify changes in prices and packages). The Medicine Prices service hotline: +45 4488 9694.

Finland

Finnish Medicines Agency Revises Regulation on Pharmacovigilance of Veterinary Medicinal Products[15]

The administrative regulation on the pharmacovigilance of veterinary medicinal products has been revised. Administrative regulation 1/2012 of the Finnish Medicines Agency entered into force on 2 July 2012, thereby repealing administrative regulation 2/2010 of the Finnish Medicines Agency previously issued on the matter. The administrative regulation applies to the pharmacovigilance of medicinal products intended for animal use. By this administrative regulation, the Finnish Medicines Agency implements nationally the requirements regarding pharmacovigilance of veterinary medicinal products in compliance with the European Union regulation. The amendments made in the updated administrative regulation concern the reference to the guideline "Volume 9B of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use."

Great Britain

Britain's MHRA Asks for Views About Giving Patients Earlier Access to Medicines[16]

The Medicines and Healthcare products Regulatory Agency (MHRA) launched a 12-week public consultation on proposals to launch an Early Access to Medicines Scheme. Under the scheme, the MHRA would provide a scientific opinion on the benefits and risks of medicines. This would assist the NHS in making decisions about making medicines available for patients with life threatening, chronic, or debilitating conditions.

Netherlands

Dutch Medicines Evaluation Board Again ISO Certified[17]

The MEB has been certified according to the ISO 9001:2008 standard for many years. This certificate is valid for three years. In 2012, the MEB had a reaudit and its ISO 9001:2008 certificate was successfully renewed.

Dutch Medicines Evaluation Board Presents Annual Report with the Theme "Continuous Improvement Through Scientific Underpinning"[18]

On 6 June, the 2011 Annual Report of the Medicines Evaluation Board was presented. This year's theme is "continuous improvement through scientific underpinning." This theme indicates that the MEB is always searching for ways to reinforce the quality of its work. Insight into the latest scientific state of affairs contributes to this to an important extent. This is why an underpinning in clinico-scientific and academic networks is one of the MEB's five strategic objectives.

North America/ South America

USA

US FDA Releases Video Explaining Accelerated Approval Program[19]

The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious diseases and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker that is used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval. Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. These studies are known as phase 4 confirmatory trials. If the confirmatory trial shows that the drug actually provides a clinical benefit, the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit, the FDA has regulatory procedures in place that could lead to removing the drug from the market. To watch the video, go to http://youtu.be/fzlePvW-Dg4.

US FDA Publishes Foods and Veterinary Medicine Strategic Plan 2012 – 2016[20]

FDA presents its Strategic Plan for the Foods and Veterinary Medicine Program (FVM) for 2012-2016. The plan takes into account all of the activities within the jurisdictions of the Center for Food Safety and Applied Nutrition and the Center for Veterinary Medicine and includes activities supported by the Office of Regulatory Affairs. The plan illustrates the breadth and complexity of the program's work and identifies priority initiatives. It outlines seven strategic program goals, each encompassing its own key objectives, as well as nearly 100 specific initiatives aimed at achieving goals and objectives. For more information, see http://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/ucm273269.htm.

US FDA Publishes "Small Business Chronicles" on Topic of Orphan Drugs[21]

This publication, which can be found at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM311928.pdf?source=govdelivery, provides an overview of issues associated with orphan drugs and a list of resources for those wanting to learn more about this topic.

US Food and Drug Administration Safety and Innovation Act (FDASIA) Signed into Law[22]

The Food and Drug Administration Safety and Innovation Act, signed into law on 9 July 2012, gives the FDA the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs, and biosimilar biologics. It also reauthorizes two programs that encourage pediatric drug development. This is the fifth reauthorization of the Prescription Drug User Fee Act or PDUFA, first enacted in 1992, and the third reauthorization

of the Medical Device User Fee Act, or MDUFA, first enacted in 2002.

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The State of Quality by Design for Generics

Report on Joint ISPE – European Generics Association Meeting on Applying QbD to Development and Manufacture of Generic Medicines

by Chris Potter, ISPE PQLI Technical Project Manager and CMC Pharmaceutical Consultant

Editor's Note: The following is an abridged version. The full article, including references and acknowledgements, can be viewed at pharmaceuticalengineering.org.

Introduction

The US FDA has made public statements that from early 2013 Abbreviated New Drug Applications (ANDAs) applicable to generic medicines should contain Quality by Design (QbD) elements. Many EU-based companies source the US.

The generic medicines industry operates at a very fast pace, in a very competitive environment, and with the need to file first as a key business goal. Companies obviously want to achieve more robust and efficient manufacturing processes and supply chains. Many practical questions regarding implementation of QbD remain open.

On 27-28 June 2012 in Brussels, Belgium, ISPE co-hosted with the European Generics Association (EGA) the first meeting in Europe to discuss application of QbD approaches to the development and manufacture of generic medicines. There were keynote presentations from eminent EU and US regulators and from the generic medicines industry, as well as case study examples and workshops with published outputs to discuss the regulatory, technical, and business implications of using QbD approaches.

Discussion Highlights

All speakers included in their content reference to at least one of the four relevant ICH guidelines, Q8 (R2), Q9, Q10, and Q11.

Also relevant are supporting Questions & Answers and Points to Consider documents and training material available from the ICH web site. Particular definitions often referenced were:

- Quality Target Product Profile (QTPP)
- Quality by Design (QbD)
- Critical Quality Attribute (CQA)
- Critical Process Parameter (CPP)
- Quality Risk Management (QRM)
- Control Strategy
- Design Space

Jean-Louis Robert, chairman of the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP)/Committee for Medicinal Products for Veterinary Use (CVMP) Quality Working Party, said that QbD is not totally new in the EU, referring to the previous CHMP Guideline on Development Pharmaceutics. However, he insisted that a sound, more systematic development approach with use of more formal risk management should facilitate the process to achieve quality and more knowledge. He pointed out that QbD does not require establishment of a design space or necessarily lead to real time release testing. Independent of the level of development ("minimum" or "enhanced, QbD") a control strategy is always required. Additionally, he stressed that a conventional specification is still required and acceptance criteria are likely to be set using a balance between clinical relevance and process capability.

Keith Webber, Deputy Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER), US FDA, said that implementation of QbD is essential to ensuring the availability of affordable, high quality generic drugs in the US. He indicated that QbD goals were to reduce product variability and defects, to increase product development and manufacturing efficiencies, and to enhance post-approval change management. The minimum ICH Q8 expectations are to define a QTPP, identify and control CQAs of drug product, determine CQAs of drug substance and relevant excipients, select an appropriate manufacturing process, and define a control strategy. He stressed that a basis of the enhanced, QbD approach was development of process understanding whereby there is linkage of critical material attributes and CPPs to relevant drug product CQAs.

Jacques Morenas of the French National Agency for Medicine and Health Products Safety (ANSM) concentrated on implementation of Q9 and Q10 in the EU and the potential impact on current EU GMP guidelines. He said Q9, Quality Risk Management (QRM) provides principles and a framework for science-based decision making. It is simple, flexible, not mandatory, facilitates communication and transparency, and supports build-up of trust between regulators and industry. He discussed an example of the application of QRM in the GMP inspection environment by referencing the work being undertaken by the CHMP Safety Working Party to develop toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities. He also described the ANSM approach to risk-based GMP inspection planning, which was derived from the recommended model elaborated by PIC/S QRM Experts Circle. With regard to Q10, Morenas identified those parts of the EU GMP guide which are being or have been revised based at least in part on ICH Q10. He concluded that Q10 allows global harmonization of a Pharmaceutical Quality System

Concludes on page 2.

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(PQS), that a PQS is mandatory to comply with EU GMP, and ICH Q10 reflects current expectations for EU GMP.

Pito Roslansky of Sandoz International GmbH showed examples of how there can be different QbD strategies and that use of prior knowledge can be very effective to reduce development time and resources. There are significant challenges applying a QbD approach, for example, compatibility with the business need to be first-to-file in the US. For the globally-sourcing industry there are challenges with: global regulatory alignment; alignment with the new US process validation guidance; low amounts of drug substance during early development; and unavailability of excipient samples for quality attribute evaluation. Nonetheless, the enhanced, QbD approach should lead to improved product and process understanding with the concomitant benefits.

All three case studies emphasised the need to balance the business environment and regulators' expectations with the amount of work and its timing in the development program and with the anticipated benefits. All described their company's iterative, science- and risk-based approach.

Francois Menard of Watson Pharmaceuticals showed with two generic drug product case studies of complex products how matching the CQA of dissolution profile of the originator product from an osmotic delivery system and from a coated multi-particulate system could be achieved successfully using a QbD approach. Use of advanced analytical methods and development of process models were described. Significant business benefits were described.

Jose Ascensao of Hovione indicated the "Hovione Way" to QbD implementation. He particularly emphasized the important role of risk management to optimize the number of variables to study in statistically-designed studies, as well as to optimize the number of experiments, and in each experiment, the range and intervals of variables to study.

Jan Ramza of Polpharma SA explained Polpharma's decision to apply QbD to development of API processes. Polpharma uses risk management to select the critical steps of the process on which to apply the QbD approach. For other steps, conventional studies to determine proven acceptable ranges are performed. New equipment and software was required to implement QbD, as was new documentation and additional training. Goals for the project were achieved.

The main points from the Workshops are:

A. Why consider QbD?

- Develop your own business case.
- Consider a pilot project.
- Involve all disciplines.

B. How do you effectively develop products and processes using QbD?

- New tools and expertise required – knowledge management, Process Analytical Technology (PAT), risk assessment, multivariate experiments and analysis
- PAT tools may be more suitably applied in development.
- IT software and infrastructure required

C. What are the regulatory expectations for QbD submissions?

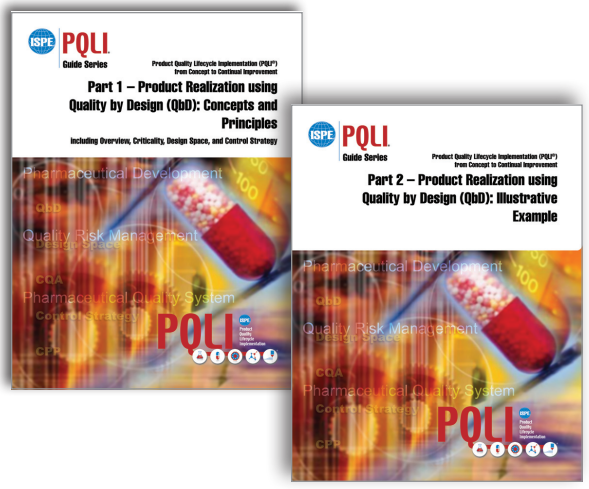
- Assessors want a well-written, clear story. Internal peer review is recommended.
- No real difference for inspections
- Use accurate ICH terminology.

Conclusion

The main conclusions from the meeting were:

- QbD is feasible for the generic medicines sector and there are benefits.
- Such meetings create the necessary platform for dialogue between regulators and industry experts.
- It is essential that implementation by the various regions remains harmonized.

Guidance on technical aspects of implementation of QbD approaches is given in Part 1, Concepts and Principles and Part 2 Illustrative Example of the ISPE PQLI Guide series.



New Guide Provides Holistic View of Ozone Sanitization Systems

The use of ozone to sanitize pharmaceutical water storage and distribution systems has increased as manufacturers of drug components and substances strive for innovative methods to reduce capital and operating costs. But, there is no regulatory or detailed industry standard or guidance on the topic. ISPE has released the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Systems*, which provides a comprehensive overview of the requirements, advantages, and disadvantages to consider when choosing ozone for sanitization over heat and chemical solutions.

New Guide Establishes Industry Baseline for Quality Laboratory Facilities Design

ISPE has produced the industry's first Guidance Document to establish a baseline for the design of Quality Laboratory Facilities. The *ISPE Good Practice Guide: Quality Laboratory Facilities* is a comprehensive guide to defining design guidelines for Quality Laboratories supporting GxP-regulated facilities producing pharmaceutical products for human and animal applications. It provides a step-by-step process that guides the reader through all phases of producing a quality lab and all the factors that must be considered at each phase. The Guide helps save time and money by facilitating effective communication between lab owners, engineers and builders about the function, operation and design parameters that must be met.

Both of these Guides are available for purchase at www.ISPE.org/Guidance-Documents

ISPE Releases New Guidance for Designing and Constructing Packaging, Labeling, and Warehousing Facilities

ISPE released new guidance relating to the design, construction and commissioning and qualification of packaging, labeling and warehousing (PACLAW) facilities. The Guide helps companies meet CGMP requirements for these types of facilities while avoiding product adulteration, product mix-up, label mix-up and misbranding. The Guide contains FDA input and is the industry's only guidance of this type for PACLAW facilities.

"PACLAW facilities are very different from other types of pharmaceutical facilities, and up until this point, there has been no consistent guidance available to help companies ensure compliance," said Guide Author Nick Davies. "With this ISPE Good Practice Guide, the industry finally has tools to ensure their PACLAW processes are efficient, compare their processes to established best practices and demonstrate compliance to regulatory agencies."

The *ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Facilities* presents an approach to satisfying CGMPs while providing realistic solutions to business and operational concerns. It addresses Quality by Design principles and establishes consistent guidelines that can be incorporated into the design and/or reconfiguration of PACLAW facilities. It covers facility design issues for most primary packaging operations, such as filling of the dosage form in the immediate container/closure system, and other packaging, labeling and warehousing processes. The Guide also provides direction on how to comply with the FDA's systems-based approach with a risk-based inspectional model as it relates to PACLAW facilities.

The *ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Facilities* is available for purchase from ISPE at www.ISPE.org/PACLAWFacilitiesGuide.

ISPE's PQLI Addresses Process Validation Topics

Introduction

The US FDA recently published a revised guidance on process validation,[1] which aligns process validation activities with a product lifecycle concept and with existing FDA guidance.[2] It is not a departure as much as an extension of the previous FDA guidance that it replaces. The new guidance is consistent with and includes concepts from ICH guidelines on Pharmaceutical Development,[3] Quality Risk Management,[4] and Pharmaceutical Quality System.[5] EMA also issued a draft revision to the Guideline on Process Validation,[6] which is circulated for public comment for completion by 31 October 2012. This document focuses on process validation information required in an EU regulatory submission. Annex 15 of EU GMP provides a similar level of detail as the previous FDA guidance regarding GMP activities.

The FDA guidance defines process validation *as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.* While this definition places more emphasis on a lifecycle approach, the objectives of process validation remain essentially the same (evidence that a process can consistently/reproducibly produce quality product) as in previous guidance documents.

Since the newly released FDA guidance has a different emphasis than the previous FDA guidance, there is an industry need for clarification on how to interpret and implement the information. ISPE is responding to that need and expanding its PQLI activities to include Process Validation.

Relatively short documents called discussion papers have been written to support and guide practical implementation from a lifecycle perspective. These documents discuss application of concepts and provide examples. It is anticipated that these documents will be amended or revised based on feedback and further understanding of implementation of the process validation lifecycle concept. Highest priority is being given to topics identified as most significantly changed compared with previous process validation expectations, including:

- Topic 1: "Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches"
- Topic 2: "Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products"

Additional topics will be covered based on stakeholder interest and feedback.

Why the Need to Address These Topics?

In the FDA Process Validation Guidance, the Agency introduces a lifecycle approach to process validation that links product and process development, *qualification of the commercial manufacturing process,* and maintenance of the process ***in a state of control*** during routine commercial production. Adherence to this approach assists in assuring the higher level goal of reliable supply of high quality product.

An important new consideration is that process validation is no longer viewed as a one-off event, but instead involves a series of activities taking place in three stages over the lifecycle of the process. The goals and typical activities of each stage are summarized in the Table below:

Stage of Process Validation	Definition	Goals	Typical Activities
Stage 1	Process Design	Define and design process	Build knowledge and understanding of input/output relationships and potential variability generated through development and scale up activities. Establish an initial strategy for process control.
Stage 2	Process Qualification	Evaluation that the designed process is capable of **reproducible** commercial manufacturing	Design of a facility and qualification of utilities and equipment. A number of Process Performance Qualification (PPQ) batches to confirm the process design and demonstrate that the commercial manufacturing process performs as expected in the commercial manufacturing facility. Level of sampling may be higher than routine monitoring; the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.
Stage 3	Continued Process Verification (CPV)	Ongoing assurance that the process remains **in a state of control**	Ongoing programs to collect and analyze product and process data (monitoring plans) to establish a continual state of control of the process. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

This is a significant change for the industry and different interpretations and approaches may be taken by manufacturers to satisfy the requirements and apply the recommendation of this guidance over the lifecycle of the process and product.

Industry may benefit from practical considerations regarding implementation given the significant change from previous FDA guidance.[2] For example, the FDA places considerable emphasis on the use of objective measures regarding gathering and assessing data, and specifically the appropriate use of statistical tools for both designing sampling plans and evaluating data. Several different approaches may be taken during the second part of PV Stage 2, Process Performance

ISPE'S PQLI Addresses Process Validation Topics

Continued.

Qualification (PPQ) and during PV Stage 3, Continued Process Verification. Rather than attempting to produce a document that addresses every aspect of the FDA Process Validation Guidance, the PQLI approach produced two relatively short papers to prompt industry discussion. These discussion papers have been reviewed by industry and FDA representatives and can be accessed on the ISPE Web site. The discussion papers give a number of practical considerations and relevant examples to support implementation and are intended to provide a basis for industry to begin assessing the choices that may be applicable to their product and business situation. In the longer term, as industry and the FDA gain experience in practical implementation of the lifecycle approach, these discussion papers can be revised and may form the basis of future Parts of the ISPE PQLI Guide series.

Benefits of These Topics

In Parts 1 and 2 of the PQLI Guide series,[7,8,9] ISPE has produced assistance to industry in meeting Stage 1 of the FDA guidance, Process Design. PQLI Part 1 provides an overview of the enhanced, Quality by Design approach to designing a product and building and capturing process knowledge and understanding, which is the first part of Stage 1, Process Design of the FDA PV Guidance. PQLI Part 1 also includes extensive discussion of how to establish a strategy for process control, which is the second part of FDA's PV Guidance Process Design stage. Considerations for employing Process Analytical Technology tools are also given. The PQLI Part 2, Illustrative Example provides a thorough illustration of the application of risk management to the product and process design phases and introduction into manufacturing of a small molecule tablet formulation, and development of part of the drug substance synthetic route. The iterative nature of risk management steps and design of experiments is also discussed and exemplified.

Given this foundation of practical "how to" approaches for implementation of Stage 1, Process Design of FDA Process Validation Guidance it is considered that suggestions for practical approaches for the second part of Stage 2, Process Qualification and of Stage 3, Continued Process Verification would be of value to industry. FDA PV Stage 2, part 1, Design of Facility and Qualification of Utilities and Equipment follows what has been performed in the pharmaceutical industry for many years and practitioners should refer to other ISPE Good Practice Guides, e.g., the Commissioning and Qualification Baseline® Guide, which provides advice and guidance that may be applied to all types of facilities, utilities, and equipment found in the healthcare industry.

The FDA PV Lifecycle Approach Stage 2, part 2, Process Performance Qualification (PPQ) introduces new elements compared with previous guidance. For example, the number of batches required for PPQ is not defined, only the objective: that the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. The FDA recommends that *objective measures (e.g., statistical metrics)* are used wherever feasible and meaningful to achieve adequate assurance. The guidance also states that in most cases, PPQ will have *a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch.* The FDA guidance does not give an indication of how to meet these objectives. Most importantly, *a manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product. The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.*

Given the importance of this stage of process validation both to the assurance of the quality of product distributed to the market and to the business situation (completion of PPQ is required to distribute the product), further "how to" considerations and examples may be useful to industry to assist with implementation. One of the most significant changes in PPQ is determining and justifying the number of process performance qualification batches, considering data generated during Stage 1 (product and process development). Consequently, as a continuation of ISPE's PQLI program, this was chosen as Topic 1 of the Process Validation Part of the PQLI series on which to provide some assistance to practitioners.

Continued Process Verification is defined *as assuring that during routine production the process remains in a state of control.*[1] The FDA guidance notes that while good process design and development should anticipate significant sources of variability, during commercial manufacturing a process is likely to encounter sources of variation and/or interactions that were not previously detected or to which the process was not previously exposed. Production data should therefore be collected to evaluate process stability and capability, and identify variability and/or potential process improvements. FDA guidance also recommends that the increased level of scrutiny, testing, and sampling determined for PPQ should continue through the process verification stage as appropriate, to establish technically defensible levels and frequency of routine sampling and monitoring for the particular product and process. The guidance provides some considerations of how to select heightened sampling and monitoring plans appropriate in Stage 3.

The FDA guidance recommends that *a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.* Additional recommendations are *that the manufacturer use quantitative, statistical methods whenever appropriate and feasible.*

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While process performance analysis to support continual improvement may have been adopted by some companies as a sound business practice, often driven by operational excellence principles, bringing this activity under the umbrella of process validation is a change for the industry. Different interpretations and approaches may be taken by manufacturers to satisfy the guidance and to apply it appropriately over the lifecycle of the process and product. There is also significant uncertainty regarding how Continued Process Verification as discussed in the new FDA guidance should be applied to existing (legacy) products.

Industry may benefit from examples of some practical approaches to determining when heightened monitoring may be required, and which aspects of the process should be included in Continued Process Verification (Stage 3) for both new and existing products. Consequently, how to apply Continued Process Verification Expectations to New and Existing Products was chosen as Topic 2 of the Process Validation discussion papers.

Some Key Points from the Topics

Topic 1: "Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches"

This paper discusses science- and risk-based approaches to determine and justify the number of Process Performance Qualification (PPQ) batches needed to demonstrate with an appropriate level of assurance that a process can reproducibly yield a quality product. The paper reviews considerations on how to estimate the risk that a process may not be capable of reproducible manufacture. The overall risk identified from this assessment may then be translated to a number of PPQ batches or to conclude that a process is not yet ready for manufacture of PPQ batches. The approach described in this paper is outlined in Figure 1.

The paper describes risk factors that could be included in an assessment of the risk that a process may not be capable of reproducible manufacture, such as the level of product knowledge and process understanding, the strength of the control strategy, and level of understanding of relationships between current process understanding and the control strategy to achieve the Critical Quality Attributes (CQAs). (See PQLI series Parts 1 and 2 for further discussion and exemplification.)

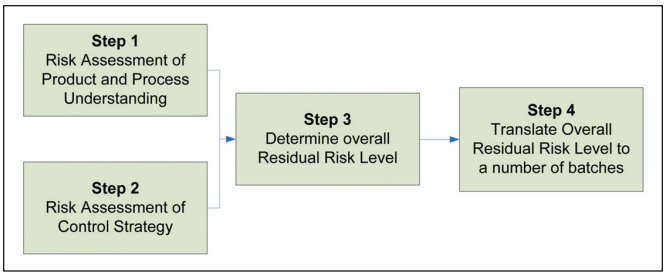

Figure 1. Workflow for Determination of Number of Stage 2 Process Performance Qualification Lots.

A non-statistical approach for assigning the number of PPQ batches based on the overall risk is described in the paper. Two statistically-based approaches are also discussed. The level of residual risk associated with the manufacturing process is used to choose a quantifiable degree of certainty that the process will ultimately demonstrate a robust (acceptable) level of output variability. The higher the residual risk, the more statistical certainty required during PPQ, prior to commercialization and hence more PPQ batches should be manufactured. In practice, the approach chosen to translate the residual risk to a number of PPQ batches, whether it is one of the three described here or another approach, should be one that is most suitable for the particular circumstances of the process to be qualified, and its suitability for application to the particular product and process should be justified.

Following this, data from the PPQ lots are analyzed using appropriate statistical methods to determine the outcome of the PPQ study and to help identify additional sampling or analyses needed in the Stage 3 Continued Process Verification program.

Topic 2: "Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products"

A potential approach to selecting parameters/attributes for the CPV plan and determining whether heightened sampling may be required and the overall process is described in this paper as applied to new and existing (legacy) products. This paper looks at Continued Process Verification as a dynamic sampling plan where the level of monitoring may increase or decrease throughout the commercial phase of the lifecycle, including the initial phase for new products on whether heightened monitoring may be required for any aspect of the process after successful completion of PPQ.

The scope of the CPV plan should include the product CQAs at minimum, but should also consider raw material and in process material attributes and process parameters that may be indicative of process performance and product quality. For all new products, a monitoring plan should be established immediately following completion of Process Qualification, Stage 2. The scope of CPV for existing (legacy) products should be defined and an initial evaluation of process performance conducted based on routine monitoring data for the identified attributes and parameters. As for a new process, this evaluation should then determine the appropriate level of sampling for ongoing monitoring. Establishing the appropriate level of monitoring at any time during Stage 3 may include consideration of the relative criticality of the impacted product CQA, the impact of unit operation and parameter variability on the product CQA and current capability, the range of experience of material variability impacting product CQAs, and the robustness of any predictive models.

The approach to analyzing process performance and prod-

...Process Validation Topics

Continued.

uct quality data should be documented and should address which input and output parameters and/or attributes will be monitored, how data will be collected, the methodology that will be used to evaluate the data (e.g., statistical methods) and the frequency of evaluation. The paper discusses:

- Establishing a Continued Process Verification Monitoring Plan
  - Selection of Parameters and Attributes to be Monitored and Level of Sampling
  - Review of the Stage 3 Plan
- Data Analysis and Review
  - Process Analysis Tools
  - Setting Control/Action Limits
  - Capability Analysis
  - Data Evaluation and Impact to Product Release Decisions
  - Frequency of Process Analysis
  - Knowledge Management
  - Responsibilities for Process Analysis
- Defining Corrective and Preventive Actions

Examples from both a small and large molecule process are given to assist with understanding for new products and an example is given of development of a Stage 3 monitoring plan for an existing product.

The Illustrative Example in Part 2 of the PQLI series is used as the basis for examples in the Stage 2 and Stage 3 discussion papers, providing continuity from Stage 1 (described in the Illustrative Example) through the PPQ part of Stage 2 to Stage 3, Continued Process Verification.

Conclusion

ISPE's two discussion papers offer practical considerations and examples for implementing aspects of the Process Performance Qualification part of PV Stage 2 and PV Stage 3, Continued Process Verification of the FDA Process Validation Guidance. The two discussion papers are:

- Topic 1: "Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches"
- Topic 2: "Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products"

A successful practical workshop was held February 2012 at the ISPE Facilities Conference in Tampa, Florida, USA with the goal of gathering and providing input to these topics and active participation from Grace McNally of the FDA. Further input is scheduled at the ISPE Contemporary Trends in Facilities and Compliance European Conference, Process Validation, Track 2 in Brussels, 17-18 September 2012, where discussion of the draft EMA guideline is planned with Catherine McHugh of the IMB and Keith Pugh of EMA. Additionally a workshop is planned for the ISPE Conference on Process Validation: Practical Application of the Lifecycle Approach in Silver Spring, Maryland, USA, 17-18 October 2012. Attendance is recommended for all those impacted by changing process validation guidelines. Further information on both conferences can be obtained from www.ISPE.org.

The discussion papers can be accessed through the ISPE website at www.ispe.org/pqli. Additional feedback is being solicited.

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Pharmaceutical Engineering Announces Finalists of the Article of the Year Award

Roger F. Sherwood Article of the Year
PHARMACEUTICAL ENGINEERING

Pharmaceutical Engineering's "Article of the Year" recognizes the contribution of authors and articles are evaluated by a panel of volunteer reviewers according to a number of criteria including: applicability, timeliness, relevancy, quality of content, and presentation.

The finalists for each "Article of the Year" are chosen from the September/October issue of the previous year, through the July/August issue of the current year. The winner will be announced and recognized at ISPE's 2012 Annual Meeting, 11-14 November in San Francisco, California, USA. The award program was established to express appreciation to all of the authors who submit their work for publication in Pharmaceutical Engineering.

We are pleased to announce the finalists of the 2011-2012 Roger F. Sherwood Article of the Year Award:

SEPTEMBER/OCTOBER 2011, VOL 31, NO 5

Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (API's): Part II

by Andrew Walsh

This article discusses how to establish true science-based limits 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.

NOVEMBER/DECEMBER 2011, VOL 31, NO 6

Online Rouge Monitoring: A Science-Based Technology to Measure Rouge Rates

by Nissan Cohen and Allan Perkins

This article presents the implementation and installation of an online rouge monitor which measures in near real-time the rouge rate and rouge accumulation (metal loss) over time helping to determine derouging and passivation frequency based on empirical data.

JANUARY/FEBRUARY 2012, VOL 32, NO 1

Risk Analysis and Mitigation Matrix (RAMM) – A Risk Tool for Quality Management

by Alex Brindle, Steve Davy, David Tiffany, and Chris Watts

This article presents a new type of risk tool. Risk Analysis and Mitigation Matrix (RAMM) was developed to be incorporated into a modern risk management system and align with latest FDA guidances.

MARCH/APRIL 2012, VOL 32, NO 2

Application of Pre-Owned Equipment in Pharmaceutical Manufacturing Operations

by Stephan Sirabian, Bob Matje, Jeff Biskup, and Witold Lehmann

This article presents considerations to be made prior to making a capital investment in pre-owned equipment for new or refurbished pharmaceutical facilities.

MAY/JUNE 2012, VOL 32, NO 3

Pressure Pulse Approach for Optimized Tank Cooling after Steaming

by Magnus Stering, Olivier Chancel, and Luc Pisarik

This article presents an approach for faster cooling after steaming or after hot cleaning in place without the risk of generating vacuum inside the vessel and without the need for any large sized vent filter.

JULY/AUGUST 2012, VOL 32, NO 4

The Use of Acceptable Daily Exposure (ADE's) for Managing the Risk of Cross Contamination in Pharmaceutical Manufacturing

by Stephanie Wilkins and Julian Wilkins

This article presents a convincing justification for the use of Acceptable Daily Exposures (ADEs) to scientifically manage the risk of cross contamination in all types of bio/pharmaceutical facilities.

2012 ISPE-CCPIE China Conference

ISPE and the China Center for Pharmaceutical International Exchange (CCPIE) of SFDA will hold their annual joint conference 24 - 25 September 2012 at the China National Convention Center in Beijing, China. This year's theme is "The Rise of China's Pharmaceutical Industry and Opportunity from Drug GMP."

Highlights include discussion on: implementation of the revised pharmaceutical GMP certification and inspection; industry technology development trends; and successful qualification cases of newly amended GMPs to unveil key factors. A networking banquet will take place to maximize communication with industry players.

Topics include: sterile manufacturing facilities engineering; practical aseptic processing; engineering practice for Grade A and B in operation; rapid microbiological identification technology; advanced aseptic processing techniques – restricted access barrier system (RABS) and isolators; disposable technologies; GAMP; environmental monitoring; data management; and the implementation of revised GMPs.

For more information and to register, visit http://www.china-pharm.net/newsletter/20120406/en/ispe/index.html.

2012 ISPE Annual Meeting: Global GMP Solutions through Innovation and Transformation

Our world is shrinking, cultures and practices are merging, and the need for idea sharing and interaction is more important than ever. To navigate the complex, evolving pharmaceutical industry, individuals and companies need the latest information on technology, application, and best practices, and want meaningful interaction with regulators and industry leaders. Soon, hundreds of pharmaceutical professionals from around the world and across the product lifecycle will gather to share that knowledge and interact with the regulatory community at one of the industry's most important events of the year – the ISPE Annual Meeting.

This year's Annual Meeting, to be held 11-14 November in San Francisco, California, USA, will offer new experiences for participants to exchange essential information on how to maintain quality, improve processes, reduce costs, and manage international supply chains:

Plenary Speakers

Stephen P. Spielberg, MD, PhD, Deputy Commissioner for Medical Products and Tobacco, FDA, USA

How the FDA is Advancing Regulatory Science through High Quality Collaboration

When Commissioner Hamburg created the position of Deputy Commissioner for Medical Products and Tobacco, she envisioned that it would "provide high-level coordination and leadership across the Centers for drug, biologics, medical devices, and tobacco products." This executive-level presentation will demonstrate how the FDA is addressing regulatory strategies and international collaboration.

Murray Aitken, Executive Director, IMS Institute for Healthcare Informatics, USA

Top Priorities and Trends for the Pharmaceutical Industry

Hear cutting-edge research in the pharmaceutical market and learn how to address those changes and what your company should be focusing on next. IMS will release quantifiable data, which will provide a global analysis of the industry as well as forecasting of top priorities and trends through 2016. Exclusive information will also be released to Annual Meeting attendees only.

International Regulatory Summit

Monday, 12 November *13.15 - 14.45*

In our global economy, the interaction between industry and regulators is crucial. This summit will bring together high-level regulators from North America, Europe, Asia, and Latin America to discuss regional regulatory challenges and examine those challenges within the context of a global regulatory environment.

Executive Series

Monday, 12 November *15.30 - 17.15*

ISPE is pleased to announce the Annual Meeting Executive Series, which will focus on the six topic areas outlined in the International Leadership Forums white paper, entitled the "Global Positioning Strategy (GPS)":

1. Next Generation Processes, Equipment, and Facilities
2. Biotechnology
3. Supply Chain Management
4. Enterprise Risk Management
5. Sustainability
6. Organizational Development

This series will feature Senior Executives who will provide insight into the importance of these subjects for the development of a manufacturing strategy; create a platform for further exploration and development of these ideas into commercial reality; and explore the global business environment, regulatory changes, and emerging technologies that will impact our industry over the remainder of this decade.

Education Sessions

Sunday – Wednesday, 11 – 14 November

Comprehensive education sessions, will include a mix of workshops, panel discussions, and presentations to present delegates with best practices, applications, technology innovation and opportunities to engage with global regulatory agencies and industry experts.

Tracks Include:

- Emerging Markets
- Facilities and Equipment
- International Regulatory
- Investigational Products
- Manufacturing Operations
- Project Management
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This article presents the various aspects of scheduling in QC laboratories.

Resource Scheduling in QC Laboratories

by Rafi Maslaton

Introduction

Today's environment reflects a transition we have been observing for the past decade driven by external economic forces, patents expiration, dwindling pipeline of new drug candidates, and increased competition. Price controls are currently enforced throughout Europe, while, in the US, changes in the healthcare system are expected to reduce profitability and drive increased demand for lower cost products. Over the next five years, $92 billion worth of name-brand drugs will come off patent. The result: more emphasis on efficient drug manufacturing and R&D and greater recognition of the strategic importance of drug manufacturing. Wall Street expects to see companies better manage their expenses, and 2012 is focused on achieving operational excellence as a means to better compete against peers in light of these trends. The labs are a critical component of any drug manufacturing and can have a major impact on the overall supply chain service level, e.g., cycle time and on-time delivery. The importance of resource planning in QC labs to meet both capacity and compliance needs has been written about previously.[1] This article is focused on the scheduling aspect of QC labs; if we are forced to choose a key focus area for a QC labs performance, it will be lab **scheduling**. Scheduling by far contributes to all aspects of the lab operation efficiency and makes it the single most important process in the QC labs. Most of the labs today are using MS Excel based tools, whiteboard, and using LIMS to define the assignments, yet these are still primarily manual scheduling techniques or communication methods that are time consuming especially for the supervisors. Lean labs initiatives have helped simplify the lab scheduling process, yet do not offer a robust and computerized scheduling solution. At the end of the day, lab scheduling heavily relies on the supervisor knowledge and experience to manage the schedule of his/her team. This article focuses on how to automate the scheduling process in the labs and provides guidance on how to better schedule the labs, and what the critical elements and considerations are for a computerized scheduling solution to enhance the overall lab performance.

Background – The Lab Environment

The following is a typical description of lab situations that could be magnified when it comes to generic or contract manufacturing (also in some of the brand labs), where there are more changes during the week (compared to typical brand labs), more products are manufactured, and less visibility or control on the incoming samples. It is not uncommon to see a daily meeting with supply chain and the QC labs discussing priority and changes to the schedule that was updated only a few hours ago. The supply chain provides a list of samples that need to be released and asks the QC labs for committed dates. Then, the labs have to make changes in their schedule and assignments, reduce their campaign size, or avoid campaigning to accommodate the supply chain requests. When you have a backlog and every efficiency gain is crucial to remediate the situation, what has just happened is completely the opposite of what needs to have happened. These requested samples by the supply chain group, which does not always fully understand the implications of scheduling changes on the labs, leads to a smaller campaign size, hence reduced efficiency and changes in what the analysts are doing, leading to another loss of efficiency (waste of set up or some preparations that need to be scrapped); this makes the backlog even more severe than a couple of days ago. With overtime, more support, and allocation of resources within the labs we eventually end up reducing the backlog to a more manageable level. In short, the supply chain group, which does not have the means to schedule the lab or understand the impact of schedule changes on

the lab, is making the calls. The labs are under a lot of pressure and are forced to follow up on the demanding requests from the supply chain; the company server is overloaded with emails complaining about the labs and no one is raising the flag saying what we are doing is the opposite of what we should be doing. What was described is actually the typical behavior of most companies during a backlog situation. This is one of the key reasons for companies to move toward a computerized scheduling solution compared with the schedule/priority list that changes by the time it is being distributed. Going back to our backlog situation, what both the supply chain and the QC labs should have done is actually increase campaign size knowing this will lead to slight delays in the delivery dates of some samples. However, it will increase the efficiency and allow the lab to catch up. The labs will increase their capacity as a result of increased campaign size, reduce the number of daily changes, and gradually will handle the backlog situation. This is not an intuitive strategy, yet it is the only one that could work in this type of situation. Of course there are exceptions and some samples should be prioritized, but the rule of thumb is not to exceed about 10% of the samples to be high priority/rush samples. Many of these issues could have been resolved with a robust computerized scheduling solution that will take into consideration all the aspects that affect both the labs' efficiency and the service level. One important note is related to resource planning: the planning aspect of the lab may have been poor and the labs were under staffed as a result to handle the requested volume, which brings us back to the importance of resource planning as discussed previously.[1] Not having sufficient resources to handle the incoming volume will put the labs in a backlog situation; poor scheduling will make this situation last longer and hinder the overall service level provided by the QC Labs.

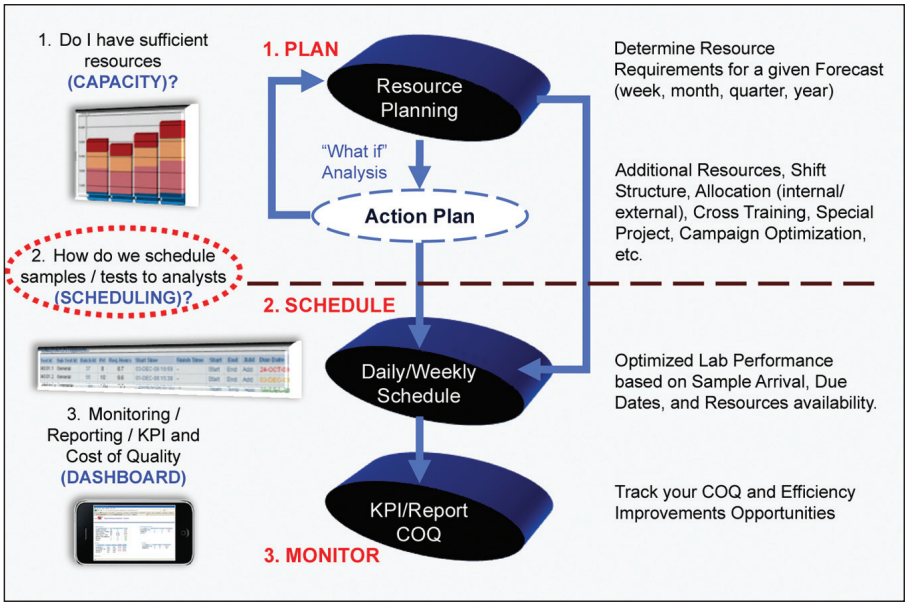

Figure 1. Managing labs operation: strategic level and daily operation.

Managing Labs Operation: Strategic and Day to Day Operation

Before diving into the scheduling process, let's first establish the overall strategic view and the role of planning scheduling and key performance indicators. QC resource modeling is one of three major steps in managing lab operations. As can be seen in Figure 1,[1] the first step is resource planning, which enables us to determine if we have sufficient number of analysts and equipment resources to meet customer/business demand. There may be short term gaps that could be managed via over-time, temporary work force, outside lab services; there may be more long term gaps that may require hiring and/or outsourcing to implement operational excellence improvements. Once we determine we have sufficient resources, we then move into the second step, the daily scheduling, which is our main topic for this article. This is the day to day lab operation scheduling effort performed primarily manually by the supervisor due to the lack of a computerized solution. In this step, the incoming samples/tests are scheduled to the various analysts based on their qualifications, proficiency, experience level, availability, due date, priority, etc. Unlike the first step of planning, which is the strategic level in managing the lab operations, this is the tactical level and requires a detailed and constant effort to schedule and maintain it. The last step is reports, Key Performance Indicators (KPI), dashboard, and overall monitoring of the lab performance. The common component of all the steps is the data set required for the lab resource modeling that is the foundation for planning, scheduling, and reporting.

Scheduling Complexity in the Lab

While manufacturing needs to schedule a batch, we have to realize what a batch represents to the lab. One batch includes samples of raw material API and excipients that require 5 to 20 different tests, samples of In Process (IP) testing, Finish Product (FG) testing, and stability. Each sample, similar to a manufacturing batch, needs to go through several instruments and can only be performed by qualified analysts. However, each batch represents several samples and each sample represents several tests. To illustrate this, here is a simple example. We will use Little's Law to make the calculation. Little's Law is named after John D.C. Little, who proved it mathematically in 1961 that "The average number of customers in a system (over some interval) is equal to their average arrival rate, multiplied by their average time in the system." A corollary has been added: "The average time in the system is equal to the average time in queue plus the average time it takes to receive service."

Little's Law can be written as:

$$L = \lambda \bullet \omega \quad \text{or} \quad \omega = \frac{L}{\lambda}$$

Where:

- L = average inventory (tests in the lab);
- λ = Start rate (batches/FG samples per week);
- ω = Cycle time (weeks)

Also:

- L = average # in queue + average # in process

Let's take the Finish Product (FG) sample and let's assume there are 10 tests per sample, the lab cycle time is (ω) 14 days, and we have (λ) 50 batches per week (assuming one batch represents one sample). This means (based on Little's Law) on average there are $(L = \lambda \bullet \omega) \rightarrow (50 \bullet 10) \bullet (14 / 7)$ different tests/tasks that need to be scheduled and managed which is equal to 1,000 tasks (some of the tests may require multiple instruments, i.e., dissolution and HPLC which increases that complexity). In comparison, manufacturing cycle time, as an example, also will be 14 days and we have a solid dose process that includes pharmacy, granulation, compression, coating, and packaging (five areas), so the number of batches needed to be managed throughout the process will be $(L = \lambda \bullet \omega) \rightarrow (50) \bullet (14 / 7)$ equal to 100 (10% of the volume compared with the lab). Now if we add the raw materials, the in-process and the stability samples and tests we are looking at 10 times the amount of activities that need to be managed and scheduled at the lab.

Now let's focus on the lab, with the exception of stability, the lab has limited control over incoming samples, and the campaigning strategy of manufacturing may not always be aligned with the lab requirements, which leads to loss of efficiency. In addition, each analyst has a different training profile; we have 50 HPLCs vs. 5 to 6 compression suites, and the pressure in the lab is much higher because the lab is a downstream operation (closer to the end of the supply chain), and hence delaying the shipments. Next we should look at the breakdown of tests and the complexity associated with scheduling each one to the appropriate center of excellence, and to the proficient and available analysts. In short, lab scheduling complexity is significant and presents additional difficulties compared with manufacturing, especially in terms of the sheer volume of activities.

The Effect of Scheduling on QC Lab

Optimizing the schedule will help maximize campaigning, while ensuring service level is not negatively affected. This is a key focus area for the supply chain in order to avoid the service level focus leading to a reduction in the lab campaigning level, which could majorly contribute to a labs inefficiency. Optimizing the schedule will ensure assigning the samples/tests to the best available analysts who are the most efficient in this method. Optimized campaign level leads to efficiency improvement, which affects the overall lab costs and service level. Other key performance indicators that are directly influenced by the scheduling effectiveness are: cycle time and on-time delivery. Optimizing the schedule will ensure the right tests are started at the right time and all tests related to a given sample are completed at approximately the same time. Poor scheduling may lead to starting with the wrong test or missing a test and finding out only later on that this test was not started, at which point it is too late and the cycle time goal is missed. On-time delivery, similar to cycle time, is significantly affected by scheduling. While cycle time focuses on getting the samples completed within the allowable negotiated cycle time with the supply chain on average, on-time delivery ensures that the exceptions are being managed as well (e.g., expedite sample although it may meet its regular cycle time, but miss its due date). Finally, with optimized schedule, the overall organization can eliminate waste associated with numerous meetings, emails, and telephone calls to manage the incoming samples. This leads us to the next related aspect of scheduling, which is the automation or the computerizing of the actual scheduling process.

Why Automate

The schedule, as discussed earlier, has a major effect on several key performance indicators in QC labs. The schedule complexity can be greater than the manufacturing or packaging. Furthermore, in more dynamic labs, the priority and due dates are frequently changed and this directly affects the lab priority and schedule. Automating the lab schedule makes sense when one considers all of the complexity, flexibility, and dynamics of the supply chain in addition to the time required to produce and change a schedule. Automating the schedule could result in freeing up more time for supervisors to manage investigations, conduct FMEA, lead root cause analyses, coach analysts, develop a training road map, analyze key performance indicators, identify areas for improvements, and communicate the lab schedule with the supply chain, etc. In a complex and dynamic lab, the scheduling process may consume two to three hours daily from each supervisor if it is done correctly, e.g., maximizing campaigning in general, identifying campaigning between finished goods and stability, and managing the on-going schedule changes. In order to automate the schedule, we need to assess what attributes are associated with the scheduling process that supervisors use during the scheduling process. Automating the schedule also will provide improvements in many of the key performance indicators as a by-product, as well as providing a more real time labs' dashboard that we can use to more accurately trace the progress on the samples/tests that are being scheduled and processed. Leveraging the scheduling algorithm can provide the supply chain with a cycle time projection for the samples in the labs, including when these are expected to be released.

Scheduling Attributes

In order to computerize the scheduling process in the lab, the various scheduling related attributes that should be considered must be identified. Based on the lab goals and business environment, these attributes should be configured to meet these goals. For example, considering the qualifications of a resource (analyst) is a requirement, this should be aligned with the learning/training management system. Adding proficiency can enhance the assignments and provide the lab with the ability to determine which analyst will be preferred to receive a certain assignment vs. other analysts. This is currently per-

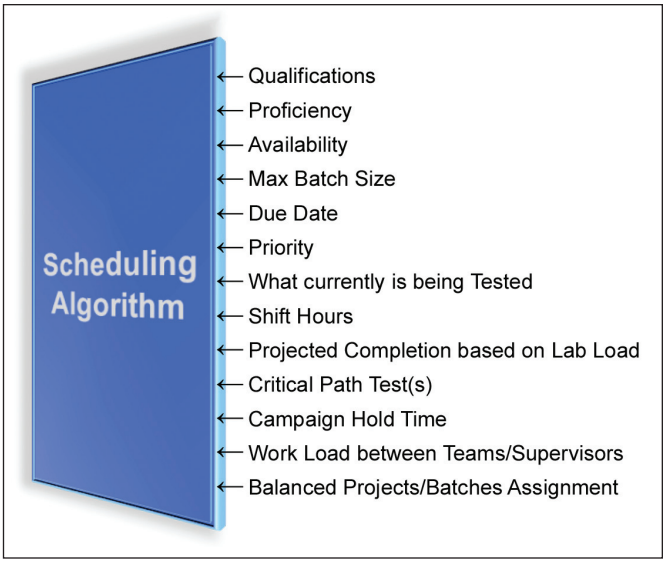

Figure 2. Scheduling attributes.

formed by the supervisor based on his/her knowledge of his/her team. In order to computerize some of these preferences, we need to communicate this information to the scheduling algorithm. Due date and priority helps determine the order in which a given test should be performed. It is important to note that two tests with the same due date may need to be assigned differently since one test may have two days of analyst and instrument time vs. perhaps five days for another test. Looking at the due date alone will not provide the proper priority. This leads to the need to project the expected completion time of these tests and compare it to the due date. One of the key aspects of scheduling is to assign the longest test (critical path) first, including the instruments involved. This is intended to ensure the analysts start on the longest test before starting a short test. When few samples of different products have arrived to the lab and if these samples once campaigned have a long test in terms of analyst hands on time and instrument time, the overall schedule adherence will improve by starting these long tests first before moving on to others. (This is generalizing yet it provides the most likelihood scenario.) The chart in Figure 3 illustrates the approach of initiating the longest test (critical path) first and while the longest test is being processed in one of the instruments, other tests could start. Other attributes are listed in Figure 2 and include items such as workload balancing between the various lab teams to enable a more rapid execution of the tasks on hand. With a computerized scheduling system, we have the information on what tests are being performed and we can use this information to schedule additional tests that require the same set up to the analyst who has already started a similar test. Other attributes include analyst availability and shift hours that will ensure high priority tests should be scheduled to the current shift if sufficient time remains or to the upcoming shift so these high priority tasks can be executed on time.

The Scheduling Process

In order to illustrate what an automated schedule would look like, I have used one of the commercially available software solutions. The process starts with receiving samples and tests from Lab Information Management System (LIMS). Simple integration between LIMS and the scheduling system will prevent any redundant data entry. (Not all QC Labs are using LIMS; if no LIMS is used, samples could be entered directly to the scheduling system.) Then, these samples are first broken down to the individual tests. Each sample has a due date and priority. With a pre-defined set of batching/campaigning rules, the algorithm will combine the samples and the tests together considering parameters, such as due date and the priority, the probability for these test, to be completed on-time, and maximum campaign size (not to over campaign). In addition, with the projection completion algorithm, we can hold the scheduling process for other upcoming samples without risking a miss of the due date. As can be seen in Figure 4, Test A is common for all the four samples that arrived and are campaigned; however, Test C is not needed for Sample #2, etc. Once the algorithm establishes the batches and their related parameters, the scheduling process begins, and now a broader picture is looked at: the analyst workload, qualifications, and proficiency, and the actual structure of the labs is being considered, e.g., center of excellence, organized by value stream, cell approach. Assignments are determined by the software algorithm and provided to the analysts with various colors of criticality where red indicates lateness, yellow indicates close to being late, and green stands for ahead of schedule. This communicates to the analysts the order of importance of assignments for the business. Once we computerize the scheduling process, other attributes of the lab performance can be managed such as analyst/workcenter/team efficiency,

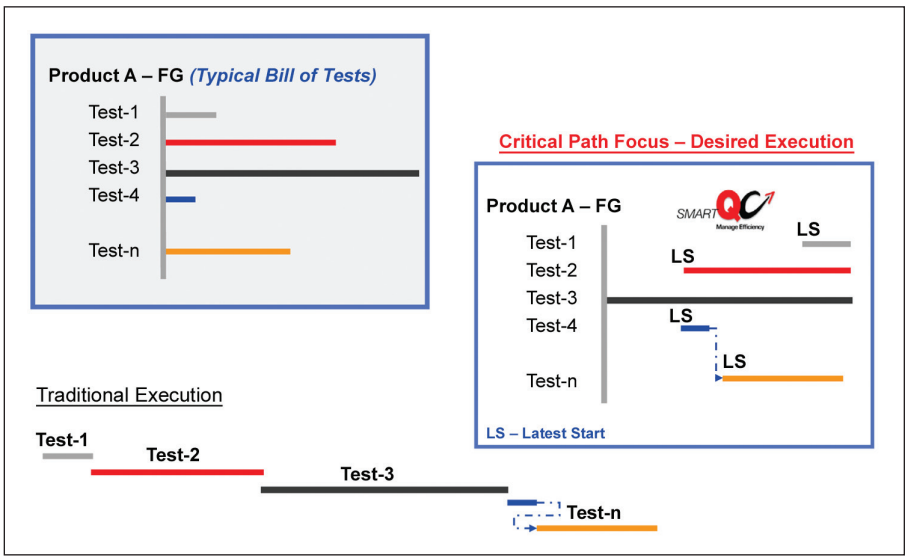

Figure 3. Critical path consideration.

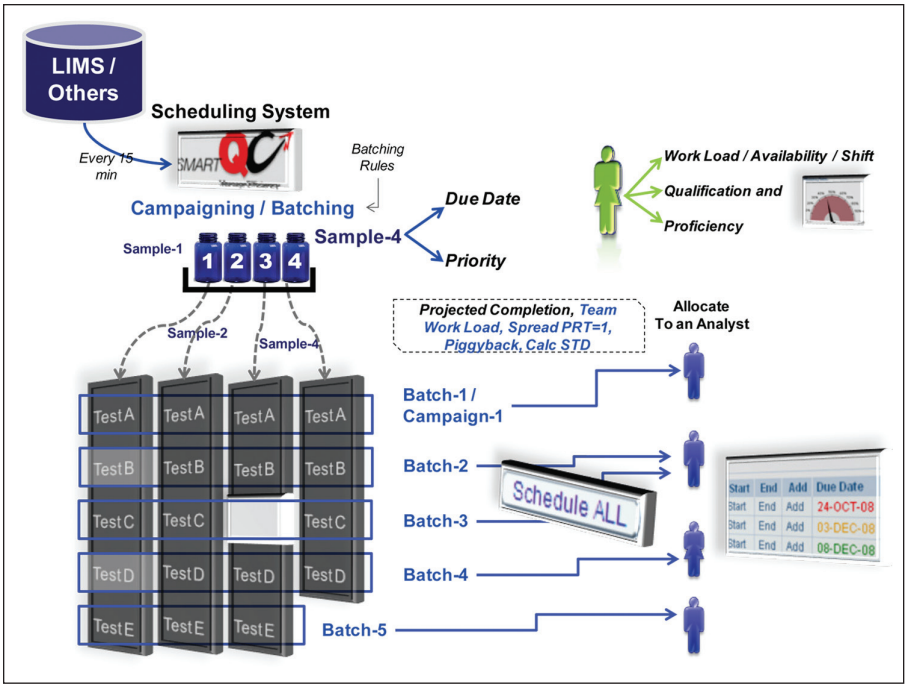

Figure 4. Automated scheduling flow.

more detailed cycle time assessment and root causes for delays, and as the critical ability to react to changes in the schedule by running the algorithm in one click. Once the algorithm is completed, each analyst will see the changes in their own dashboard and can react accordingly. This is one of the most challenging tasks to accomplish when using a manual whiteboard or simple communication as we need to update each affected analyst by the change.

Summary

QC laboratories are one of the most complicated environments to schedule, especially in labs that have a high product mix and diversified products that are tested with large number of analysts and instruments. In order to schedule this level of complexity, a robust computerized solution is required to minimize the time spent by the supervisors and provide the flexibility to react to schedule changes and optimize the overall lab performance in terms of cycle time, on-time delivery, and efficiency. Improving campaigning by leveraging a computerized solution can significantly reduce overtime and improve efficiency. These are key in reducing lab costs and provide a more reliable supply chain partner to the manufacturing. While having the right number of resources using a resource model is key in ensuring the lab ability to support incoming samples, the ability to effectively schedule the lab will help manage the daily and weekly fluctuations that are inherent in our current business conditions that call for low inventory and an agile supply chain.

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About the Author

Rafi Maslaton, President, cResults, an IPS affiliate, has more than 19 years of diversified experience in operations, manufacturing engineering, information systems, and business management issues for fortune 500 firms. Prior to joining cResults, he served as COO of Sparta Systems, the maker of TrackWise, overseeing the complete project life cycle for clients. Maslaton has managed operational excellence projects for more than 100 QC laboratories and works with Fortune 500 clients, such as Abbott, Amgen, Baxter, Bausch and Lomb, Bayer, Centocor/OBI, C.R. Bard, Eli Lilly, Fort Dodge, Genentech, J&J, Merck, Novartis, Par, Pfizer, Pharmacia, Roche, Sandoz, Shire, Schering-Plough, Teva, Wyeth, Agere Systems, HADCO, IBM, Intel, Lucent, Motorola, Nortel Network, Philips, Raytheon, and Siemens. Maslaton developed the first resource planning, scheduling, and cost of quality software for the QC laboratories Smart-QC and the first batch record and efficiency management software solution for QA cME. He can be contacted by email: rmaslaton@cresultsconsulting.com.

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The State of Quality by Design for Generics

Report on Joint ISPE – European Generics Association Meeting on Applying QbD to Development and Manufacture of Generic Medicines

by Chris Potter, ISPE PQLI Technical Project Manager and CMC Pharmaceutical Consultant

Overview

On 27-28 June 2012 in Brussels, Belgium, ISPE co-hosted with the European Generics Association (EGA) the first meeting in Europe to discuss application of Quality by Design (QbD) approaches to the development and manufacture of generic medicines. Over two days there were keynote presentations from eminent EU and US regulators and from the generic medicines industry, as well as workshops with outputs available to participants to discuss the regulatory, technical, and business implications of developing generic medicines and associated processes for both products and active ingredients. Importantly, three case studies were presented showing application of different QbD approaches, which indicated that companies developing and manufacturing generic medicines are very active in, and can derive benefits from, implementing the concept of QbD.

Why Hold the Meeting?

The US FDA has made public statements that from early 2013 US Abbreviated New Drug Applications (ANDAs) applicable to generic medicines should contain QbD elements. Many companies source the US and operate at global level, therefore have activities in both the US and the EU.

The concept of Quality by Design is defined in ICH regulatory guideline Q8 (R2)[1] as:

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

QbD is derived from implementation of harmonized regulatory guidelines in the EU, US, and Japan for Pharmaceutical Development (ICH Q8)[1], Quality Risk Management (ICH Q9)[2], Pharmaceutical Quality System (ICH Q10)[3], and Development and Manufacture of Drug Substances (ICH Q11).[4] Some other regions have also embraced these guidelines, e.g., Canada and Australia. It is a voluntary concept which applies to all medicines and active substances and is not intended to create new regulatory requirements. It is equally important to generic and originator medicines. The regulatory expectations in the EU are not clear for many generic (and originator) companies, and it is not clear from the statement in ICH Q8 regarding opportunities for "regulatory flexibility," what could be achieved.

QbD does have some differences of technical approach compared with a "traditional" approach and the business challenges of investment, given that payback is later in the product lifecycle, are significant:

- How much?
- When in the development program?
- What parts of the process, all or just some steps?

The generic medicines industry operates at a very fast pace, in a very competitive environment, and with the need to file first as a key business goal. Companies obviously want to achieve more robust and efficient manufacturing processes and supply chains but successful companies will be those taking into consideration the dynamics of the generic medicines sector.

Originator companies have reported[5] significant business benefits when developing new products using QbD, and when applying QbD to make improvements to existing marketed products.

Many practical questions, however, remain open.

Speakers and Structure of the Meeting

The regulatory keynote speakers are leaders for their region. Jean-Louis Robert is chairman of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP)/Committee for Medicinal Products for Veterinary Use (CVMP) Quality Working Party and served on the Expert Working Group for ICH Q8, and the Implementation Working Group which produced follow up Questions and Answers, and Points to Consider documents. He works for the Labortoire National de Sante, Luxembourg. Robert discussed "Demystifying Quality by Design from a Regulatory Perspective."

Jacques Morenas from the French National Agency for Medicines and Health Products Safety (ANSM) was a member of the ICH Q9 and Q10 Expert Working Groups, was a past chair of PIC/S, and is a global leader from a compliance/inspection perspective on implementation of ICH Q8, Q9, and Q10. Morenas discussed "Implementation of Q9 and Q10 in the EU: A Regulatory Inspection Point of View."

Keith Webber is Deputy Director of the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the US FDA and has been involved in developing policy in the US for application of QbD to generic drugs. Webber presented "A US Regulatory Perspective on the Implementation of QbD for Generic Drugs."

Pito Roslansky as Head of Strategic Projects, Global Product Development, Sandoz International GmbH, gave a generic medicines industry perspective on the application and use of QbD in a global context, entitled, "The Quality by Design

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Paradigm and the Generics Industry."

There were also three excellent and relevant case studies explaining the practical application of QbD to different stages of the development of a generic medicine from:

- Francois A. Menard, Watson Pharmaceuticals Inc., US
- Jose Ascensao, Hovione, Portugal
- Jan Ramza, Polpharma SA, Poland

Three interactive Workshop sessions discussed topics relevant to the generic medicines industry using prepared questions based on content from the earlier presentations, these being:

A. Why consider QbD?
B. How do you effectively develop products and processes using QbD?
C. What are the regulatory expectations for QbD submissions?

The meeting was very well attended with representation from large and small generic companies located throughout Europe and the near east, and from a range of relevant disciplines.

Discussion Highlights

All speakers included in their content reference to at least one of the four relevant ICH guidelines, Q8 (R2), Q9, Q10, and Q11, and many stressed that all four guidelines are required to achieve the ICH quality vision, which was developed at the Brussels, ICH meeting in July 2003:

"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science."

Also relevant are supporting Questions & Answers[6] and Points to Consider[7] documents and training material[8] available from the ICH web site. Particular definitions often referenced were:

- Quality Target Product Profile (QTPP)
- Quality by Design (QbD)
- Critical Quality Attribute (CQA)
- Critical Process Parameter (CPP)
- Quality Risk Management (QRM)
- Control Strategy
- Design Space

An important message from the regulators from Workshop C (What are the regulatory expectations for QbD submissions?) was that industry in both their submissions and internal GMP documentation should use accurate terminology and ideally not use new terms.

Robert said that QbD is not totally new in the EU, referring to the previous CHMP Guideline on Development Pharmaceutics[9]. However, he insisted that a sound, more systematic development approach with use of more formal risk management should facilitate the process to achieve quality and should automatically generate more knowledge. He pointed out that QbD does not require establishment of a design space or necessarily lead to real time release testing. Independent of the level of development ("minimum" or "enhanced, QbD") a control strategy is always required. Additionally, he stressed that a conventional specification is still required and acceptance criteria are likely to be set using a balance between clinical relevance and process capability.

Webber said that implementation of QbD is essential to ensuring the availability of affordable, high quality generic drugs in the US. He indicated that QbD goals were to reduce product variability and defects, to increase product development and manufacturing efficiencies, and to enhance post-approval change management. The minimum ICH Q8 expectations are to define a QTPP, identify and control CQAs of drug product, determine CQAs of drug substance and relevant excipients, select an appropriate manufacturing process, and define a control strategy. He also elaborated on what could be involved if an enhanced, QbD approach were chosen, for example, drug substance and excipient properties to consider. He stressed that a basis of the enhanced, QbD approach was development of process understanding whereby there is linkage of critical material attributes and CPPs to relevant drug product CQAs.

Morenas concentrated on implementation of Q9 and Q10 in the EU and the potential impact on current EU GMP guidelines. He said Q9, Quality Risk Management (QRM) provides principles and a framework for science-based decision making. It is guidance introduced in Part III of the EU GMP guide and it is not an "SOP." It is simple, flexible, not mandatory, facilitates communication and transparency, and supports build-up of trust between regulators and industry. He discussed an example of the application of QRM in the GMP inspection environment by referencing the work currently being undertaken by the CHMP Safety Working Party to develop toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities.[10] He also described the ANSM approach to risk-based GMP inspection planning, which was derived from the recommended model elaborated by PIC/S QRM Experts Circle.[11] With regard to Q10, Morenas identified those parts of the EU GMP guide which are being or have been revised based at least in part on ICH Q10. He concluded that Q10 allows global harmonization of a Pharmaceutical Quality System (PQS), that a PQS is mandatory to comply with EU GMP, and ICH Q10 reflects current expectations for EU GMP.

Roslansky showed examples of how there can be different QbD strategies and that use of prior knowledge can be very effective to reduce development time and resources. For the

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generic industry there are significant challenges applying a QbD approach, for example, compatibility with the business need to be first-to-file in the US. For the globally-sourcing industry, there are challenges with: global regulatory alignment; alignment with the new US process validation guidance; low amounts of drug substance during early development; and unavailability of excipient samples for quality attribute evaluation. Nonetheless, the enhanced, QbD approach should lead to improved product and process understanding with the concomitant benefits.

All three case studies emphasized the need to balance the business environment and regulators' expectations with the amount of work and its timing in the development program and with the anticipated benefits. All described their company's iterative science- and risk-based approach, which can, however, be summarized in Figure 1 taken from ISPE's PQLI Guide, Part 1 – Product Realization using Quality by Design: Concepts and Principles.[12]

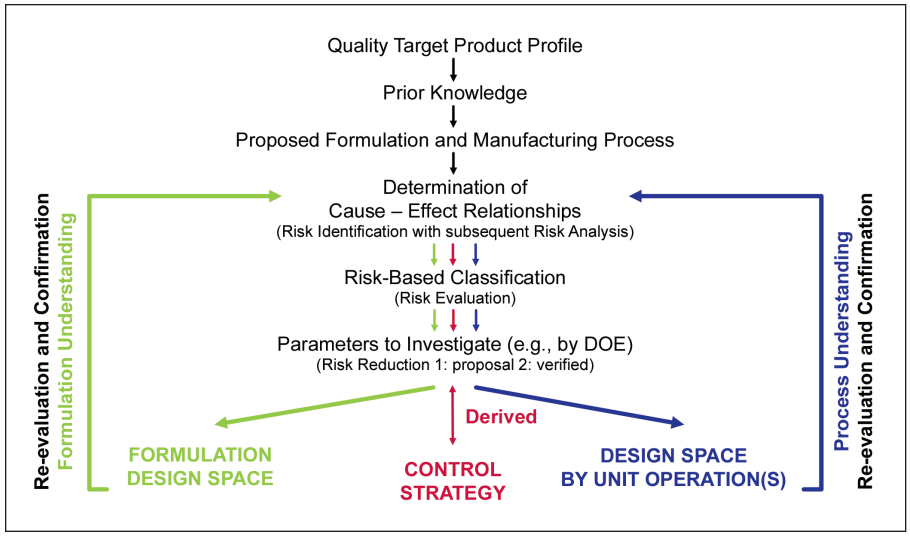

Figure 1. Iterative Enhanced, QbD Approach to Drug Product Development (also applicable to drug substance).

Menard from Watson showed with two generic drug product case studies of complex products how matching the CQA of dissolution profile of the originator product from an osmotic delivery system and from a coated multi-particulate system could be achieved successfully using a QbD approach. Use of advanced analytical methods and development of process models were described. Significant business benefits were described, such as better process robustness, less deviations/rejections, improved cost of goods, and customer service.

Ascensao indicated the "Hovione Way" to QbD implementation using spray drying of an API as an example. He particularly emphasized the important role of risk management to optimize the number of variables to study in statistically-designed studies, as well as to optimize the number of experiments, and in each experiment, the range and intervals of variables to study.

Ramza explained Polpharma's decision to apply QbD to chemical process development of APIs. Polpharma uses risk management to select the critical steps of the process on which to apply the QbD approach. For other steps, conventional studies to determine proven acceptable ranges are performed. New equipment and software was required to implement QbD, as was new documentation and training of people in many disciplines. Goals for the project were achieved.

The main points from the Workshops were:

A. Why consider QbD?

- Develop your own business case.
- Consider a pilot project.
- Involve all disciplines.

B. How do you effectively develop products and processes using QbD?

- New tools and expertise required – knowledge management, Process Analytical Technology (PAT), risk assessment, multivariate experiments and analysis
- PAT tools may be more suitably applied in development.
- IT software and infrastructure required

C. What are the regulatory expectations for QbD submissions?

- Assessors want a well-written, clear story. Internal peer review is recommended.
- No real difference for inspections
- Use accurate terminology.

Conclusion

The main conclusions from the meeting were:

- QbD is feasible for the generic medicines sector and there are benefits.
- Such meetings create the necessary platform for dialogue between regulators and industry experts to clarify misconceptions.
- It is essential that implementation by the various regions remains harmonized, otherwise the divergences might defeat the initial purpose.

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The EGA looks forward to more opportunities to address QbD with regulators and will work jointly with other trade associations to organize a workshop with EMA in 2013.

Guidance on technical aspects of implementation of QbD approaches is given in Part 1, Concepts and Principles[12] and Part 2 Illustrative Example[13] of the ISPE PQLI Guide series.

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